Original Article

Post-chemotherapy liver atrophy does not impact the outcome after hepatectomy performed under a parenchymal-sparing approach

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Background: Major hepatectomy in patients with colorectal liver metastases (CLM) and post-chemotherapy liver atrophy is associated with increased complications. Whether the performance of parenchymal-sparing hepatectomy (PSH) in those patients can be safer is unknown.

Methods: Databases at two institutions were queried, and 74 CLM patients who underwent preoperative chemotherapy and curative PSH were reviewed. Pre- and post-chemotherapy total liver volumes (TLVs) were computed with Synapse 3D software, and the degree of atrophy was calculated as the difference in percentage. The cut-off value for significant degree of atrophy was set at 10%. Risk factors for post-chemotherapy liver atrophy were assessed using logistic regression, while multivariate analysis was computed to identify risk factors for postoperative complications.

Results: With median CLM number of 6 (range, 1–20) and median CLM size of 3.3 cm (range, 1–14 cm), all patients underwent complex PSH. The 90-day mortality was 1%; Clavien-Dindo >2 complications occurred in 17%, with 6 (8%) post-hepatectomy liver failure (PHLF) events; 33 (45%) patients experienced ≥10% post-chemotherapy atrophy, of which pre-chemotherapy TLV was the only independent predictor [odds ratio (OR) =1.741; 95% confidence interval (CI): 1.120–2.386; P=0.02]. At multivariate analysis, none of the investigated variables showed significant association with PHLF or complications, which were not significantly increased in patients who experienced liver atrophy.

Conclusions: As opposed to what observed after major hepatic resections, a significant degree of post-chemotherapy liver atrophy does not represent a source of postoperative complications in CLM patients undergoing PSH.

Keywords: Hepatic atrophy; preoperative chemotherapy; parenchymal-sparing hepatectomy (PSH); postoperative hepatic insufficiency; colorectal liver metastases (CLMs)

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Introduction

In the last decades, the use of effective systemic chemotherapy, together with the advances in surgical techniques, have led to a significant increase in long-term overall survival for patients with colorectal liver metastases (CLMs), which to date may be estimated at up to 58% at 5 years (1,2). However, extensive preoperative systemic chemotherapy is not associated with negligible morbidity and mortality rates, which must be considered (3-9). Indeed, chemotherapy-associated liver injury (CALI) can be anticipated based on the type and number of chemotherapy courses (10,11). CALI may be associated with the development of post-hepatectomy liver failure (PHLF), especially in patients submitted to extensive liver surgery (6,7,12).

Among the different factors reported to be associated with postoperative mortality, including PHLF, sepsis, and postoperative hemorrhage, the occurrence of liver atrophy after preoperative chemotherapy is emerging as a marker of liver dysfunction that can be a source of postoperative complications after major hepatectomy (11,12). In detail, it has been reported that liver atrophy (≥10%) after prolonged (≥7 cycles) chemotherapy is an independent factor for PHLF and death after hepatectomy (12).

Highlight box

Key findings

- In patients with colorectal liver metastases (CLMs) undergoing parenchymal-sparing hepatectomy (PSH), post-chemotherapy liver atrophy is not associated with increased postoperative complications.

What is known and what is new?

- Extensive preoperative chemotherapy is associated to liver injury and parenchymal atrophy, which is described to enhance the risk of liver failure after major hepatic resections.
- Up to 44.6% of the herein included patients developed liver atrophy after systemic chemotherapy.

What is the implication, and what should change now?

- PSH has proven to be an effective and safe approach in CLM patients, also in those who developed significant post-chemotherapy liver atrophy because of preoperative chemotherapy.

Consistently, Omichi *et al.* (13) reported that the use of portal vein embolization (PVE) with adequate hypertrophy might reduce PHLF rates in patients with liver atrophy undergoing major resections, suggesting the use of PVE in these settings for CLM patients. Conversely to using PVE and extensive liver surgery, parenchymal-sparing hepatectomy (PSH) may allow safe and complete resection of CLMs even in cases of high tumor burden or deeply located tumors, preserving more liver volume (14-16). This approach showed lower morbidity and mortality than the staged approaches (17,18). In this study, we sought to investigate the actual incidence and the clinical-pathological features of liver atrophy after preoperative chemotherapy in patients undergoing hepatectomy for CLM performed under the PSH approach. We present this article in accordance with the STROBE reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-642/rc) (19).

Methods

Study design and data collection

This retrospective study was conducted in two university tertiary-referral hospitals on prospectively collected data. The cohorts of consecutive patients who underwent preoperative chemotherapy and curative PSH at the IRCCS Humanitas Research Hospital (Milan, Italy) and Pisa Hospital (Pisa, Italy) were reviewed. The study protocol was in accordance with the ethical guidelines established in the 1975 Declaration of Helsinki (as revised in 2013), and it was also compliant with the procedures of the local ethical committees. No ethical approval was required for this study, due to its retrospective observational nature. No experimental interventions were herein done. Written informed consent for data use was obtained from all patients.

Study endpoint

The study endpoint was to assess the clinical impact of post-chemotherapy liver atrophy on patients undergoing PSH for CLM. For this purpose, the occurrence of liver atrophy

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was recorded and then computed against the occurrence of postoperative morbidity and mortality.

Study eligibility criteria

Consecutive patients with multiple CLMs treated with preoperative chemotherapy and PSH in the two institutions between May 2010 and December 2019 were included. Only patients with available volumetry of the pre- and post-chemotherapy abdominal enhanced computed tomography (CT) images were selected. Patients who underwent preoperative PVE or were treated by major hepatectomies were excluded. Patients treated with thermal ablation alone or in association with hepatic resection were excluded.

Definitions

The nomenclature and extent of hepatic resection were recorded according to the Brisbane classification (20). Hepatic resections were considered major when at least three adjacent segments were removed. Complications were defined and graded based on the Clavien-Dindo classification (21). PHLF was defined and graded based on the definition of the International Study Group of Liver Surgery (22). Bile leak was determined and graded based on our previously reported protocol (23). Postoperative mortality was recorded at 90 days after surgery. Total liver volume (TLV) was defined as the mean volume of normal liver parenchyma, excluding tumors. Liver atrophy was defined as the decrease in the TLV between pre- and post-chemotherapy CT scans. The cut-off value of a significant degree of atrophy was set at 10%: a value previously demonstrated to reliably predict PHLF (12). Future liver remnant (FLR) volume was set at 40% of the preoperative TLV. TLV and FLR were measured using the software Synapse 3D (Fujifilm, Tokyo, Japan), which proved to be accurate for the purpose (24).

Oncological strategy

All patients were discussed at a multidisciplinary meeting, where the indications for neoadjuvant systemic chemotherapy and surgical resection were provided. Preoperative work-up consisted of contrast-enhanced CT scans of the abdomen and/or liver-specific magnetic resonance performed not more than 30 days before the scheduled operation date. All the included patients received neoadjuvant systemic chemotherapy with modern protocols as recommended by international guidelines (2). They were staged after 4–6 cycles and scheduled for surgery once there was evidence of response. Chemotherapy response was monitored by using the Response Evaluation Criteria in Solid Tumors. In the case of progressive disease, a second-line chemotherapy was usually scheduled. Only patients amenable to complete resection of metastatic disease with curative intent (R0- or R1-vascular hepatectomy) were considered for surgery, regardless of the number and size of CLMs. PSH was the preferred surgical approach, which was applied according to the previously published criteria (14-17). As said, the minimum value of FLR was set at 40%. In addition, patients' eligibility for resection was decided based on performance status, liver function tests, and FLR, as previously described (25).

Liver analysis

Hepatic volumetry based on pre- and post-chemotherapy CT scans was performed. The hepatic portal phase was used for CT volumetry, where both hepatic veins and portal vessels appear opacified, using a 2 mm slice thickness. The liver boundary was traced to exclude the surrounding structures and organs, delimiting the liver area on every single cut. The hepatic veins and portal vessels were traced so that hepatic segments could be precisely identified, and the vessels' volume could be subtracted from the TLV. Similarly, the volume of the tumors was calculated and excluded (*Figure 1*; Figure S1).

Surgical technique

Surgical technique was comparable in the two study centers. After performing a J-shaped laparotomy and exploring the peritoneal cavity, partial or complete mobilization of the liver was achieved. Intraoperative ultrasound (IOUS) was systematically performed to confirm the number and site of the preoperatively diagnosed CLMs, reveal additional lesions, and guide resection as previously reported (14-18). To improve intraoperative staging, contrast enhanced IOUS was also selectively accomplished (26). The main pillar of this approach was avoiding major intrahepatic vessel amputation (27). Consequently, in the presence of vascular contact, lesions from the Glissonean pedicles or hepatic veins were detached if no signs of infiltration were evident at IOUS (R1vasc resection) (14,18,28). Whenever not feasible, partial vascular resection and reconstruction were

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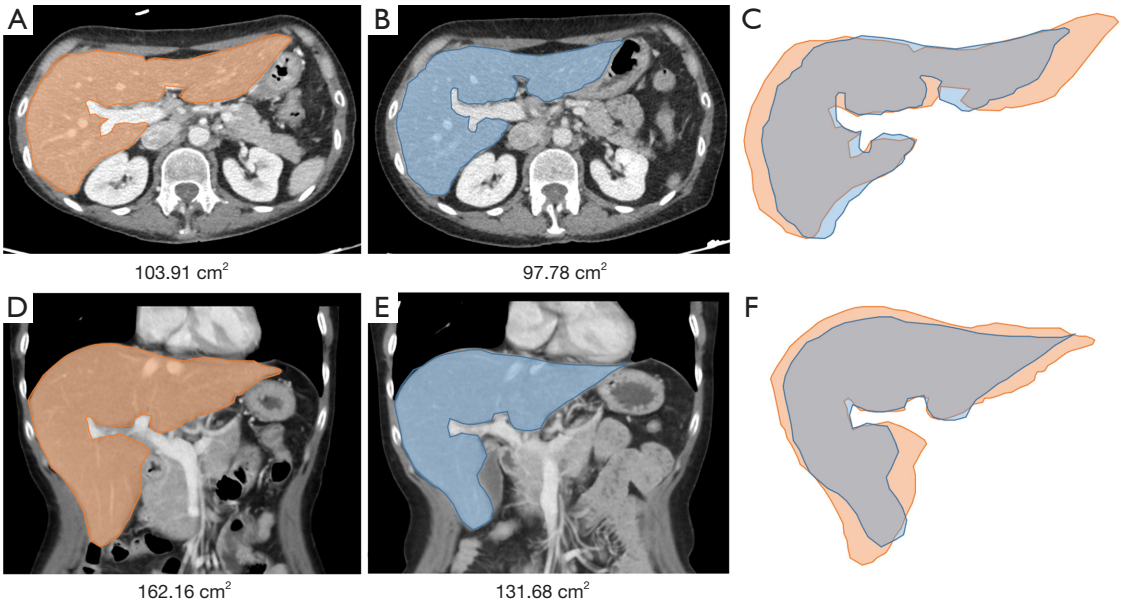

Figure 1 Representative case volumetry. TLV was calculated by using the software Synapse 3D (Fujifilm, Tokyo, Japan). Before chemotherapy the areas were estimated as 103.91 cm^2 (A) and as 162.16 cm^2 (D). After chemotherapy, the same areas were estimated as 97.78 cm^2 (B) and as 131.68 cm^2 (E). The corresponding degree of atrophy was 14%. The pink and grey images (C,F) show the differences on these representative measured areas of the liver. TLV, total liver volume.

conducted, as previously described (28,29). Parenchymal transection was achieved under low central venous pressure with the intermittent Pringle's maneuver by using the crush-clamping technique with Kelly-clasia; vessels smaller than 2 mm were transected by using coagulation devices, while thicker vessels were ligated with 3-0 sutures.

Selection of predictors of liver atrophy

The preoperatively determined variables deemed to be associated with the development of post-chemotherapy liver atrophy were the following: sex, age, a previous history of hepatectomy, the site of the primary tumor, the RAS status, the level of carcinoembryonic antigen (CEA) and cancer antigen 19-9 (CA19-9), the number of CLM, the size of CLM, the CLM distribution in the liver, the number of preoperative systemic chemotherapy lines, the number of preoperative systemic chemotherapy courses, the type of preoperative systemic chemotherapy including the use biological target therapies, the quality of underlying liver, the TLV values pre- and post-chemotherapy TLV, the values of tumor volume pre- and post-chemotherapy.

Selection of predictors of postoperative complications

The variables deemed to be associated with the development of postoperative complications were the following: sex, age, a previous history of hepatectomy, the number of CLM, the size of CLM, the CLM distribution in the liver, the number of preoperative systemic chemotherapy lines, the number of preoperative systemic chemotherapy courses, the type of preoperative systemic chemotherapy including the use biological target therapies, the quality of underlying liver, the TLV values pre- and post-chemotherapy TLV, the values of tumor volume pre- and post-chemotherapy, the length of operation, the length of the Pringle's maneuver, the number of resection areas, and the blood loss.

Statistical analysis

Categorical variables were reported as numbers and percentages. Continuous variables were reported as the median and interquartile range. Since normal distribution could not be confirmed for any variable, non-parametric statistical tests (Mann-Whitney for continuous variables)

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were preferentially used. Univariable and multivariable analyses were performed by logistic regression analysis to evaluate predictors of severe post-chemotherapy liver atrophy and postoperative complications. Receiver-operator characteristic (ROC) curves and associated area under the curves (AUCs) were generated for the relevant metrics to estimate the discriminatory ability for detecting post-chemotherapy liver atrophy. The effect size of these variables was reported as odds ratio (OR) and 95% confidential interval (95% CI). All tests were two-tailed, and a P<0.05 was considered significant for all tests. Computations were performed by using the software R version 4.0.2.

Results

Patients

A total of 74 patients were considered for the study. The median age of the patients was 63 years [interquartile range (IQR), 56–71 years], and 45 (60.8%) patients were male. Thirty-six (49%) patients had primary tumors in the left colon, twenty-two (30%) in the right colon, and the others had tumors in the rectum. The median number of CLM was 6 (IQR, 3–10), and the median tumor size was 3.3 cm (IQR, 1.8–5.0 cm). Sixty-three (85.1%) patients received a single line of chemotherapy, 8 (10.8%) patients underwent two lines, and 3 (4.1%) patients had three or four lines of chemotherapy prior to surgery. The median number of chemotherapy cycles was 8 (IQR, 6–11). One patient was preoperatively treated with panitumumab only, while most patients (85.1%) received 5-fluorouracil (5-FU)-based chemotherapy or capecitabine-based chemotherapy (12.2%) as follows: oxaliplatin (n=38, 51.4%), irinotecan (n=11, 14.9%), oxaliplatin + irinotecan (n=22, 29.7%), and capecitabine or anti-EGFR alone (n=3, 4.1%). Anti-VEGF antibody (bevacizumab) was added in 45 (60.8%) patients, anti-EGFR antibody (cetuximab or panitumumab) was added in 13 (17.6%) patients, 3 (4.1%) patients received both while thirteen (17.6%) patients did not receive any biologic agents.

Overall, the median TLV was 1,480 mL (IQR, 1,345–1,713 mL) before chemotherapy and 1,404 mL (IQR, 1,235–1,583) after chemotherapy. Of these 74 patients, 33 (44.6%) showed significant (≥10%) liver atrophy, 22 (29.7%) showed an inferior degree of atrophy, and 19 (25.7%) had hypertrophy after chemotherapy. *Table 1* details the baseline characteristics, with data classified according to the occurrence of liver atrophy (<10% *vs.* ≥10%). These two groups were statistically similar, even if patients with severe atrophy had higher levels of onco-markers, a greater proportion of m-KRAS, a higher median number of CLMs, a more frequent bilobar distribution of metastases, a higher median number of chemotherapy cycles with a more frequent use of irinotecan-oxaliplatin combined regimens with anti-VEGF.

Table 2 details the surgical data, including the amount of intraoperative blood loss, the length of operations, and the Pringle maneuver, reflecting the complexity of PSH. Notably, such complex data were equally distributed regardless of the degree of liver atrophy. Data regarding liver pathology were available in 44 (59.5%) patients; among them, 14 (32%) patients had normal hepatic parenchyma, 19 (43%) had steatosis or steatohepatitis, and 25% had fibrosis at the final histology of the non-tumoral liver. No differences in these data were found in relation to the degree of liver atrophy.

Postoperative complications

Overall, 47 (63.5%) patients experienced postoperative complications. Of these, 34 (45.9%) were minor complications, as graded as Clavien-Dindo 1–2, while 13 (17.6%) were major complications, as graded as Clavien-Dindo 3a–4. Six patients (8.1%) experienced PHLF. Only one postoperative death was observed (1.4%). Although the complication rate was similar in both groups, the rate of PHLF showed a trend towards significance (2.4% *vs.* 15.2%) in patients with significant liver atrophy (*Table 2*).

Predictors of liver atrophy

Table 3 shows the multivariate analysis of factors potentially associated with the development of post-chemotherapy liver atrophy. For that analysis, the variables included in the model were those resulted to be statistically significant at the univariate model: TLV pre-chemotherapy, number of cycles of chemotherapy, type of chemotherapy regimen, size, and number of CLMs. TLV measured before chemotherapy was the only variable that was found to be an independent predictor of atrophy (OR =1.741; 95% CI: 1.120–2.386; P=0.02). For the ROC curve analysis, the value of 1,387.865 mL was set as the best cut-off value associated with 87.9% sensibility and 47.6% specificity (AUC =0.684; 95% CI: 0.562–0.806; P=0.003) for predicting significant post-chemotherapy liver atrophy (*Figure 2*).

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Table 1 Comparison of the characteristics between patients with degree of atrophy <10% and ≥10% after preoperative chemotherapy

Characteristics	Overall	Degree of atrophy <10%	Degree of atrophy ≥10%	P value
All patients	74	41 (55.4)	33 (44.6)	–
Gender				0.45
Female	29 (39.2)	17 (41.5)	12 (37.4)	
Male	45 (60.8)	24 (58.5)	21 (63.6)	
Age, years	62.67 [56.35, 71.00]	63.26 [57.00, 69.81]	62.25 [56.13, 71.21]	0.93
Previous hepatectomy				0.41
No	59 (79.7)	31 (75.6)	28 (84.8)	
Yes	15 (20.3)	10 (24.4)	5 (15.2)	
Site of the primary				0.47
Right colon	22 (29.7)	13 (31.7)	9 (27.3)	
Left colon	36 (48.6)	22 (53.7)	14 (42.4)	
Rectum	14 (18.9)	5 (12.2)	9 (27.3)	
Unknown	2 (2.7)	1 (2.4)	1 (3.0)	
RAS mutated	30 (40.5)	15 (36.6)	15 (45.5)	0.53
CEA (ng/mL)	5.75 [3.38, 13.55]	5.10 [3.15, 11.00]	7.00 [3.55, 16.27]	0.37
CA19-9 (IU/mL)	10.15 [4.25, 27.90]	10.20 [4.50, 25.95]	12.20 [3.75, 24.90]	0.99
Number of CLM	6.00 [3.00, 10.00]	4.00 [2.50, 8.50]	6.00 [4.50, 11.00]	0.10
Max size of CLM (cm)	3.30 [1.80, 5.00]	3.50 [2.00, 5.00]	2.80 [1.70, 5.00]	0.59
CLM distribution				0.14
Unilobar	23 (31.1)	12 (29.3)	11 (33.3)	
Bilobar	51 (68.9)	29 (70.7)	22 (66.7)	
Lines of preoperative chemotherapy				0.26
1	63 (85.1)	36 (87.8)	27 (81.8)	
2	8 (10.8)	5 (12.2)	3 (9.1)	
3	1 (1.4)	0	1 (3.0)	
4	2 (2.7)	0	2 (6.1)	
Regimen				0.50
Irinotecan-based	11 (14.9)	7 (17.1)	4 (12.1)	
Oxaliplatin-based	38 (51.4)	23 (56.1)	15 (45.5)	
Both	22 (29.7)	10 (24.4)	12 (36.4)	
Other	3 (4.1)	1 (2.4)	2 (6.1)	
Biologicals				0.20
Anti-EGFR	13 (17.6)	10 (24.4)	3 (9.1)	
Anti-VEGF	45 (60.8)	22 (53.7)	23 (69.7)	
Both	3 (4.1)	1 (2.4)	2 (6.1)	
None	13 (17.6)	8 (19.5)	5 (15.2)	

Table 1 (*continued*)

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Table 1 (*continued*)

Characteristics	Overall	Degree of atrophy <10%	Degree of atrophy ≥10%	P value
Preoperative chemotherapy courses	8.00 [6.00, 11.00]	7.00 [6.00, 9.00]	8.50 [6.00, 12.00]	0.14
Underlying liver				0.78
Normal	14 (31.8)	9 (36.0)	5 (26.3)	
Steatosis/steatohepatitis	19 (43.2)	10 (40.0)	9 (47.4)	
Fibrosis	11 (25.0)	6 (24.0)	5 (26.3)	
TLV pre-chemotherapy (mL)	1,480.16 [1,344.53, 1,712.75]	1,395.50 [1,251.50, 1,610.93]	1,604.00 [1,412.70, 1,776.00]	0.12
TLV post-chemotherapy (mL)	1,404.47 [1,234.94, 1,582.56]	1,486.57 [1,316.00, 1,722.00]	1,305.80 [1,154.29, 1,451.91]	0.009
Tumor volume pre-chemotherapy (mL)	55.42 [17.02, 159.50]	48.88 [17.02, 97.91]	80.08 [18.50, 271.12]	0.12
Tumor volume post-chemotherapy (mL)	20.25 [5.38, 56.63]	17.62 [5.00, 60.44]	28.88 [5.88, 52.10]	0.74

Data are presented as number, n (%) or median [range]. CEA, carcinoembryonic antigen; CA19-9, cancer antigen 19-9; CLM, colorectal liver metastasis; TLV, total liver volume.

Table 2 Surgical data and postoperative complications overall and by degree of atrophy after preoperative chemotherapy

Variables	Overall	Degree of atrophy <10%	Degree of atrophy ≥10%	P value
All patients	74	41 (55.4)	33 (44.6)	–
Number of resection areas	3.00 [2.00, 6.00]	3.00 [2.00, 5.00]	3.00 [2.50, 6.00]	0.17
Length of operation (min)	488.00 [396.00, 642.00]	471.50 [362.50, 605.00]	520.00 [410.00, 670.00]	0.31
Length of pringle maneuver (min)	111.00 [70.00, 161.00]	91.00 [65.00, 151.00]	133.00 [80.00, 207.00]	0.05
Blood loss (mL)	300.00 [200.00, 500.00]	300.00 [150.00, 500.00]	350.00 [200.00, 500.00]	0.78
Clavien-Dindo (grade 1–2)	47 (63.5)	26 (63.4)	20 (60.6)	0.93
Clavien-Dindo (grade ≥3a)	13 (17.6)	7 (17.1)	6 (18.2)	>0.99
Death 90 days	1 (1.4)	1 (2.4)	0	>0.99
PHLF	6 (8.1)	1 (2.4)	5 (15.2)	0.11
Biliary leak	4 (5.4)	1 (2.4)	3 (9.1)	0.78

Data are presented as number, n (%) or median [range]. PHLF, post-hepatectomy liver failure.

Table 3 Multivariable analysis of predictors of post-chemotherapy liver atrophy

Variables	Post-chemotherapy liver atrophy		
	Odds ratio	95% confidence interval	P value
TLV pre-chemotherapy	1.741	1.120–2.380	0.02
Preoperative chemotherapy courses	1.126	0.751–1.291	0.54
Irinotecan-based CT	0.810	0.097–1.139	0.78
Oxaliplatin-based CT	0.921	0.167–1.014	0.78
Anti-VEGF (yes *vs.* no)	0.761	0.049–1.459	0.59
Anti-EGFR (yes *vs.* no)	0.631	0.010–1.954	0.67
Size of CLMs (by increasing of 1 cm)	0.911	0.341–1.892	0.96
Number of CLMs (by increasing of 1 unit)	0.841	0.134–1.397	0.22

TLV, total liver volume; CT, computed tomography; CLM, colorectal liver metastasis.

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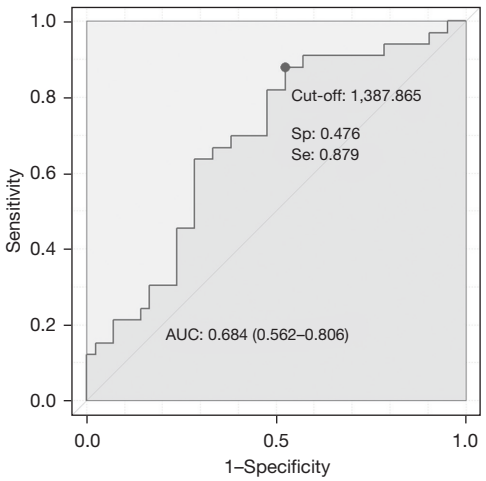

Figure 2 ROC curve analysis. The figure shows the ROC curve analysis of the pre-chemotherapy total liver volume. The value of 1,387.865 mL was set as the best cut-off value associated with 87.9% sensibility and 47.6% specificity (AUC =0.864; 0.562–0.806; P=0.003) for predicting significant post-chemotherapy liver atrophy. ROC, receiver-operator characteristic; AUC, area under the curve.

Predictors of complications

Table 4 shows the results of the univariable analysis of risk factors of postoperative complications. At the later multivariable analysis, the duration of the surgical procedure was identified as the sole independent risk factor for postoperative morbidity (OR =1.003; 95% CI: 1.000–1.007; P=0.02) (*Table 5*).

Discussion

To date, an increasing number of patients with CLMs receive preoperative systemic chemotherapy, aiming to induce a response to the liver tumor burden whether or not they are technically resectable. However, preoperative chemotherapy has several drawbacks. Various studies reported how preoperative chemotherapy causes various degrees of liver injury, including steatosis, steatohepatitis, or sinusoidal injury, and may increase the risk of postoperative morbidity/mortality as the duration of chemotherapy is prolonged (2-9). In particular, significant atrophy of the liver, observed in association with prolonged chemotherapy, may be produced by direct injury and loss of hepatocytes and, consequentially, by impairment in liver regeneration (11-13,30). Of note, Tani *et al.* (11) were the first to report this event, albeit the actual incidence and pathophysiology remain unclear. Such a phenomenon may become clinically relevant in patients with major or extended hepatic resection. In fact, this was reported by the University of Texas MD Anderson group who also suggested using PVE to reduce the risk of post-chemotherapy liver atrophy associated with PHLF (12,13).

In this study, we first showed an occurrence of significant post-chemotherapy liver atrophy in up to 45% of the patients, which is higher than what was reported by Tani *et al.* (11) and by Yamashita *et al.* (12), who reported 38% and 19%, respectively. Undoubtedly, the post-chemotherapy liver atrophy phenomenon exists and should be considered when balancing the pros and cons of prolonged systemic therapy, particularly in technically upfront resectable patients. Certainly, post-chemotherapy liver atrophy should be considered as a marker of CALI (30). Second, we showed that patients with a significant degree of liver atrophy did not experience a significant increase in postoperative morbidity or mortality when operated under the PSH approach. Indeed, the incidence of postoperative complications between patients with and without liver atrophy was comparable. Notably, the rate of PHLF showed a trend towards significance (2% *vs.* 15% in patients without and with liver atrophy respectively) that likely with a larger patient cohort would reveal a statistically significant result. The only independent risk factor for postoperative morbidity was the length of operation, possibly expressing the complexity of the surgical procedure.

Of note, previous studies that reported how the degree of atrophy is predictive of postoperative morbidity (PHLF, refractory ascites, and pleural effusion) included a considerable proportion of major hepatectomy (up to 48%) (12,30). Considering that the degree of liver atrophy appears to be associated with the residual liver functional reserve, with a worsening of the indocyanine green retention test at 15 minutes (ICG-R15) up to 14%, caution should be stated in case of extensive liver surgery (30). When a significant post-chemotherapy TLV decrease is observed, accurate preoperative assessment of functional liver reserves should be performed, and procedures to preserve liver parenchyma should be planned to minimize postoperative complications and death. Again, the assessment of liver volume appears to be mandatory in liver surgery with the clear indication of using formulas that give a dynamic perspective of the volume. This may be influenced by the patient's clinical status, which is not a static condition (31).

Along this line, we found that the only predictor of post-

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Table 4 Comparison of the characteristics between patients with and without postoperative complications

Characteristics	Not complicated	Complicated	P value
All patients	27 (36.5)	47 (63.5)	–
Male gender	17 (63.0)	28 (59.6)	>0.99
Age, years	64.21 [58.32, 70.79]	62.00 [55.73, 70.83]	0.61
Previous hepatectomy	8 (29.6)	7 (14.9)	0.27
Site of the primary			0.75
Right colon	6 (22.2)	16 (34.0)	
Left colon	13 (48.1)	23 (48.9)	
Rectum	7 (25.9)	7 (14.9)	
RAS mutated	13 (48.1)	17 (36.2)	0.26
CEA (ng/mL)	6.45 [3.68, 9.75]	5.05 [3.18, 18.80]	0.75
CA19-9 (IU/mL)	10.15 [7.73, 20.33]	8.95 [2.00, 32.93]	0.24
Number of CLM	5.00 [3.00, 7.00]	6.50 [3.00, 11.00]	0.43
Max size of CLM (cm)	2.00 [1.50, 3.70]	3.65 [2.50, 5.50]	0.02
Bilobar CLM	19 (70.4)	13 (27.7)	0.37
Lines of preoperative chemotherapy			0.57
1	22 (81.5)	41 (87.2)	
2	3 (11.1)	5 (10.6)	
3	1 (3.7)	0	
4	1 (3.7)	1 (2.1)	
Regimen			0.15
Oxaliplatin + irinotecan	4 (14.8)	18 (38.3)	
Irinotecan-based	3 (11.1)	8 (17.0)	
Oxaliplatin-based	18 (66.7)	20 (42.6)	
Biologicals			0.37
Anti-EGFR	6 (22.2)	7 (14.9)	
Anti-VEGF	16 (59.3)	29 (61.7)	
Both	0	3 (6.4)	
Preoperative chemotherapy courses	6.50 [5.00, 9.25]	8.00 [7.00, 12.00]	0.036
Length of operation (min)	410.00 [321.00, 519.00]	541.00 [454.50, 721.00]	0.003
Length of pringle maneuver (min)	89.00 [57.00, 140.00]	120.00 [81.00, 205.50]	0.051
Blood loss (mL)	300.00 [200.00, 500.00]	300.00 [150.00, 500.00]	0.53
Underlying liver			>0.99
Normal	9 (33.3)	5 (10.6)	
Steatosis/steatohepatitis	13 (48.1)	6 (12.8)	
Fibrosis	5 (18.5)	6 (12.8)	
Unknown	–	30 (63.8)	

Table 4 (*continued*)

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Table 4 (*continued*)

Characteristics	Not complicated	Complicated	P value
TLV pre-chemotherapy (mL)	1,578.00 [1,337.72, 1,672.00]	1,456.59 [1,349.57, 1,803.83]	0.50
TLV post-chemotherapy (mL)	1,348.00 [1,200.00, 1,502.00]	1,408.00 [1,265.00, 1,685.59]	0.14
Tumor volume pre-chemotherapy (mL)	14.00 [5.00, 49.52]	97.91 [37.61, 214.79]	<0.001
Tumor volume post-chemotherapy (mL)	5.00 [3.00, 19.03]	35.91 [12.57, 69.74]	<0.001
Liver atrophy	20 (74.1)	35 (74.5)	>0.99
Liver atrophy ≥10%	13 (48.1)	20 (42.6)	>0.99

Data are presented as n (%) or median [range]. CEA, carcinoembryonic antigen; CA19-9, cancer antigen 19-9; CLM, colorectal liver metastasis; TLV, total liver volume.

Table 5 Multivariable analysis of predictors of postoperative complications

Variables	Postoperative complications		
	Odds ratio	95% confidence interval	P value
Liver atrophy ≥10%	0.645	0.221–1.882	0.42
Preoperative chemotherapy courses	1.058	0.917–1.220	0.43
Length of operation (min)	1.003	1.000–1.007	0.02
Max size of CLM (cm)	1.101	0.836–1.448	0.49

CLM, colorectal liver metastasis.

chemotherapy liver atrophy was the pre-chemotherapy TLV. While the TLV depends on factors, such as the body mass index or the body surface area, and an absolute value might be considered meaningless, a given low TLV value means, probably, a low functional liver reserve that becomes clinically relevant once there is the association between significant post-chemotherapy atrophy and major hepatectomy. Such evidence enhances the importance of performing liver volumetry before liver surgery with the aim of gathering all the information needed to anticipate a given risk of postoperative complication. At the same time, major or extended hepatectomy should be avoided in case of small TLV and/or post-chemotherapy liver atrophy, and PSH should be the approach of choice.

The current analysis did not find a significant association between the duration of preoperative chemotherapy and the degree of atrophy. Nevertheless, we observed a higher median number of cycles in the group experiencing a degree of atrophy ≥10%. Similarly, while some types of liver injuries are directly associated with specific chemotherapeutic agents, such as oxaliplatin-induced liver atrophy (31-34), no significant differences were observed between patients with and without a degree of atrophy ≥10% in relation to the chemotherapeutic agent administered. In addition, we did not find associations between the use of bevacizumab and the development of liver atrophy as was previously reported (35-38). CALI likely includes a wide range of different conditions that we still need to understand.

The limitations of this study include its retrospective design, the risk of selection bias, the relatively small sample size, and the lack of a comparison group. Additionally, the results concerning the predictors of complications should be cautiously evaluated due to the low number of events of severe complications, PHLF, and postoperative death. On the other hand, the current analysis was performed on a prospectively collected database of patients treated for complex PSH for multiple bilateral CLM with the availability of volumetric data, which are not commonly reported particularly for complex PSH. Finally, the lack of comparison group is a limitation in common with the main publications herein discussed (12,13).

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Conclusions

In conclusion, this study showed that hepatectomy for CLM performed under the PSH approach may be safely performed even in patients presenting with post-chemotherapy liver atrophy. Additional studies investigating the TLV changes during preoperative chemotherapy are required.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-642/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This research was carried out in accordance with the Declaration of Helsinki (as revised in 2013). No ethical approval was required for this study, due to its retrospective observational nature. No experimental interventions were herein done. Written informed consent for data use was obtained from all patients.

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