Neoadjuvant chemotherapy does not affect future liver remnant growth and outcomes of associating liver partition and portal vein ligation for staged hepatectomy

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Background. *The only potentially curative treatment for patients with colorectal liver metastases is hepatectomy. Associating liver partition and portal vein ligation for staged hepatectomy has emerged as a method of treatment for patients with inadequate future liver remnant. One concern about associating liver partition and portal vein ligation for staged hepatectomy is that preoperative chemotherapy may negatively affect the volume increase of the future liver remnant and outcomes.*

Methods. *This study from the International Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy Registry (NCT01924741) includes 442 patients with colorectal liver metastases registered from 2012–2016. Future liver remnant hypertrophy (absolute increase, percent increase, and kinetic growth rate) and clinical outcome were analyzed retrospectively in relation to type and amount of chemotherapy. The analyzed groups included patients with no chemotherapy, 1 regimen of chemotherapy, >1 regimen, and a group that received monoclonal antibodies in addition to chemotherapy.*

Results. *Ninety percent of the patients received neoadjuvant oncologic therapy including 42% with 1 regimen of chemotherapy, 44% with monoclonal antibodies, and 4% with >1 regimen. Future liver remnant increased between 74–92% with the largest increase in the group with 1 regimen of chemotherapy. The increase in milliliters was between 241 mL (>1 regimen) and 306 mL (1 regimen). Kinetic growth rate was between 14–18% per week and was greatest for the group with 1 regimen of chemotherapy. No statistical significance was found between the groups with any of the measurements of future liver remnant hypertrophy.*

Conclusion. *Neoadjuvant chemotherapy, including monoclonal antibodies, does not negatively affect future liver remnant growth. Patients with colorectal liver metastases who might be potential candidates for associating liver partition and portal vein ligation for staged hepatectomy should be considered for neoadjuvant chemotherapy. (Surgery 2016;■:■-■.)*

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COMPLETE RESECTION of all hepatic metastases remains the only potentially curative treatment for colorectal liver metastases (CRLM). The overall survival (OS) after resection of CRLM is reported to be ≈ 43% at 5 years and ≈20–5% at 10 years.[1-6] Unfortunately, only about one-fourth of patients presenting with CRLM are amenable for resection.[7] The remaining majority of patients may be treated by downsizing chemotherapy and about one-third of those patients are reported to be converted to resection.[8] Despite neoadjuvant chemotherapy, half of the patients that become resectable are not suitable for one-stage hepatectomy. The reasons they are not suitable for one-stage hepatectomy are bilobar metastases and/or location of metastases near major vascular or biliary structures with a predicted too small future liver remnant (FLR).[9] In these situations, portal vein occlusion (PVO), either by portal vein ligation or more commonly portal vein embolization has been used to increase the FLR and facilitate a staged hepatectomy. After PVO, resection can be performed in 64–73% of eligible patients.[10,11] The reasons of failure to proceed with stage 2 operation include inadequate increase of FLR volume and tumor progression.[10,12]

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is a new variant of the 2-stage hepatectomy. At the first stage, the portal vein of the liver part to be resected is ligated and the liver parenchyma is divided along the line of transection (in situ split). At stage 2 the resection is performed along the in situ split transection line.[13] Between 29–100% of the patients with CRLM undergoing ALPPS have been reported to receive neoadjuvant chemotherapy including monoclonal antibodies.[13-19] The 2 major concerns about the negative impact of neoadjuvant chemotherapy are related to impaired hypertrophy of FLR under neoadjuvant chemotherapy and the potentially adverse effect on morbidity after hepatectomy.

There are conflicting results reported on the effect of neoadjuvant therapy on liver hypertrophy. Some previous studies have demonstrated no adverse effect of neoadjuvant chemotherapy on the FLR increase, including bevacizumab.[20,21] Others have found an impaired growth of the FLR in patients with >6 cycles of chemotherapy.[22,23] It also was found that postoperative complications and poor outcomes were related to small FLR in the setting of major hepatectomy.[24] Furthermore, addition of bevacizumab (anti-vascular epidermal growth factor, anti-VEGF) to the chemotherapy regimens may decrease the hypertrophy of the FLR compared with chemotherapy alone.[25] Other studies have shown no increase in postoperative complications after chemotherapy and bevacizumab.[26,27] The effect of chemotherapy including monoclonal antibodies on the hypertrophy of the FLR in patients with colorectal liver metastasis undergoing ALPPS has not yet been evaluated. The hypothesis in this study was that there is no significant difference in hypertrophy of the FLR in relation to the amount of neoadjuvant chemotherapy administered to the patients.

The primary aim of this study was to evaluate whether neoadjuvant oncologic treatment of CRLM affects FLR growth. The secondary aim was to evaluate if comorbidity, age, sex, body mass index, or postoperative complications after stage 1 impacts FLR growth.

MATERIALS AND METHODS

This study is a retrospective analysis of prospectively collected data of patients with CRLM enrolled in the International ALPPS Registry (NCT01924741; www.alpps.net). The registry was initiated in 2012 and serves to centralize data collected as a single standardized data set for all patients undergoing ALPPS worldwide. This study was approved by the Cantonal Ethics Committee Zurich (KEK 2013-0326). The research proposal for this study was approved by the registry board on May 20, 2014, and a short version of the study plan was published on the registry website (http://www.alpps.net/?q=Chemotherapy_Bjornsson).

From 2012–2016, 442 patients with CRLM were registered. In the present study, 91 centers from 30 countries have participated. All patients in the International ALPPS Registry with colorectal liver metastases were included in this study from the start date of the registry until May 13, 2016. Inclusion criteria were patients undergoing ALPPS for CRLM. Exclusion criteria were other diagnoses than CRLM.

The data in the registry is organized in the following main groups: demographics, current disease, comorbidity, stage 1, stage 2, liver function, and hospital complications. Complications were graded according to Clavien-Dindo.[28]

The registry specifies which segments of the liver are affected by the tumor, which segments constitutes the FLR, if there were metastases in the FLR, to which segments portal branches were ligated and if any wedge resections were performed during stage 1. Regarding the technical aspects of the operation, it was registered if hanging maneuverer and/or anterior approach was used, if coverage was used to cover the resection surface between stage 1 and stage 2, and if a hepaticojejunostomy was constructed.

Table I. Demographic information and preoperative volumes of the FLR

	No neoadjuvant therapy (n = *45*)	*1 regimen of chemotherapy* (n = *185*)	*>1 regimen of chemotherapy* (n = *16*)	*Monoclonal antibodies* (n = *196*)
Age (mean ± 1 SD)	62 ± 12 (*n* = 43)	60 ± 10 (*n* = 182)	60 ± 10 (*n* = 16)	58 ± 12 (*n* = 196)
Sex female/male	19/25	69/114	4/12	65/129
BMI (mean ± 1 SD)	27 ± 4 (*n* = 43)	26 ± 7 (*n* = 184)	26 ± 6 (*n* = 16)	26 ± 4 (*n* = 195)
Charlson score (mean ± 1 SD)	6 ± 1	6 ± 1	7 ± 1	6 ± 1
Synchronous presentation	51% (*n* = 23)	65% (*n* = 120)	56% (*n* = 9)	80% (*n* = 157)
Metachronous presentation	40% (*n* = 18)	21% (*n* = 38)	38% (*n* = 6)	15% (*n* = 31)
No. tumors preoperatively (mean ± 1 SD)	4 ± 3 (*n* = 31)	6 ± 5 (86)	4 ± 3 (*n* = 8)	5 ± 4 (*n* = 115)
Preoperative volume of FLR				
sFLR (mean ± 1 SD)	21% ± 7 (*n* = 35)	25% ± 9 (*n* = 150)	21% ± 7 (*n* = 15)	23% ± 8 (*n* = 155)
Clean FLR/TLV (mean ± 1 SD)	26% ± 6 (*n* = 31)	26% ± 8 (*n* = 113)	27% ± 11 (*n* = 11)	27% ± 9 (*n* = 111)
Clean volume FLR in mL (mean ± 1 SD)	331 ± 110 (*n* = 36)	384 ± 152 (*n* = 153)	342 ± 141 (*n* = 15)	362 ± 135 (*n* = 161)
Duration of neoadjuvant therapy, mo (mean, 95% CI)		5 (4–6; *n* = 113)	8 (6–10; *n* = 13)	6 (5–7; *n* = 172)

sFLR, Standardized future liver remnant; *TLV*, total liver volume.

Time for growth of FLR was calculated as time between stage 1 and the date for the last computed tomography (CT) or magnetic resonance imaging before stage 2. Liver growth was assessed by the following variables: absolute difference (in milliliters) between clean FLR volume of FLR before stage 2 and clean volume before stage 1, percentage increase of the FLR and as kinetic growth rate (KGR). Clean volume of the FLR is the tumor-free volume of the FLR; the volume of the tumor/tumors in the FLR was measured and subtracted from the total volume of the FLR rendering the clean FLR volume. KGR was calculated according to a previously published method.[29] Data completeness for all 3 growth variables were 79%, 78%, and 69% (mL, percent, and KGR, respectively).

Statistics. The difference in growth of the FLR between the groups with no oncologic treatment, 1 regimen of chemotherapy, >1 regimen and chemotherapy and monoclonal antibodies were compared with analysis of variance. The differences in bilirubin, international normalized ratio (INR), and creatinine also were compared with analysis of variance. To evaluate the effect of age, body mass index, duration of neoadjuvant oncologic therapy, Charlson comorbidity score, sex, and complications after stage 1, on the increase of FLR volume analysis of covariance were performed. In this model age, body mass index, duration of neoadjuvant therapy, Charlson comorbidity score were covariates, sex and complications after stage 1 were fixed factors. Results are expressed as mean (SD) if not otherwise stated. Post-hoc analysis was performed with Bonferroni correction. Difference in frequency distribution was evaluated with χ^2 test. Analyses were performed with IBM SPSS (version 23, IBM Corp, Armonk, NY).

RESULTS

Study population. In the study, 404 patients (91%) completed both stages, 10 patients did not complete the second stage of ALPPS, and data was lacking for the remaining 28 patients. Three patients did not proceed because of complications (2 grade with V and 1 with grade IV B) and progression of liver metastases. For 24 patients data were lacking regarding the reason for failing to proceed to stage 2. Interval between stage 1 and stage 2 was reported for 297 patients and was 11 ± 9 days. In addition, 224 (51%) patients were reported not to have any comorbidity or regular pharmacologic therapy, and 217 (49%) patient were reported to have some comorbidity or pharmacologic treatment. Charlson score[30] was calculated for the 4 groups (Table I). Main demographic data are depicted in Table I.

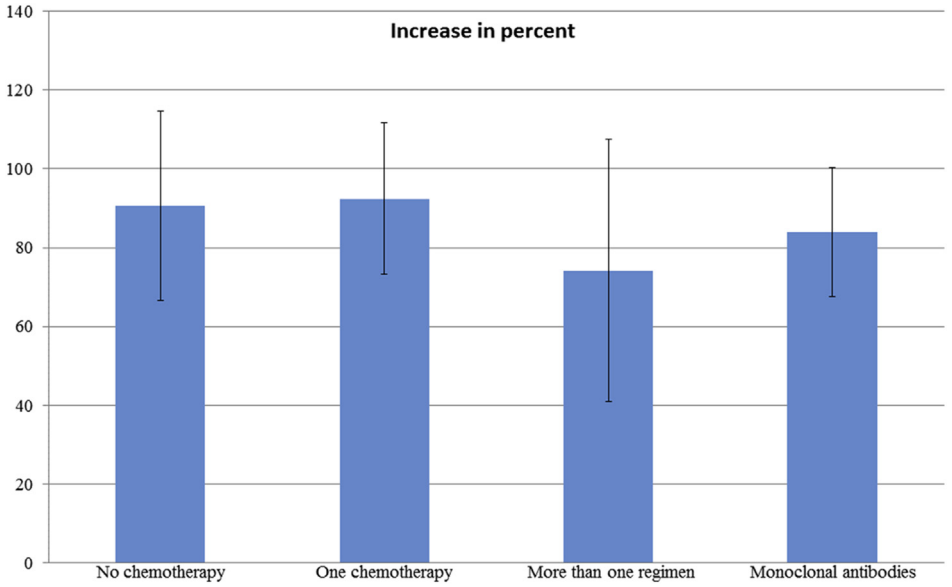

Fig 1. Increase of FLR expressed in percent. FLR increased 91% (95% CI, 66–115) for the group with no chemotherapy, 92% (95% CI, 73–112) for the group with 1 regimen of chemotherapy, 74% for the group with >1 regimen of chemotherapy (95% CI, 41–107), and 84% (95% CI, 68–100) in the group with monoclonal antibodies. *Error bars* show SD.

Effect of chemotherapy on liver hypertrophy. Clean FLR increased 263 ± 139 mL and 82% ± 24 in 11 days ± 9 for the whole cohort. KGR was 15 ± 10% per week.

In addition, 397 patients (90%) received neoadjuvant chemotherapy; 185 (42%) patients received 1 regimen of chemotherapy, 16 (4%) patients received >1 regimen, and 196 (44%) patients also received monoclonal antibodies. Furthermore, 45 (10%) patients received no neoadjuvant chemotherapy.

Analysis of the different groups revealed that the FLR volume increased between 76–90%, with the smallest increase seen in the group with 1 regimen of chemotherapy (Fig 1). The largest increase of FLR, measured as increase in percent, was in the group with >1 regimen of oncologic treatment. The increase in milliliters was between 227 mL (>1 regimen) and 272 mL (monoclonal antibodies; Fig 2). KGR was between 13–16% per week and was lowest for the groups with no oncologic treatment and greatest for the group with 1 regimen of chemotherapy (Fig 3).

Comparing the increase of FLR between patients with no oncologic therapy, patients with 1 or several regimens of neoadjuvant chemotherapy, and patients with monoclonal antibodies, and including the effect of the covariates show no statistical significant differences between the 4 groups.

Analyzing the effect of irinotecan- or oxaliplatin-based chemotherapy on the increase of the FLR reveals that the group with irinotecan-based chemotherapy had a greater increase expressed as milliliters ($P = .004$) of the FLR compared with the group with oxaliplatin-based chemotherapy. The difference was not significant when the increase was measured as increase in percent or KGR (Table II).

Analyzing the subgroups in the group with monoclonal antibodies reveal that there is no difference between irinotecan- or oxaliplatin-based chemotherapy (Table III).

Comparing short (≤4 weeks) with long (>4 weeks) interval between chemotherapy and stage 1 reveal that there was no significant difference in hypertrophy, regardless if the increase of the FLR was measured in milliters, percent, or KGR.

Effects of covariates on liver hypertrophy. There are some covariates that have a significant effect on the increase of the FLR. The duration of neoadjuvant therapy had a significant effect, as has sex and age. The effect of these covariates was not significant for all 3 different measures of FLR hypertrophy. The effect of duration of therapy was significant if the increase was measured as KGR ($P = .019$) and as increase in milliliters ($P = .03$). The effect of age was significant when the increase was measured as increase in milliliters ($P = .003$) and increase in percent ($P = .031$). See Table IV for the effect of the covariates.

Neoadjuvant oncologic treatment. The most common chemotherapy was folinic acid, fluorouracil, oxaliplatin (FOLFOX) in all 3 groups. In

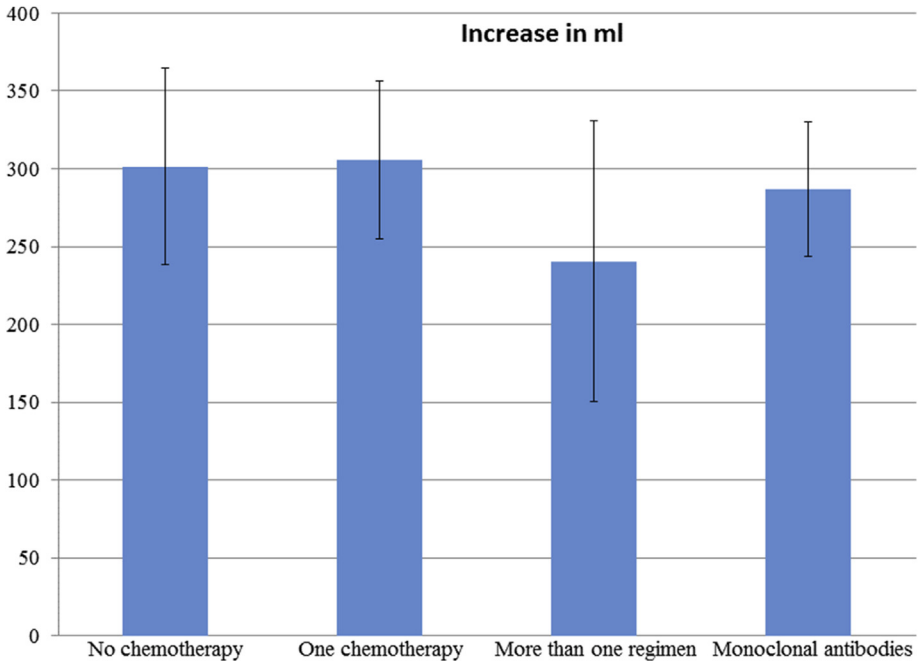

Fig 2. Increase of FLR in milliliters. FLR increased 301 mL (95% CI, 238–364) for the group with no chemotherapy, 306 mL (95% CI, 255–356) for the group with 1 regimen of chemotherapy, 241 mL (95% CI, 150–331) for the group with <1 regimen of chemotherapy, and 287 (95% CI, 244–330) in the group with monoclonal antibodies. *Error bars* show SD.

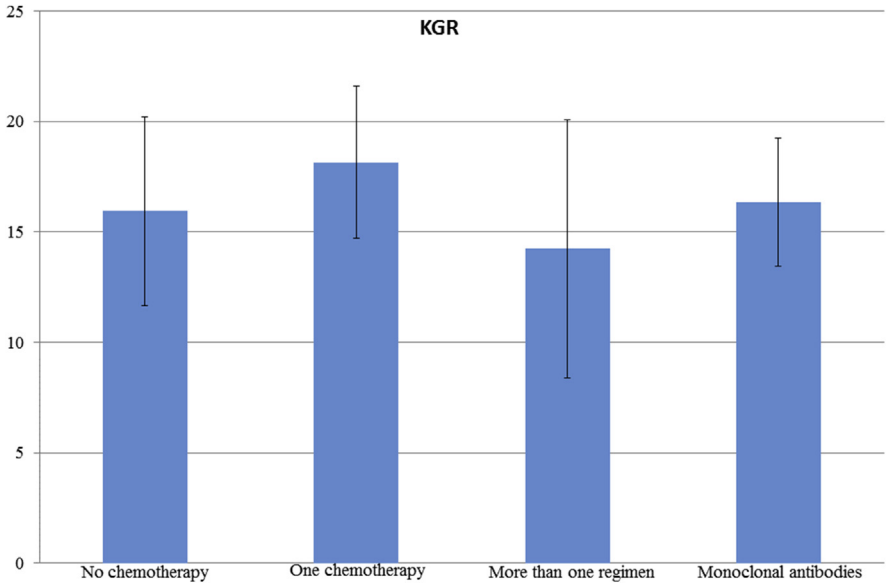

Fig 3. The KGR. FLR increased 16 (95% CI, 12–20) for the group with no chemotherapy, 18 (95% CI, 15–22) for the group with 1 regimen of chemotherapy, 14 (95% CI, 8–20) for the group with >1 regimen of chemotherapy, and 16 (95% CI, 13–19) in the group with monoclonal antibodies. *Error bars* show SD.

the group with 1 regimen of chemotherapy, 48% of the patients received FOLFOX. In the group with >1 chemotherapy, 44% received FOLFOX as the first regimen, and 52% in the group that also received monoclonal antibodies had FOLFOX as the first regimen. The most common monoclonal antibody was bevacizumab used in 100 (51%) of the patients. The details of neoadjuvant chemotherapy are presented in Table V.

Clinical course. The incidence of postoperative complications was reported for 373 patients after stage 1 and for 352 patients after stage 2.

Table II. Comparison of increase of the FLR for patients with irinotecan- and oxaliplatin-based chemotherapy

	Irinotecan	*Oxaliplatin*	P *value*
No. of patients	21	107	
Increase of the FLR			
mL	343 ± 145 (n = 17)	251 ± 122 (n = 87)	.004
Percent	101 ± 46 (n = 16)	80 ± 42 (n = 81)	ns
KGR	17 ± 10 (n = 15)	16 ± 10 (n = 80)	ns

Table III. Comparison of increase of the FLR for patients with irinotecan- and oxaliplatin-based chemotherapy and monoclonal antibodies

	Irinotecan and monoclonal antibodies	*Oxaliplatin and monoclonal antibodies*	P *value*
No. of patients	57	106	
Increase of the FLR			
mL	287 ± 168 (n = 42)	261 ± 156 (n = 86)	ns
Percent	88 ± 62 (n = 42)	84 ± 53 (n = 85)	ns
KGR	15 ± 8 (n = 38)	15 ± 9 (n = 80)	ns

Complications were graded according to the Clavien-Dindo score.[28] A total of 101 (27%) patients had a complication after stage 1 and of those were 22 (6%) grade ≥3b. Postoperative mortality after stage 1 was 0.5% (n = 2). After stage 2, 201 patients (57%) had a postoperative complication, and of those, 57 (16%) were grade ≥ 3b. Of the patients with a complication grade ≥3b, 11 patients had the complication grade ≥3b after stage 1, 11 after stage 2, and 51 patients had a complication grade ≥3b after stage 1 as well as after stage 2. Postoperative mortality after stage 2 was 6% (21 patients). Data regarding radicality was available in 346 cases and R0 was confirmed in 335 (97%) of those patients and R1 in 11 patients (3%). For 97 patients, R-status was not reported.

Bilirubin, INR, and creatinine were reported preoperatively 5 days after stage 1, before stage 2, and 5 days after stage 2 (Table VI). Patients with >1 regimen of chemotherapy had a greater level of bilirubin after stage 1 and before stage 2. After stage 2 the difference was not significant, neither was the difference in INR.

Table IV. Effect of each covariate on the increase of FLR, measured as KGR, increase in percent and increase in milliliters

Increase of FLR measured as	*Covariate*	P *value*
KGR	Sex	ns
	Complications after stage 1	ns
	Age	ns
	BMI	.024*
	Duration of neoadjuvant therapy	.019†
	Charlson comorbidity score	ns
Increase in percent	Sex	ns
	Complications after stage 1	.045‡
	Age	ns
	BMI	ns
	Duration of neoadjuvant therapy	ns
	Charlson comorbidity score	ns
Increase in mL	Sex	.007¶
	Complications after stage 1	ns
	Age	.003§
	BMI	ns
	Duration of neoadjuvant therapy	.03||
	Charlson comorbidity score	ns

*FLR decrease with increasing BMI.
†FLR decrease with increased duration of neoadjuvant therapy.
‡Patients with complications ≥ 3b had a larger increase of FLR volume.
§Men had a larger increase.
¶Increase of FLR decreased with increased age.
||Increase of FLR volume decreased with increased duration of neoadjuvant therapy.
BMI, Body mass index.

DISCUSSION

This data from the international ALPPS registry (NCT01924741) about patients with CRLM undergoing ALPPS confirmed that neoadjuvant oncologic therapy, including monoclonal antibodies, did not negatively affect or impair the hypertrophy of the FLR compared with patients who did not receive any neoadjuvant oncologic therapy. The effect of some of the covariates was significant, although not for all 3 measurements. The results should be interpreted as the clinical impact of neoadjuvant chemotherapy was limited for FLR hypertrophy.

The effect of chemotherapy on the increase of FLR in the setting of ALPPS was poorly studied. One previous study has shown that preoperative chemotherapy results in smaller increase of FLR compared with no chemotherapy. It was a small study with other diagnoses (cholangiocarcinoma and gallbladder cancer) included in addition to

Table V. Patients with 1 regimen of chemotherapy, >1 regimen, and patients with chemotherapy and antibodies

Table with neoadjuvant chemotherapy	*Name of the regimen*	*First regimen*	*Second regimen*	*Third regimen*	*Fourth and fifth regimen*
1 chemotherapy regimen (n = 188)					
	FOLFOX	48% (n = 90)			
	FOLFIRI	11% (n = 21)			
	Xelox	7% (n = 13)			
	Other	10% (n = 19)			
	Regimen not specified	24% (n = 45)			
>1 chemotherapy regimen (n = 16)					
	FOLFOX	44% (n = 7)	6% (n = 1)		
	FOLFIRI	13% (n = 2)	25% (n = 4)	6% (n = 1)	
	Xelox	13% (n = 2)	6% (n = 1)		
	Other	31% (n = 5)	63% (n = 10)	13% (n = 2)	
Chemotherapy and antibodies (n = 196)					
	FOLFOX and bevacizumab	33% (n = 64)	2% (n = 4)		
	FOLFOX and cetuximab	12% (n = 23)	1% (n = 2)		5:e regimen 0.5%; n = 1
	FOLFOX and panitumumab	7% (n = 13)			
	FOLFIRI and bevacizumab	19% (n = 38)	6% (n = 12)	1.5% (n = 3)	
	FOLFIRI and cetuximab	11% (n = 22)	2% (n = 4)		4:e regimen 1.5%; n = 3
	FOLFIRI and panitumumab	0.5% (n = 1)	1% (n = 2)	0.5% (n = 1)	
	Xelox and bevacizumab	4% (n = 8)			
	Xelox and cetuximab	1% (n = 2)			
	Xeloda and bevacizumab	1% (n = 2)			
	Xeloda and cetuximab	1% (n = 2)			
	Other	11% (n = 21)	10% (n = 19)	7% (n = 13)	1% (n = 2)

FOLFIRI, Fluorouracil, irinotecan and folinic acid; *Xelox*, capecitabine and oxaliplatin.
Duration of therapy was 5 months (4–6, 95% CI; n = 113) in the group with 1 chemotherapy. Total duration of therapy was 8 months (6–10, 95% CI; n = 13) in the group with >1 chemotherapy and 6 months (5–7, 95% CI; n = 172) in the group that also received monoclonal antibodies.

CRLM, and only patients with CRLM received neoadjuvant chemotherapy. It was therefore difficult to draw a firm conclusion about the effect of preoperative chemotherapy on the hypertrophy of the FLR in that study.[31] Other studies in the settings of PVO have found no effect on the increase of FLR.[32,33] The impact of monoclonal antibodies on the hypertrophy of the FLR mainly has been studied for bevacizumab. Addition of bevacizumab may impair the increase of FLR compared with only chemotherapy, as shown for a relatively small number of patients.[25] This differs from the results of the present data, reported in this article; there was no significant difference in increase of the FLR, whether monoclonal antibodies were administrated or not in addition to chemotherapy.

These results were more consistent with previous results from case-matched series that have shown chemotherapy and bevacizumab not to impair the increase of FLR volume.[26] There was no significant difference in number of extended resections compared with right hepatectomies between the groups. There was either no significant difference in number of patients with postoperative complication ≥3b after stage 1.

The preoperative volume of the FLR was lower in the group with no chemotherapy and the group with >1 regimen. This may affect the capability of

Table VI. Perioperative data with liver function tests preoperatively, 5 days after stage 1, before stage 2, and 5 days after stage 2, and number of patients with right and extended right hemihepatectomies and complications after stage 1 and stage 2

	No neoadjuvant therapy (n = *45*)	*1 regimen of chemotherapy* (n = *185*)	*>1 regimen of chemotherapy* (n = *16*)	*Monoclonal antibodies* (n = *196*)	*Comparison among the groups*
Liver function tests, preoperative values					
Bilirubin μmol/L (mean, 95% CI)	15 (10–22; *n* = 37)	12 (11–15; *n* = 157)	11 (9–14; *n* = 15)	10 (9–11; *n* = 171)	*P* = .063
INR (mean, 95% CI)	1.1 (1–1.2; *n* = 37)	1 (1–1.1; *n* = 147)	1 (1–1.1; *n* = 15)	1 (1–1.1; *n* = 167)	ns
Creatinine μmol/L (mean, 95% CI)	75 (68–82; *n* = 35)	73 (70–77; *n* = 138)	80 (73–87; *n* = 12)	70 (68–73; *n* = 155)	ns
Liver function tests, 5 days after stage 1					
Bilirubin μmol/L (mean, 95% CI)	29 (16–50; *n* = 37)	20 (17–24; *n* = 157)	36 (15–63; *n* = 15)	19 (16–22; *n* = 170)	*P* = .044
INR (mean, 95% CI)	1.2 (1.1–1.2; *n* = 37)	1.2 (1.1–1.2; *n* = 152)	1.3 (1.1–1.4; *n* = 15)	1.1 (1.1–1.2; *n* = 166)	ns
Creatinine μmol/L (mean, 95% CI)	74 (65–83; *n* = 35)	68 (63–73; *n* = 133)	81 (65–100; *n* = 13)	90 (62–141; *n* = 155)	ns
Liver function tests, before stage 2					
Bilirubin μmol/L (mean, 95% CI)	27 (16–40; *n* = 37)	17 (15–20; *n* = 157)	30 (13–52; *n* = 15)	17 (14–21; *n* = 168)	*P* = .022
INR (mean, 95% CI)	1.2 (1.1–1.3; *n* = 37)	1.2 (1.1–1.2; *n* = 150)	1.2 (1.1–1.2; *n* = 15)	1.1 (1.1–1.2; *n* = 159)	ns
Creatinine μmol/L (mean, 95% CI)	81 (68–99; *n* = 35)	69 (65–72; *n* = 133)	84 (67–102; *n* = 13)	66 (62–71; *n* = 148)	*P* = .012
Liver function tests, 5 days after stage 2					
Bilirubin μmol/L (mean, 95% CI)	39 (23–60; *n* = 32)	36 (30–43; *n* = 1,137)	44 (21–83; *n* = 14)	41 (35–48; *n* = 162)	ns
INR (mean, 95% CI)	1.3 (1.2–1.4; *n* = 32)	1.3 (1.3–1.4; *n* = 131)	1.3 (1.2–1.4; *n* = 14)	1.3 (1.2–1.3; *n* = 156)	ns
Creatinine μmol/L (mean, 95% CI)	73 (67–79; *n* = 30)	75 (67–85; *n* = 117)	71 (59–84; *n* = 12)	67 (61–73; *n* = 147)	ns
No. of right hemihepatectomies	19 (53%)	64 (44%)	8 (50%)	68 (39%)	ns
No. of extended right hemihepatectomies	16 (44%)	56 (38%)	8 (50%)	78 (45%)	ns
No. of patients with complications	4	4	1	14	ns
≥ grade 3b after stage 1 and no. of patients with liver failure ≥3b	1	0	1	1	.021*
No. of patients with complications	5	21	5	31	ns
≥ grade 3b after stage 2 and no. of patient with liver failure ≥3b	0	4	1	7	ns

*The group with >1 chemotherapy had more patients with liver failure ≥3b after stage 1.

regeneration because these 2 groups also had lower KGR. However, the preoperative volume measured as sFLR and FLR/TLV did not differ between the groups.

The mechanisms behind the possible effect of chemotherapy on liver regeneration remain elusive. Chemotherapy is known to have the potential to cause liver injury; oxaliplatin-based therapy may cause sinusoidal obstruction syndrome, and irinotecan is associated with an increased risk of steatohepatitis.[34] The molecular and cellular mechanism behind chemotherapy-associated liver injury mostly is based on animal models. One potentially contributing factor may be the effect of oxaliplatin on the cell cycle.[35] In this study, patients with an irinotecan-based chemotherapy regimen had a greater increase of the FLR, if measured in milliliters.

Patients with CRLM requiring ALPPS, have an advanced disease, which is often defined as being borderline resectable. For this cohort of patients it is known that the resection rate increases with preoperative chemotherapy,[36] and the R0 resection rate may increase if there is a morphologic downsize response. Although the value of neoadjuvant chemotherapy may be questioned in patients with limited CRLM,[37,38] it may improve progression-free survival as well as overall survival (OS) in patients with multiple, bilobar metastases.[39] Furthermore, patients who are not resectable at presentation sometimes may be converted to resectability with downsizing chemotherapy.[7] With this taken into account, combined with the results in this study, preoperative chemotherapy should be considered for all patients with CRLM evaluated at presentation as in need of an ALPPS procedure. Preoperative chemotherapy may further assess the biology of the tumor and patients that respond to chemotherapy are most likely those who benefit from operation, and the response may predict the prognosis. The effect of duration of chemotherapy on FLR hypertrophy for the groups that received oncologic therapy was statistically significant when the increase was measured as KGR and as absolute increase in FLR volume. This could indicate that the metastatic disease should be monitored closely during chemotherapy and operation should be considered at earliest possible opportunity. The difference in interval between chemotherapy and stage 1 revealed that there was no difference in increase for patients with short or long interval. However, the data did not allow analyzing the effect for the different groups.

The effect of age on the regeneration capacity after hepatectomy, including ALPPS, in the setting of CRLM, is not well studied in human. There were data from animal studies, indicating that regeneration was impaired in older compared with younger individuals.[40] Other studies, in humans, indicated that the functional regeneration was similar in older patients.[41] In this study, the isolated effect of age was significant when the increase of FLR was measured in milliliters and as increase in percent, but the effect was lost when all the covariates were analyzed together.

The effect comorbidity has on hepatic regeneration is not well studied, and the literature regarding the subject is scant because no previous studies were found. In this study, there was no connection between comorbidity and an impaired increase of FLR volume. The classification of comorbidity may not reflect the patient's actual health status. Charlson score was not validated for comparing comorbidities between different groups in this setting, but was originally constructed to predict mortality.[42] A clear drawback of Charlson score in the present setting was the dominant effect of metastatic malignant disease on scoring for all patients.

In this study, which is the largest analysis of ALPPS for patients with colorectal liver metastases, postoperative mortality was comparable with the mortality after TSH, which has been reported to be between 3.8–7%, compared with the mortality in this study, which is 6.5%.[43-45] Furthermore, the percentage of patients that proceeded through both stages in this study was greater than reported after portal vein embolization and TSH.[44,46] In this study, 92% of the patients underwent stage 2 and radicality was achieved in 97% of those patients (89% of the whole cohort), compared with ≤38% drop-out rate for patients undergoing TSH.[47] One must also keep in mind the patients who were suitable for ALPPS had a very advanced disease and ALPPS may be the only operative treatment possible.

There were some limitations to this study. Data entry was voluntary and reporting bias of the participation centers cannot be excluded completely. Furthermore, the data were not complete for all patients, and the number of patients with no chemotherapy and >1 regimen was relatively low. Therefore, the statistical analysis was weaker than could be expected from the total number of patients included in this study. The reason for proceeding to operation without neoadjuvant treatment was not reported, and there may be a bias herein. The volume measure was performed at each center, and the method for

volume measure may differ between centers; however, the method is considered to be constant for each patient.

Furthermore, the retrospective noncontrolled nature of this study was a weakness that only could be overcome by a prospective, randomized, controlled trial. As ALPPS has yet not been compared with TSH in a randomized, controlled trial, it seems unlikely that a properly powered study investigating the effect of chemotherapy on hypertrophy will be conducted soon.

In this study, which is the largest study of the effect of chemotherapy on the increase of the FLR in the 2-staged resection including ALPPS, it was shown that chemotherapy and monoclonal antibodies do not have negative effect on the growth of FLR.

Despite a limited number of patients not receiving neoadjuvant chemotherapy, the results from this study indicated that patients who are candidates for ALPPS probably were not exposed to greater risk of inadequate liver hypertrophy if treated with neoadjuvant oncologic therapy. This finding along with the advanced tumor stage of this patient category suggested that the best-tailored neoadjuvant oncologic treatment may be applied without significant impact on the hypertrophy of the liver in the context of ALPPS.

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