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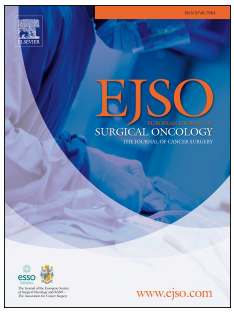

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Estimation of the future remnant liver function is a better tool to predict post-hepatectomy liver failure than platelet-based liver scores

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Abstract

Introduction: Recently, there has been increasing interest in the preoperative prediction and prevention of post-hepatectomy liver failure (PHLF). This is a particular concern in colorectal liver metastases (CRLM), when surgery follows potentially hepatotoxic chemotherapy. Platelet-based liver scores (PBLS) such as APRI and FIB-4 are predictive of chemotherapy-associated liver injury (CALI) and PHLF. Estimation of the future liver remnant function (eFLRF) by combining ^{99m}Tc-Mebrofenin Hepatobiliary Scintigraphy (HBS^{BSA}) with future liver remnant volume ratio (FLRV%), is predictive of PHLF and related mortality. We hypothesized that a HBS^{BSA} based formula was a better predictor for PHLF than PBLS in chemotherapy-pretreated CRLM.

Methods: Between 2012 and 2016, 140 patients underwent liver resection for CRLM following systemic therapy. HBS^{BSA}, FLRV%, eFLRF and PBLS were calculated and compared for their value in predicting PHLF.

Results: eFLRF and FLRV% had a better predictive value for PHLF than HBS^{BSA} alone and APRI and FIB-4 (AUC = 0.800, 0.843 versus 0.652, 0.635 and 0.658 respectively). In a subgroup analysis (Oxaliplatin all, Oxaliplatin ≥ 6 cycles, Irinotecan all and Irinotecan ≥ 6 cycles), eFLRF was the only factor predictive for PHLF in all subgroups (all: $p \leq 0.05$). Prediction of HBS^{BSA} for chemotherapy associated steato-hepatitis (CASH) reached significance ($p = 0.06$). FIB-4 was predictive for sinusoidal obstruction syndrome (SOS) ($p = 0.011$). Only weak correlation was found between HBS^{BSA} and PBLS.

Conclusion: eFLRF is a better predictor of PHLF than PBLS or HBS^{BSA} alone. PBLS seem to measure other aspects of liver function or damage than HBS^{BSA}.

Keywords: liver failure; colorectal cancer; liver metastasis; hepatectomy; liver function;

platelet count

Introduction:

Since chemotherapeutical, biological and loco-regional treatments in colorectal liver metastatic disease result in longer survival, prolonged morbidity and mortality due to post-hepatectomy liver failure (PHLF) cannot be accepted anymore. Preoperative estimation of the future liver remnant function is therefore of vital importance before major liver resection, and should also be considered when performing minor liver resections in damaged livers. Different pathological entities have been described following systemic chemotherapy: sinusoidal obstruction syndrome (SOS), chemotherapy associated steato-hepatitis (CASH) and nodular regenerative hypertrophy (NRH) [1]. SOS, a pathological finding after (prolonged) administration of Oxaliplatin can lead to more intraoperative bleeding and blood transfusions. CASH can be induced by longstanding treatment with Irinotecan, resulting in reduced regenerative capacity and liver function. NRH is a condition seen after liver due to disturbed blood supply, resulting in diminished liver function. These different forms of CALI may exacerbate the impaired liver function after liver resection, resulting in temporary PHLF and consequently higher incidence of morbidity and mortality after liver resection..

Predicting the minimal liver remnant after surgery is a matter of measuring the future liver remnant volume and of estimating the functional and regenerative capacity of the liver. Different tests can be used to estimate preoperative liver function prior to liver surgery for colorectal liver metastasis (CRLM). As long as the liver function is grossly preserved, scores used for assessing and grading severe liver dysfunction, such as the model of end-stage liver disease (MELD) are of little use to assess subtle changes of liver function and regeneration capacity in CALI. As an alternative, and as liver fibrosis is a marker of liver tissue damage and predictive of long-term outcomes in several liver diseases, scores, based on routinely performed biological tests and that predict fibrosis, have been tested for their potential to predict CALI. Most of these tests are platelet-based liver scores (PBLS) and are based on platelet count, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT), e.g. the AST to Platelets Ratio Index score (APRI) and the Fibrosis-4 score (FIB-4) [2].

Liver function can also be assessed by ^{99m}Tc-Mebrofenin Hepatobiliary Scintigraphy (HBS) [3]. Because a good correlation between Indocyanine Green Retention Test at 15 min (ICGR15) and

^{99m}Tc-Mebrofenin HBS has been demonstrated, HBS has been validated as a tool to measure total liver function and functional remnant liver after liver resection [4]. To compensate for variations in individual metabolic needs, HBS clearance is divided by Body Surface Area (HBS^{BSA}) and expressed as %/min/m². Our own previously published HBS^{BSA}-based method combining HBS^{BSA} with liver volumetry of the future liver remnant on magnetic resonance imaging (MRI), was able to estimate the future liver remnant function (eFLRF) [5]. By using a cut-off value of 2.3 %/m²/min, the need for preoperative portal vein embolization (PVE) or ligation (PVL) could be predicted and PHLF could be avoided [6].

Until now, no direct comparison of predictive accuracy between PBLS and HBS^{BSA} based methods has been conducted. We hypothesize that a HBS^{BSA} based formula is a better predictor of PHLF than PBLS in liver surgery for CRLM pretreated with chemotherapy.

Methods

Patients

All consecutive patients between April 2012 and August 2016 undergoing hepatectomy for CRLM after systemic chemotherapy, were included. The study was approved by the Medical Ethics Committee of the Antwerp University Hospital. Written informed consent was obtained from each participating patient.

Preoperative evaluation

Age, gender and Body Mass Index (BMI, kg/m^2) were recorded. Major hepatectomy was recorded as resection of 3 or more liver segments. Total liver volume (TLV) and future liver remnant volume (FLRV) were measured with MRI. Major metastatic volumes were considered as non-functional liver tissue and subtracted from TLV. Future Liver Remnant Volume % (FLRV%) was calculated: (FLRV% = FLRV/TLV x 100). HBS^{BSA} was performed to measure global liver function (%/min), regardless of the tumor volume [7]. eFLRF was calculated: (eFLRF = FLRV % x HBS^{BSA}). Methodology for FLRV%, HBS^{BSA}, and eFLRF calculations have been previously described [5].

The indication for PVE/PVL was made according to the cut-off value for eFLRF below 2.3 %/min/m² [6]. Two stage hepatectomy was performed in bi-lobar CRLM when one stage resection was impossible. Associated liver partition with PVL in staged hepatectomy (ALPPS) was indicated when a very low eFLRF predicted still an insufficient liver function if only PVE was performed.

Preoperative AST (U/L), ALT (U/L) and platelet count ($x10^9$/L) were determined.

Calculation of PBLS

APRI and FIB-4 were calculated in a post-hoc analysis. They were not used as "decision making tools" for PVE/PVL.

APRI and FIB-4 were calculated: (APRI = (AST / AST^{ULN*}) / (Platelet count) x 100)

(FIB-4 = (age x AST) / (Platelet count x √ ALT)

(* ULN = Upper Limit of Normal range)

Chemotherapy

Four subgroups were defined according the type and number of cycles of the preoperative chemotherapy: *Oxaliplatin all*: patients receiving any regimen with of Oxaliplatin; *Oxaliplatin ≥ 6 cycles*: only those patients receiving ≥ 6 cycles of Oxaliplatin; *Irinotecan all*: patients receiving any regimen of Irinotecan; *Irinotecan ≥ 6 cycles*: only those patients receiving ≥ 6 cycles of irinotecan.

Pathology

On histopathological examination of the resection specimen, SOS was diagnosed in case of severe centrilobular or midzonal sinusoidal dilatation or worse and in presence of NRH based on reticulin stain. CASH was diagnosed in case of severe steato-hepatitis: more than 33% steatosis and presence of inflammatory cells [8].

Postoperative evaluation

PHLF was scored according to the International Study Group of Liver Surgery (ISGLS) criteria [9], characterized by an increased INR and hyperbilirubinemia on or after postoperative day 5. Grade A PHLF requires no change in the patient's clinical management. In grade B PHLF, clinical management deviates from the regular course but without invasive therapy. Grade C is defined by the need for invasive therapy. In this study, analysis was based on evaluation of the total incidence of PHLF. PHLF-related mortality was defined as mortality caused by PHLF within 3 months after hepatectomy.

Statistical analysis

Statistical analysis was performed using SPSS software (version 21, Chicago, IL). The normal distribution of continuous variables was assessed with the Shapiro-Wilk method. Normally distributed variables were expressed as means with standard deviations and compared using Student's t-test. Non-parametric continuous variables were expressed as medians with range and compared using the Mann-Whitney U test. Categorical data were expressed as percentages (%). Nominal data were compared using the Chi-square or Fisher's exact test. Recipient Operating Characteristics (ROC) with Area Under the Curve (AUC) was performed and predictive values were analyzed using univariate logistic regression model. Multivariate analysis was performed with all significant factors, excluding the factor(s) linked to each other due to contribution in the same formula. In that case, the factor with highest AUC was chosen for multivariate logistic regression. The independent factors predictive of PHLF were analyzed in the 4 subgroups of patients using a univariate logistic regression model. The predictive value for CASH and SOS of the liver function tests was evaluated with univariate analysis. Correlation was calculated by Spearman correlation analysis. Significance was defined as p-value < 0.05.

Results

Characteristics of the 140 study patients undergoing systemic therapy prior to liver surgery for CRLM are summarized in Table 1. Major hepatectomy was performed in almost 50% (69/140) of cases. In

14.3% (20/140), eFLRF was below the threshold value of 2.3 %/m²/min: interventions to stimulate liver regeneration were indicated. PVE prior to right or left hepatectomy was performed in 11/20 and PVL in the first stage of a two-stage resection in 8/20 patients. ALPPS was performed in only 1/20. At post-operative evaluation, eFLRF had recovered to > 2.3 %/min/m² in all 20 patients.

Oxaliplatin-based regimens were administered in 62.1% (87/140) and Irinotecan-based regimens in 37.9% (53/140). In 45% (63/140) postoperative pathological analysis of the non-tumoral liver tissue was available: severe SOS was seen in 36.5% (23/63) and severe CASH in 30.2% (19/63). PHLF occurred in 15% (21/140) patients, all following major hepatectomy. 16/140 PHLF were classified as grade A. Only 5/140 patients developed a grade B PHLF and no grade C was recorded. There was no PHLF-related mortality.

ROC-analysis demonstrated a high sensitivity and specificity for both FLRV% and eFLRF in predicting PHLF (AUC = 0.800 and 0.843 respectively). HBS^{BSA}, APRI and FIB-4 had lower AUC values (0.652, 0.635 and 0.658 respectively) (Figure 1).

Table 2 summarizes univariate and multivariate analysis of the different risk factors for PHLF. Univariate analysis showed both types of volumetric evaluation (major hepatectomy and FLRV%) were significant factors in predicting PHLF ($p = 0.001$ and $p < 0.001$ respectively). Functional evaluation by APRI and FIB-4 scores reached statistical significance ($p = 0.035$ and $p = 0.033$ respectively), whereas HBS^{BSA} showed a trend towards significance ($p = 0.057$). Combining volumetric and functional evaluation by eFLRF was predictive of PHLF ($p < 0.001$). The type of preoperative chemotherapy (Oxaliplatin or Irinotecan) and the administration of 6 or more cycles were not shown to independently increase the risk of PHLF. Major hepatectomy, FIB-4 and eFLRF were selected as significant and unrelated factors for multivariate regression analysis and remained all significant for PHLF ($p = 0.034$, $p= 0.014$ and $p =0.002$ respectively). The choice to include these parameters in multivariate analysis was motivated as: (1) eFLRF is related with FLRV% as part of the formula leading to eFLRF (eFLRF = FLRV% x HBS^{BSA}), (2) FIB-4 is related to APRI by sharing same parameters in their formula (platelets and AST), (3) eFLRF has a higher AUC compared to

FLRV% and (4) FIB-4 has a higher AUC than APRI. CASH but not SOS was associated with an increased risk of PHLF (p = 0.024).

Table 3 summarizes the results of univariate analysis in the 4 subgroups of chemotherapy treated patients. eFLRF was predictive of PHLF in each subgroup (*Oxaliplatin all*: $p < 0.001$; *Oxaliplatin ≥ 6 cycles*: p = 0.001; *Irinotecan all*: p = 0.030 and *Irinotecan ≥ 6 cycles*: p = 0.051). The FIB-4 had no predictive value in any subgroup. Major hepatectomy was only predictive in the subgroup *Oxaliplatin all* (p = 0.004).

In Table 4, FIB-4 is a significant predictor of SOS, but not of CASH (P = 0.011). HBS^{BSA} showed a trend towards significance in predicting CASH (P = 0.060) but had no value for SOS-prediction.

Spearman's Correlation analysis showed significant but only weak association between HBS^{BSA} and APRI and between HBS^{BSA} and FIB-4. Correlation coefficient (ρ) and p-value were respectively: ρ = -0.170 (p = 0.046) ; ρ = -0.165 (p = 0.052).

Discussion

This study investigated the accuracy of different predictive factors for PHLF in 140 patients undergoing liver resection for CRLM after preoperative chemotherapy. The main finding was that FLRV% (preoperative liver volumetry) and eFLRF , by combining liver volumetry with a functional assessment using HBS^{BSA}, were both the best predictors for PHLF. Tests evaluating liver function or preoperative liver damage (HBS^{BSA}, APRI and FIB-4) were all less predictive of PHLF than the volumetric based measurements of FLRV% and eFLRF. These findings suggest that the extent of resected liver tissue remains the major factor influencing the occurrence of PHLF in hepatectomy after chemotherapy. FLRV is used in many centers prior to liver resection. FLRV% < 30% and long duration chemotherapy (> 12 weeks) were independent predictors of PHLF in liver resection for CRLM [10]. Liver-related complications were independently associated with major hepatectomy (resection ≥ 3 segments) and blood transfusion, but were not associated with preoperative

chemotherapy [11]. A shrinkage of 10% in TLV with concomitant impairment of the hepatic function after aggressive preoperative chemotherapy for CRLM has been described [12], confirming the usefulness of performing the preoperative eFLRF method, based on both FLRV related to TLV and total liver function.

In the current study, PHLF occurred more often in patients with underlying CASH than in patients with SOS. This confirms earlier reports, demonstrating higher morbidity and increased 90-day mortality after liver resection for CRLM in CASH [13]. A meta-analysis including 28 studies has demonstrated a 3.45-fold increase of CASH in patients who received Irinotecan-based chemotherapy [14]. In the current analysis, no association between SOS and PHLF was observed. Previous studies showed no relationship between Oxaliplatin and post-operative morbidity [11, 15]. However, 9 or more cycles of Oxaliplatin was the only predictive factor for PHLF [16]. These contradicting conclusions concerning the impact of CALI may be explained by differences in the histopathological examination of non-tumoral liver tissue. In atypical liver resections, only a small sample of non-tumoral tissue is available for pathological examination. Moreover, CALI may be focal, leading to sampling error and potential under- and overestimation of CALI [11].

A comparison between the different tests, showed in this study that PBLS and HBS^{BSA} had similar predictive value. Several papers argue for the predictive value of PBLS in PHLF following liver resection for CRLM post-chemotherapy.

The APRI-score was originally designed to evaluate extensive fibrosis and cirrhosis in chronic hepatitis C patients by combining the opposing effects on AST and platelet count. Liver parenchymal damage is reflected by elevated AST and liver fibrosis results in lowered platelet count. This simple index could identify significant fibrosis in chronic hepatitis C patients with a high degree of accuracy (AUC = 0.88) [17]. More recently, APRI was shown to be a predictive factor for poorer postoperative liver function and higher postoperative complication rate in surgery for hepatocellular carcinoma [18]. As Oxaliplatin can lead to major histopathological changes [1, 13], such as perisinusoidal and centrilobular fibrosis, APRI is an accurate tool to predict PHLF and CALI in surgery for CRLM pretreated with Oxaliplatin (ROC AUC = 0.72) [2]. APRI was the only independent predictive factor

for severe SOS (ROC AUC = 0.85) after preoperative Oxaliplatin [19]. NRH can be considered as the most severe form of SOS: it was best predicted by APRI and was an independent factor for PHLF [20]. FIB-4 score predicts fibrosis in chronic hepatitis C [21, 22] and is considered a useful index for predicting postoperative outcome after surgery for hepatocellular carcinoma [23]. In Oxaliplatin-treated patients, FIB-4 was predictive of severe SOS (ROC AUC = 0.78) [19]. Both APRI and FIB-4 were found to be predictive of SOS, with APRI being most significant for severe SOS [24].

HBS^{BSA} with ^{99m}Tc-Mebrofenin has been validated as a tool for measuring total and regional liver function, thus allowing estimation of the future remnant liver function (FLRF) following liver resection [3, 4]. Mebrofenin is eliminated almost completely by the liver through biliary excretion. It shares the same metabolic pathway as bilirubin and toxins [25] and results correlate well with the indocyanine green test [4]. For this reason, it can be used in normal livers, as well as in livers with parenchymal damage, regardless of the type and grade of parenchymal liver dysfunction [26]. The study group of Amsterdam has shown that estimation of eFLRF by HBS^{BSA} can predict PHLF and PHLF-related mortality in patients with normal and damaged liver parenchyma. It was considered a better predictor for PHLF than FLRV% alone [27]. PHLF after major liver resection occurred more often when HBS^{BSA} was below the cut-off value of 2.69%/m²/min [26]. The Amsterdam group showed the ability of SPECT combined with CT to measure segmental liver function and to predict the function of the future liver remnant [28, 29]. Implementation of HBS with SPECT/CT by using the cut-off value as indication for preoperative PVE in the same center was able to decrease significantly PHLF [30]. In our previously published work of [5, 6], we described an alternative to the Amsterdam method: eFLRF was calculated by multiplication of the FLRV%, measured on MRI-volumetry, with the total liver function measured by HBS^{BSA}. We estimate that volumetric assessment with MRI was more precise than volumetry from combined SPECT/CT scanning, especially in non-anatomical liver resections. A cut-off value of 2.3%/m²/min was shown to be more predictive of PHLF and its related mortality than FLRV% alone. When this cut-off value was used as a selecting tool for preoperative PVE or PVL, PHLF and PHLF-related mortality was avoided [6].

Only weak correlation was found between HBS^{BSA} and FIB-4 and between HBS^{BSA} and APRI in the present study. This suggests that both types of tests detect different types of liver parenchymal damage and dysfunction. Indeed, FIB-4 was able to predict SOS, whereas the liver excretion based test (HBS^{BSA}) seemed to better reflect the presence of CASH.

The fact that eFLRF allows combined assessment of the future liver remnant volume and liver function probably explains why this formula seems more accurate to predict the risk of PHLF than PBLS. To our knowledge, no combined volume-function formula has been used with PBLS as function evaluation. The current study indeed demonstrates the superiority of eFLRF over PBLS not only in the overall population, but also in different subgroups defined by type of chemotherapy and number of cycles.

The principal limitation of this study is the preoperative selection bias on basis of eFLRF. PVE, PVL or ALLPS was performed according to a cut-off for eFLRF <2.3%/min/m², and therefore might have improved outcome of patients initially at high risk for PHLF. However, no patient with resectable CRLM was denied surgery based on preoperative eFLRF. A second limitation is that FLRV% and eFLRF were similarly predictive of PHLF in univariate analysis, although eFLRF was slightly superior to FLRV% in ROC-analysis. This suggests that liver function in this patient cohort was not sufficiently poor to significantly demonstrate the superiority of eFLRF over FLRV%. Nevertheless, in almost 60% of patients, CASH or SOS could be observed on histopathological analysis of the resected specimen, with almost 2/3 of patients receiving 6 or more cycles of Oxaliplatin or Irinotecan prior to surgery. In summary, the authors do realize the major impact of FLRV% in the final predictive value of eFLRF but are also convinced that adding HBS^{BSA} is adding a small extra value to the volumetric aspects.

Conclusion:

This study demonstrates the superiority of a eFLRF over PBLS in prediction of PHLF in liver surgery for CRLM, although FLRV% contributes to a large extent in this method to the predictive value.

Conflict of interest

All authors: no conflicts of interest to the present article to disclose.

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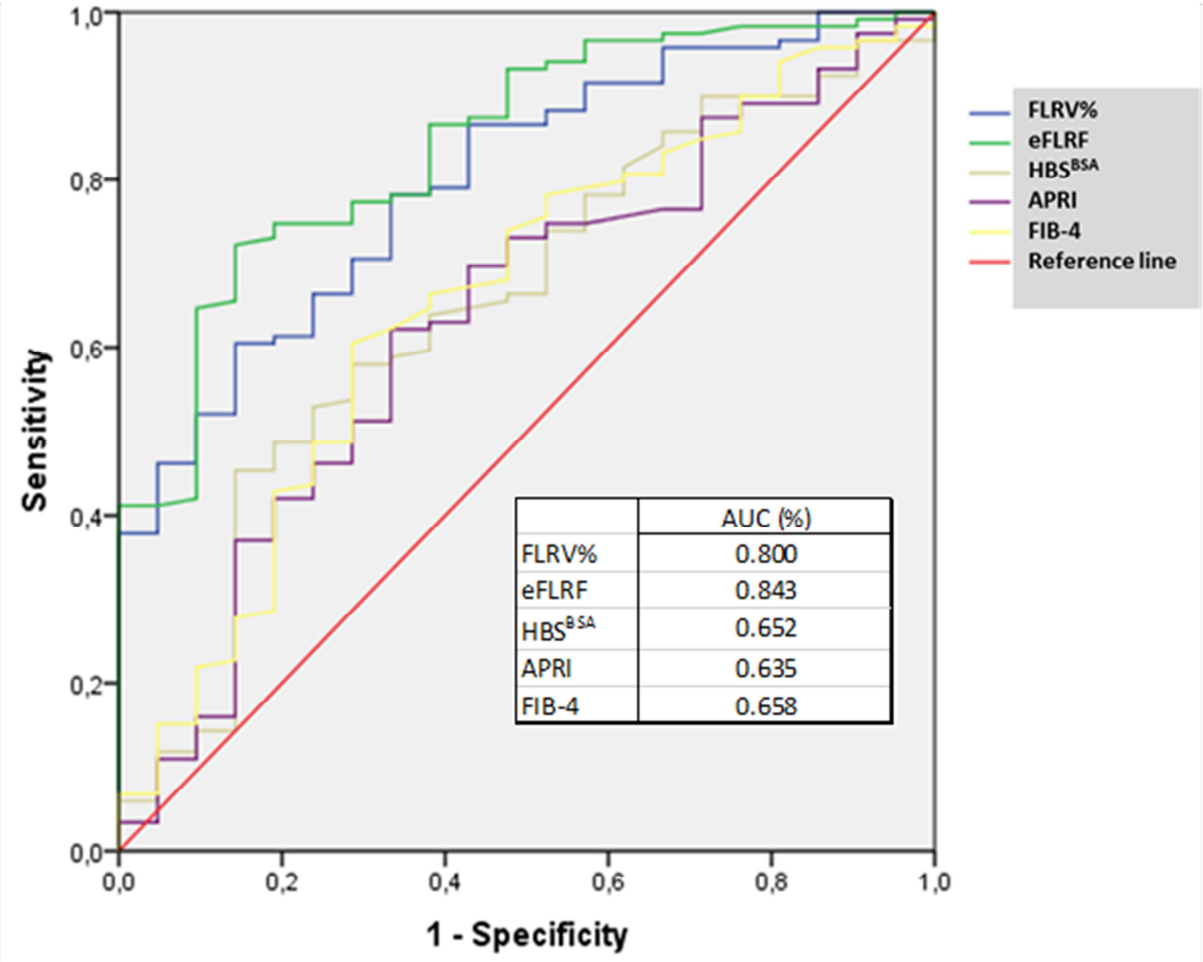
Table 1 : Basic characteristics in 140 patients who underwent preoperative chemotherapy prior to hepatectomy for colorectal liver metastasis.

		n (%) *or* mean ± SD
Total		140
Age	years	62.6 ± 9.7
Gender	M/F	90 / 50 (64.3% / 35.7%)
BMI	kg/m²	26.1 ± 4.1
Resection size		
Minor hepatectomy (< 3 segments)		71/140 (50.7%)
Major hepatectomy (≥ 3 segments)		69/140 (49.3%)
Right or left hemi-hepatectomy		39/140 (27.9%)
eFLRF score	%/min/m²	4.6 ± 1.3
FLRV%	%	77.8 ± 17.7
HBS^{BSA}	%/min/m²	6.0 ± 1.3
Preoperative manipulation of liver regeneration (cut off eFLRF <2.3%/min/m²)		20/140 (14.3%)
PVE		11 (7.9%)
2 stage hepatectomy with PVL at stage 1		8 (5.7%)
ALPPS		1 (0.7%)
Platelet based scores		
APRI		0.47 ± 0.33
FIB-4		1.64 ± 1.1
Preoperative systemic therapy		
Oxaliplatin based regimen		87/140 (62.1%)
Oxaliplatin ≥ 6 cycles		56/140 (40%)
Irinotecan based regimen		53/140 (37.9%
Irinotecan ≥ 6 cycles		33/140 (23.6%)
Post hepatectomy liver failure (PHLF)		21/140 (15%)
Grade A		16 (11.4%)
Grade B		5 (3.6%)
Grade C		0
Peri-operative mortality		0
Postoperative pathology		
Total available		63/140
SOS		23/63 (36.5%)
CASH		19/63 (30.2%)

Abbreviations: BMI: Body Mass Index; eFLRF: estimated Future Liver Remnant Function; FLRV%: Future Liver Remnant Volume Remnant ratio; HBS^{BSA}: Hepatobiliary Scintigraphy corrected by Body Surface Area; PVE: Portal Vein Embolisation; PVL: Portal Vein Ligation; ALPPS : Associated liver partition with portal vein ligation in staged hepatectomy; FIB-4: Fibrosis-4 score; CALI: Chemotherapy associated liver injury; SOS: Sinusoidal Obstruction Syndrome; CASH: Chemotherapy Associated Steatohepatitis

Figure 1: ROC analysis of predictive factors for PHLF in liver resection for colorectal liver metastasis after preoperative chemotherapy: FLRV% (volumetric-only test) and eFLRF (combination of volumetric and functional tests) are better predictors for PHLF than HBS^{BSA}, APRI and FIB-4 scores (functional-only tests).



Abbreviations: ROC: Recipient Operating Characteristics; AUC: Area under the Curve; PHLF: Post Hepatectomy Liver Failure; FLRV%: Future Liver Remnant Volume Remnant ratio; eFLRF: estimated Future Liver Remnant Function; HBSBSA: Hepatobiliary Scintigraphy corrected by Body Surface Area; APRI: Aspartate aminotransferase to Platelets Ratio Index; FIB-4: Fibrosis-4

Table 2: Predictive factors for PHLF in liver resection for colorectal liver metastasis after preoperative chemotherapy: univariate and multivariate analysis.

	No PHLF	PHLF	Univariate	Multivariate	
Total	119	21	p =	OR (95% CI)	p =
Age	62.4 ± 9.8	64.0 ± 9.5	NS		
BMI	26.1 ± 4.1	26.3 ± 4.2	NS		
Volumetric evaluation					
Major hepatectomy (≥ 3 segments)	49 (41%)	20 (95%)	0.001	0.094 (0.011-0.840)	0.034
FLRV%	80.9 ± 15.5	60.6 ± 19.7	< 0.001		
Functional evaluation					
HBS^{BSA}	6.1 ± 1.3	5.5 ± 1.1	0.057		
APRI	0.45 ± 0.29	0.62 ± 0.47	0.035		
FIB-4	1.55 ± 1.00	2.12 ± 1.31	0.033	1.833 (1.131-2.971)	0.014
Combined volumetric and functional evaluation					
eFLRF (FLRV% x HBS^{BSA})	8.4 ± 1.2	3.3 ± 1.0	<0.001	0.354 (0.186-0.676)	0.002
Preoperative chemotherapy					
Oxaliplatin all	72 (61%)	15 (71%)	NS		
Oxaliplatin ≥ 6 cycles	46 (39%)	10 (48%)	NS		
Irinotecan all	47 (40%)	6 (29%)	NS		
Irinotecan ≥ 6 cycles	28 (24%)	5 (24%)	NS		
Postoperative pathology					
Total	56	7			
SOS	21 (38%)	2 (29%)	NS		
CASH	14 (25%)	5 (71%)	0.024		

Abbreviations: PHLF: Post Hepatectomy Liver Failure; BMI: Body Mass Index; FLRV%: Future Liver Remnant Volume Remnant ratio; HBS^{BSA}: Hepatobiliary Scintigraphy corrected by Body Surface Area; APRI: Aspartate aminotransferase to Platelets Ratio Index; FIB-4: Fibrosis-4 score; eFLRF: estimated Future Liver Remnant Function; CALI: Chemotherapy associated liver injury; SOS: Sinusoidal Obstruction Syndrome; CASH: Chemotherapy Associated Steatohepatitis

Table 3: Predictive factors for PHLF in 4 subgroups divided according the type and number of cycles of preoperative chemotherapy: univariate analysis

	No PHLF	PHLF	OR (95% CI)	p =
	Oxaliplatin all (n = 87)			
Patients	72/87 (83%)	15/87 (17%)		
Major hepatectomy	29/72 (40%)	14/15 (93%)	0.48 (0.006-0.387)	0.004
FIB-4	1.65 ± 1.10	1.98 ± 1.12		NS
eFLRF	4.85 ± 1.10	3.20 ± 0.84	0.225 (0.107-0.471)	<0.001
	Oxaliplatin ≥ 6 cycles (n = 56)			
Patients	46/56 (82%)	10/56 (18%)		
Major hepatectomy	21/46 (46%)	10/10 (100%)		NS
FIB-4	1.80 ± 1.25	2.22 ± 1.27		NS
eFLRF	4.74 ± 1.17	2.99 ± 0.65	0.19 (0.069-0.521)	0.001
	Irinotecan all (n = 53)			
Patients	47/53 (89%)	6/53 (11%)		
Major hepatectomy	21/47 (45%)	6/6 (100%)		NS
FIB-4	1.42 ± 0.85	1.61 ± 0.66		NS
eFLRF	4.93 ± 1.36	3.39 ± 1.51	0.375 (0.155-0.908)	0.030
	Irinotecan ≥ 6 cycles (n = 33)			
Patients	28/33 (85%)	5/33 (15%)		
Major hepatectomy	12/28 (43%)	5/5 (100%)		NS
FIB-4	1.44 ± 0,90	1.75 ± 0.64		NS
eFLRF	4.90 ± 1.36	3.29 ± 1.67	0.407 (0.165-1.004)	0.050

Abbreviations: PHLF : Post Hepatectomy Liver Failure; FIB-4 : Fibrosis-4 score; eFLRF: estimated Future Liver Remnant Function; FLRV%: Future Liver Remnant Volume Remnant ratio; HBS^{BSA} : Hepatobiliary Scintigraphy corrected by Body Surface Area

Table 4: Predictive factors of SOS and CASH after preoperative chemotherapy: univariate analysis.

	No SOS	SOS	OR (95% CI)	p =
HBSBSA	6.3 ± 1.5	6.1 ± 1.4		NS
APRI	0.36 ± 0.27	0.51 ± 0.24	0.089 (0.008-1.031)	0.053
FIB-4	1.26 ± 0.67	1.80 ± 0.75	0.342 (0.150-0.778)	0.011

	No CASH	CASH	OR (95% CI)	p =
HBSBSA	6.5 ± 1.5	5.7 ± 1.2	1.558 (0.982-2.472)	0.060
APRI	0.42 ± 0.29	0.41 ± 0.24		NS
FIB-4	1.42 ± 0.77	1.58 ± 0.69		NS

Abbreviations: SOS: Sinusoidal Obstruction Syndrome; CASH: Chemotherapy Associated Steatohepatitis; HBSBSA: Hepatobiliary Scintigraphy corrected by Body Surface Area; APRI: Aspartate aminotransferase to Platelets Ratio Index; FIB-4: Fibrosis-4 score

Table 1 : Basic characteristics in 140 patients who underwent preoperative chemotherapy prior to hepatectomy for colorectal liver metastasis.

		n (%) *or* mean ± SD
Total		140
Age	years	62.6 ± 9.7
Gender	M/F	90 / 50 (64.3% / 35.7%)
BMI	kg/m²	26.1 ± 4.1
Resection size		
Minor hepatectomy (< 3 segments)		71/140 (50.7%)
Major hepatectomy (≥ 3 segments)		69/140 (49.3%)
Right or left hemi-hepatectomy		39/140 (27.9%)
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