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Optimal Future Liver Remnant in Patients Treated with Extensive Preoperative Chemotherapy for Colorectal Liver Metastases

Junichi Shindoh, MD, PhD¹, Ching-Wei D. Tzeng, MD¹, Thomas A. Aloia, MD¹, Steven A. Curley, MD¹, Giuseppe Zimmiti, MD¹, Steven H. Wei, PA-C¹, Steven Y. Huang, MD², Armeen Mahvash, MD², Sanjay Gupta, MD², Michael J. Wallace, MD², and Jean-Nicolas Vauthey, MD¹

Jean-Nicolas Vauthey: jvauthey@mdanderson.org

¹Department of Surgical Oncology, Unit 1484, The University of Texas MD Anderson Cancer Center, Houston

²Department of Diagnostic Radiology, Unit 1471, The University of Texas MD Anderson Cancer Center, Houston

Abstract

Background—Patients with colorectal liver metastases (CLM) are increasingly treated with preoperative chemotherapy. Chemotherapy associated liver injury is associated with postoperative hepatic insufficiency (PHI) and mortality. The adequate minimum future liver remnant (FLR) volume in patients treated with extensive chemotherapy remains unknown.

Methods—All patients with standardized FLR >20 %, who underwent extended right hepatectomy for CLM from 1993–2011, were divided into three cohorts by chemotherapy duration: no chemotherapy (NC, $n = 30$), short duration (SD, 12 weeks, $n = 78$), long duration (LD, >12 weeks, $n = 86$). PHI and mortality were compared by using uni-/multivariate analyses. Optimal FLR for LD chemotherapy was determined using a minimum p -value approach.

Results—A total of 194 patients met inclusion criteria. LD chemotherapy was significantly associated with PHI (NC + SD 3.7 vs. LD 16.3%, $p = 0.006$). Ninety-day mortality rates were 0 % in NC, 1.3 % in SD, and 2.3% in LD patients, respectively ($p = 0.95$). In patients with FLR >30 %, PHI occurred in only two patients (both LD, 2/20, 10 %), but all patients with FLR >30 % survived. The best cutoff of FLR for preventing PHI after chemotherapy >12 weeks was estimated as >30 %. Both LD chemotherapy (odds ratio [OR] 5.4, $p = 0.004$) and FLR < 30 % (OR 6.3, $p = 0.019$) were independent predictors of PHI.

Conclusions—Preoperative chemotherapy >12 weeks increases the risk of PHI after extended right hepatectomy. In patients treated with long-duration chemotherapy, FLR >30 % reduces the rate of PHI and may provide enough functional reserve for clinical rescue if PHI develops.

Preoperative chemotherapy is increasingly used for colorectal liver metastases (CLM).¹ Although there is still disagreement in its use for resectable CLM, up to 25 % of patients who present with CLM are able to undergo liver resection in modern series, with the majority of patients currently receiving preoperative chemotherapy at major centers.^{2–5} In addition to more patients undergoing resection, the operations are of increasing magnitude as more tumors become potentially resectable due to better chemotherapy and improving

surgical techniques. At referral centers, major or extended hepatectomies can represent up to 60 % of resections.⁶⁻⁸

With greater use of portal vein embolization (PVE), more borderline resectable CLM are being converted into potentially resectable lesions by preoperatively growing the future liver remnant (FLR).⁹⁻¹¹ Using a two-stage approach, even bilateral CLM can be aggressively treated in a multidisciplinary approach in which the metastases in the future liver remnant are surgically resected in the first stage followed by major or extended hepatectomy in the second stage. This approach can lead to 5-year overall survival (OS) of up to 50 %.¹² Although we have previously defined 20 % as the minimum safe FLR for patients with normal livers undergoing extended hepatectomies, the optimal cutoff has yet to be determined in patients treated with preoperative chemotherapy.¹³ Whereas PVE can be used to overcome predicted FLR limitations because hypertrophy is not limited by chemotherapy alone, the effects of extended preoperative chemotherapy can still negatively impact postoperative outcomes.^{14,15}

Although several studies have reported the use of PVE after preoperative chemotherapy, no study has analyzed the consequences of chemotherapy duration and FLR volume on complications, such as postoperative hepatic insufficiency (PHI) and death from liver failure.^{16,17} Although we and others previously proposed 30 % as minimal requirement of FLR for patient extensively treated with chemotherapy, this was empirically proposed and not validated based on detailed volumetric analysis of outcome.^{16,18}

Previous reports indicated an association between duration of chemotherapy and surgical complications.¹⁹ Recently, Narita et al. reported a cutoff FLR value of 48.5 % for predicting PHI in patients treated with long duration chemotherapy (>12 weeks).²⁰ However, to our knowledge, no study has evaluated the relationship between FLR volume and duration of chemotherapy. Therefore, we hypothesized that there was an association between duration of chemotherapy and adequate FLR that would predict morbidity and mortality. In this study, we studied postoperative complications in a cohort of patients who underwent extended right hepatectomy after various durations of chemotherapy to determine a safe cutoff for FLR.

PATIENTS AND METHODS

Patients

We retrospectively analyzed our institutional liver tumor study group database to study all patients who underwent extended right hepatectomy for CLM between October 1993 and December 2011. We excluded patients with FLR < 20 % of standard liver volume (SLV), our previously published cutoff for safe hepatectomy in normal livers.¹³ The University of Texas MD Anderson Cancer Center institutional review board approved this study.

Cohorts and Chemotherapy Duration

The patients were divided into three groups based on the duration of preoperative chemotherapy: 1) “no chemotherapy” (NC) group ($n = 30$); 2) “short duration” (SD) group with neoadjuvant chemotherapy < 12 weeks ($n = 78$); and 3) long duration (LD) group with chemotherapy for >12 weeks ($n = 86$; Fig. 1). The 12-week threshold was based on the duration of chemotherapy adopted in the recent EORTC randomized, controlled trial for perioperative chemotherapy for CLM, which included 6 cycles of FOLFOX4 [5-fluorouracil, leucovorin, oxaliplatin].²¹ Neoadjuvant chemotherapy was defined as any chemotherapy completed within 1 year before surgery.

Preoperative Imaging and FLR Calculation

All patients received preoperative liver volumetry evaluation using computed tomography (CT) images. FLR volume was estimated according to our previously reported method.²² Calculation of SLV was performed by the formula: $SLV = -794.41 + 1267.28 \times \text{body surface area (m}^2\text{)}$.²³ The ratio of the estimated FLR volume to the baseline SLV was defined as the standardized FLR. Right PVE, which is generally extended to segment 4 for extended right hepatectomies at our institution, was considered when the predicted FLR $\geq 20\%$. Technical details of PVE at our institution were previously described.^{9,10}

Hepatectomy and Postoperative Morbidity and Mortality

Extended right hepatectomy was defined as either a right hepatectomy extending beyond the middle hepatic vein or an anatomic right trisectionectomy. Liver resections were performed with intent for R0 resection using our two-surgeon technique.^{8,24} Postoperative morbidity was classified by standardized grading criteria, with complications of grade III or higher defined as major morbidities due to the invasive nature of their treatment.²⁵ PHI was defined as a peak total bilirubin >7 mg/dL.²⁶ Posthepatectomy mortality was analyzed at 90 days.

Statistics

Continuous variables were compared using the Mann-Whitney *U* test. Categorical variables were compared using chi-squared test or Fisher's exact test as appropriate. We used logistic regression models to evaluate potential associations of clinical variables with postoperative complications and 90-day mortality. For the multivariate analysis, a full model was fit with variables for which univariate $p < 0.1$ to avoid overfitting. A minimum p -value approach was used to find the best cutoff value of FLR for preventing postoperative liver insufficiency after long duration (>12 weeks) preoperative chemotherapy. Statistical significance was defined as $p < 0.05$. All analyses were performed using JMP 9 (SAS institute Japan, Tokyo, Japan).

RESULTS

Patient Characteristics and Chemotherapy

Of 247 patients who underwent extended right hepatectomy during the study period, 194 met inclusion criteria with FLR $>20\%$. Patient characteristics are shown in Table 1. The median age of the patients was 56 (range, 25–85) years, and 101 of 194 patients (52.1 %) were male. All patients were serologically negative for hepatitis and were not cirrhotic by pathology. Maximum size of tumor was comparable among the groups. However, the number of tumor tended to be larger in patients who underwent preoperative chemotherapy.

The majority of patients in this study received preoperative chemotherapy with an oxaliplatin-based regimen and combination use of bevacizumab (98/164, 59.8 %). Multiple-line chemotherapy was more prevalent in the LD group. A greater number of patients received an irinotecan-based regimen in this group compared with SD group (21.8 vs. 51.2%, $p < 0.001$). Ninety percent of patients in the NC group were from before year 2007 and 68% of patients in SD group were from years 2007–2011. However, the percentage of patients who underwent more than 3 months of chemotherapy were relatively constant (40–50%) over the decade and no specific time trend was confirmed.

Comparisons of Three Patient Cohorts

PVE was performed in 83 cases (42.8 %), and there was no intergroup difference in proportion of patients who received PVE ($p = 0.15$) or in preoperative FLR volume ($p = 0.21$). Surgical time and blood transfusion rate were comparable among the groups. Rates

and grades of morbidity increased with duration of chemotherapy, but this trend was not statistically significant. Rates of bile leak, and 90-day mortality were not different among the three groups (Table 1).

Postoperative Hepatic Insufficiency and Mortality

Incidence of PHI in patients with FLR >20% was significantly higher in the LD group (LD, 14/86, 16.3% vs. SD + NC, 4/104, 3.7%, $p = 0.006$). Ninety-day mortality rates due to all causes were 3.3 % (1/30) in NC, 3.9 % (3/78) in SD, and 4.7 % (4/86) in LD cohorts, respectively ($p = 0.89$). Ninety-day mortality rates due to liver insufficiency were 0 % in NC, 1.3 % (1/78) in SD, and 2.3 % (2/86) in LD, respectively ($p = 0.95$; Fig. 2a). Other causes of deaths were cardiac event ($n = 2$), cerebral hemorrhage ($n = 1$), methicillin-resistant *Staphylococcus aureus* infection ($n = 1$), and death from unknown cause outside of the country.

In the 143 patients with FLR between 20–30 %, there were 16 cases of PHI with all 8 total deaths (5.6 %) occurring in this group. In the 51 patients with FLR >30 %, liver insufficiency was observed in only 2 (3.9 %) patients (both in the LD group), and none of these patients died from postoperative complications (Fig. 2b).

Minimum FLR in Long-Duration Chemotherapy Patients

To determine optimal FLR with extensive chemotherapy, minimum p -value approach was used. As shown in Fig. 3, odds ratio to predict PHI was highest and the p -value in likelihood test was minimum at FLR 29 % in patients who received preoperative chemotherapy for >12 weeks.

Risk Factors of Postoperative Hepatic Insufficiency

To identify predictors of PHI in the entire cohort, multivariate logistic regression analysis were performed for 12 clinical factors: age >65 years, gender, body mass index (BMI) >25, diabetes, duration of chemotherapy >12 weeks, FLR <30 %, portal vein embolization, surgical time >180 minutes, Pringle's maneuver, estimated blood loss >1,000 g, intraoperative transfusion, and postoperative bile leak (Table 2). Of these 12, independent predictors of PHI were male sex (odds ratio [OR] 4.19; 95 % confidence interval [CI] 1.3–16.5; $p = 0.015$), long duration of chemotherapy >12 weeks (OR 5.36; 95% CI 1.66–21.6; $p = 0.004$), and FLR <30% (OR 6.31; 95 % CI 1.32–52.3; $p = 0.019$). Although not a preoperative factor, bile leak also was independently associated with PHI (OR 5.76; 95 % CI 1.39–25.2; $p = 0.016$).

DISCUSSION

This study is the first to show the dynamic balance of FLR and preoperative chemotherapy duration and their combined effect on posthepatectomy morbidity and mortality. In our multivariate analysis, the two modifiable risk factors for PHI were long-duration chemotherapy >12 weeks and FLR <30 %. Whereas FLR >20 % is adequate with either short-duration or no chemotherapy, greater FLR is needed for long-duration chemotherapy. To safely reduce PHI and mortality risk, FLR >30 % is needed for patients after >12 weeks of chemotherapy.

Irreversible PHI and subsequent death are the most feared complications from extended hepatectomies. We know that the former is a strong predictor of the latter.^{13,26} Preoperatively estimating sufficient FLR may help to decrease posthepatectomy morbidity and mortality. In patients who have received no or short-duration chemotherapy, extended hepatectomy can be safely performed with FLR 20–30% as indicated by the absence of PHI

or mortality, which validates our previous report.¹³ However, in patients who have received long-duration chemotherapy, the current study indicates a significant increase in PHI in FLR 20–30 % compared with FLR >30 %. Of note, although there were two cases of PHI, no death from liver failure was observed in patients with FLR >30 %. Therefore, a combination of chemotherapy duration and FLR volume seems to be a critical component of hepatic reserve directly affecting morbidity and mortality.

The risk and benefit of chemotherapy have been previously reported.^{27–29} The risk of surgical complications increases with the duration of preoperative treatment.^{19,30} Extended preoperative chemotherapy (9 cycles FOLFOX) does not improve pathologic response.¹⁵ Longer chemotherapy has not been shown to improve survival over shorter courses, but it has been associated with liver injury and PHI.¹⁵ In the EORTC randomized trial of perioperative chemotherapy for CLM,²¹ the use of perioperative chemotherapy (FOLFOX) decreased the rate of nontherapeutic laparotomy but was associated with an increase in post-hepatectomy complications. However, it should be noted that FLR volume was not considered and the study predated the era of portal vein embolization. Although prolonged chemotherapy is associated with posthepatectomy morbidity, the current data are important for a small number of patients who become resectable only after multiple line of chemotherapy.^{30,31} In these patients, long-term survival is still expected if curative resection is feasible.

Previous studies have found an inconsistent correlation between histopathological changes from chemotherapy such as sinusoidal injury or steatohepatitis and complications.^{4,5,32,33} Some centers have used laparoscopy for evaluation of chemotherapy-associated hepatic injury. However, visual evaluation of hepatic changes is subjective and unreliable as a predictor of outcome. Similarly, histopathological review is not an efficient approach, because it requires biopsies fraught with sampling error, and the result may be reader-dependent. The current finding of an association between duration of chemotherapy, FLR, and outcome may reduce the need for resorting to laparoscopy or biopsy in patients who need major resection after chemotherapy.

There are several limitations of the study. Whereas we studied specific cutoff values for chemotherapy duration and FLR and analyzed these groups as categorical variables, the relationship between the two is likely to be continuous. In addition, because the incidence of PHI was very low in the NC or SD groups, it is difficult to confirm whether FLR 20–30% is truly acceptable or not in these two groups. Finally, the small size of our retrospective cohort points out the need for further prospective studies or at least validation studies. Nonetheless, no previous study has studied and determined the “safe” FLR cutoff for major resection in relation to duration of preoperative chemotherapy.

In summary, this paper provides important information regarding adequate hepatic reserve in patients who have received preoperative chemotherapy. The data emphasize the need for systematic volumetry before major resection, and the results should help in the appropriate selection of patients for portal vein embolization. The present study is based on FLR, a static variable in liver volumetry. Therefore, future studies should consider the integration of dynamic evaluations of hepatic reserve, such as degree of hypertrophy, indocyanine green clearance test, or hepatobiliary scintigraphy to further enhance the safety of major resection after chemotherapy.^{34–36}

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FIG. 1.
Study population

FIG. 2. Postoperative liver insufficiency and mortality from liver failure. **a** FLR >20 %, **b** FLR >30 %. *PHI* postoperative hepatectomy insufficiency

FIG. 3. Changes in odds ratio (**a**) and *p*-value in likelihood test (**b**) while adjusting cutoff value of FLR for prediction of postoperative hepatic insufficiency in patients treated with chemotherapy (>12 weeks). Cutoff value of FLR 29 % was associated with highest odds ratio and lowest *p* value in prediction of postoperative hepatic insufficiency

TABLE 1

Patient characteristics and postoperative outcomes according to duration of preoperative chemotherapy

	NC (N = 30)	SD (N = 78)	LD (N = 86)	P (among 3 groups)	P (SD vs. LD)
Age (yr)	67 (37–79)	54 (33–76)	56 (25–85)	0.009	0.57
Sex (male %)	19/30 (63.3 %)	38/78 (48.7 %)	44/86 (51.2 %)	0.39	0.88
Size of tumor (mm)*	35 (20–75)	35 (25–57)	32 (20–60)	0.95	0.85
No. of tumors (2)	16/30 (55.2 %)	61/78 (78.2 %)	70/86 (81.4 %)	0.01	0.75
Preoperative chemotherapy (wk)	NA	8 (2–12)	24 (14–96)	–	<0.0001
No. of chemotherapy line					
1	NA	73/78 (93.6 %)	67/86 (77.9 %)	–	0.04
2	NA	5/78 (6.4 %)	14/86 (16.3 %)	–	0.08
3	NA	0/78 (0 %)	5/86 (5.8 %)	–	0.09
Cytotoxic chemotherapy					
Oxaliplatin	NA	60/78 (76.9 %)	50/86 (58.1 %)	–	0.017
CPT-11	NA	17/78 (21.8 %)	44/86 (51.2 %)	–	0.0001
5-FU	NA	74/78 (94.9 %)	73/86 (84.9 %)	–	0.07
Biologic agent					
Bevacizumab	NA	50/78 (64.1 %)	41/86 (47.7 %)	–	0.03
Cetuximab/Panitumumab	NA	8/78 (10.3 %)	5/86 (5.8 %)	–	0.42
Portal vein embolization	9/30 (30.0 %)	40/78 (51.3 %)	34/86 (39.5 %)	0.15	0.13
Preoperative FLR (%)	23.9 (20.1–56.9)	27.5 (20.1–66.4)	25.1 (20.4–64.1)	0.21	0.07
Surgery time (min)*	240 (136–347)	248 (171–326)	195 (113–315)	0.15	0.09
Transfusion	10/30 (33.3 %)	14/78 (17.9 %)	23/86 (26.7 %)	0.19	0.18
Complication					
Any	10/30 (33.3 %)	33/78 (42.3 %)	45/86 (52.3 %)	0.16	0.2
Major	5/30 (16.7 %)	17/78 (21.8 %)	23/86 (26.7 %)	0.65	0.46
Bile leak	2/30 (6.7 %)	6/78 (7.7 %)	12/86 (14.0 %)	0.51	0.3
Hepatic insufficiency	0/30 (0 %)	4/78 (5.1 %)	14/86 (16.3 %)	0.02	0.04
Liver failure death	0/30 (0 %)	1/78 (1.3 %)	2/86 (2.3 %)	0.95	0.93
Mortality					
30-d	1/30 (3.3 %)	2/78 (2.6 %)	1/86 (1.2 %)	0.96	0.93
90-d	1/30 (3.3 %)	3/78 (3.9 %)	4/86 (4.7 %)	0.95	0.89

Data are median (range) or *median (interquartile range)

NC no chemotherapy group, SD short-duration chemotherapy group, LD long-duration chemotherapy group, FLR future liver remnant

TABLE 2

Risk factors of postoperative liver insufficiency

	Hepatic insufficiency		Univariate analysis			Multivariate analysis		
			P	OR	95 % CI	P	OR	95 % CI
Age (yr)								
>65	5/44 (11.4 %)	0.596						
65	13.15 (8.7 %)							
Gender								
Male	14/101 (13.9 %)	0.018		3.58	1.23–13.0	0.015	4.19	1.3–16.5
Female	4/93 (4.3 %)							
BMI								
>25	13/110 (11.8 %)	0.195						
25	5/70 (6.3 %)							
Diabetes								
Y	3/17 (17.7 %)	0.288						
N	15/168 (8.9 %)							
Duration of preoperative chemotherapy (wk)								
>12	14/86 (16.3 %)	0.002		5.06	1.73–18.4	0.004	5.36	1.66–21.6
12	4/108 (3.7 %)							
FLR								
30 %	16/143 (11.2 %)	0.096		3.08	0.84–20.0	0.019	6.31	1.32–52.3
>30 %	2/51 (3.9 %)							
Portal vein embolization								
Y	7/83 (8.4 %)	0.725						
N	11/111 (9.9 %)							
Operation time (min)								
>180	9/119 (7.6 %)	0.305						
180	9/75 (12 %)							
Pringle maneuver								
Y	17/154 (11 %)	0.066		4.72	0.92–86.3	0.054		
N	1/39 (2.6 %)							
Blood loss (mL)								

	Hepatic insufficiency	Univariate analysis			Multivariate analysis		
		P	OR	95 % CI	P	OR	95 % CI
>1000	4/26 (15.4 %)	0.281					
1000	14/168 (8.3 %)						
Transfusion							
Y	8/47 (17 %)	0.048	2.56	0.92–6.95	0.237		
N	10/135 (7.4 %)						
Bile leak							
Y	6/20 (30 %)	0.002	5.78	1.88–17.9	0.162	5.76	1.39–25.2
N	12/174 (6.9 %)						

BMI body mass index, FLR future liver remnant, OR odds ratio, CI confidence interval, Y yes, N no