Clinics in Surgery

Research Article
Published: 26 Sep, 2016

Unresectable Liver Metastases from Colorectal Cancer: Any Limits for Radical Hepatectomy?

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Abstract

Introduction: Complex therapeutic strategies were developed to allow surgical resection of initially unresectable or hardly resectable colorectal liver metastases. That consists on downsizing chemotherapy, one- or two-stage hepatectomy. However, some patients could not complete all therapeutic steps. The aim of this study is to assess associated factors of failure and occurrence of postoperative complications.

Methods: Univariate and multivariate analysis were performed to highlight associated factors that may compromise the success of the therapeutic strategy. Actuarial survival was assessed comparing patients who completed all therapeutic strategy to those who failed and those treated by palliative chemotherapy.

Results: Among 63 patients with initially hardly resectable or unresectable LM, 45 were selected to intend surgical resection. Non-response to down-sizing chemotherapy was associated to a body mass index (BMI) ≥25 kg/m² (OR=0.073). In two-stage hepatectomy, size of LM ≥5 cm (OR = 0.093) was the associated factors of failure to reach the second step surgery. Especially when pooled with a number of LM ≥5 (0.012). Occurrence of postoperative morbidity was associated to the necessity of perioperative transfusion (OR=12). Postoperative mortality was associated to the need of perioperative transfusion (OR=23.25). Especially when pooled to size of LM ≥5 cm (OR=5.47). Three-year overall survival rate was 64.9% when patients completed therapeutic strategy.

Conclusion: despite the limits of our study, we identified associated factors of poor response to chemotherapy, of failure of two-step surgery and occurrence of postoperative complications.

Abbreviations

BMI**:** Body Mass Index; CRC: Colorectal Cancer; LM: Liver Metastases; FLR: Future Liver Remnant; ALPPS: Associated Liver Partition and Portal vein ligation for Staged hepatectomy**;** HIPEC**:** Hyperthermic Intraperitoneal Chemotherapy**;** FOLFOX: Folinic Acid + Fluorouracil + Oxaliplatin**;** FOLFIRI: Folinic Acid + Fluorouracil + Irinotecan**;** Fol Fox Iri: Folinic acid + Fluorouracil + Oxaliplatin + Irinotecan

Introduction

Colorectal cancer (CRC) is the third cause of death in the world. Near 50-60% of patients will develop liver metastases (LM) and near 50% will die from their liver disease [1]. Despite significant medical and oncological progresses, surgical resection remains the best therapeutic option [2]. After macroscopically complete liver resection (R0/R1) and bio-chemotherapy, the 5-year survival rate can reach 58% in selected patients [2,3]. However, less than 10-15% of patients are considered as initially "easily" resectable, and this is more comprehensive when multiple bilobar LM are present, mainly because of tumor location, number and size of LM [4,5]. For them, resection is proposed when R0/R1 hepatectomy leaving behind two adjacent liver segments with appropriate outflow and inflow can be assured. Furthermore, to avoid postoperative liver failure, the future liver remnant (FLR) should represents at least 25-30% of the total liver volume or > 0.5-0, 6% of body weight in patients with healthy liver, 30-40% in patients with underlying "injured" liver parenchyma (i.e. sinusoidal obstruction syndrome, steatosis, or steatohepatitis), and more than 40% in the presence of sever fibrosis or cirrhosis [6-9].

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Received Date: *17 Aug 2016*
Accepted Date: *22 Sep 2016*
Published Date: *26 Sep 2016*

Citation:
Amroun KL, Piardi T, Chetboun M, Sommacale D, Kianmanesh R, Djerada Z, et al. Unresectable Liver Metastases from Colorectal Cancer: Any Limits for Radical Hepatectomy?. Clin Surg. 2016; 1: 1141.

Table 1: Patients and procedures characteristics.

Number of patients	N=45
Number of liver resection (procedures)	N=70
Patients	
Age, mean ± SD; median (range)	59.8± 9.4; 59 (42-80)
Sex ratio M/F	1.6
BMI ≥ 25 (kg/cm^2)	60% (27)
PS 0-1	93,3% (42)
ASA 1	13,3% (6)
2	60% (27)
3	26,7% (12)
Primary tumor	
Localization: colon right, left; rectum; unknown	22,2% (10); 64,4% (29); 11,1% (5); 2,2% (1)
T stage I/II	8,9% (4)
III/IV	91,1% (41)
N stage N0	8,9% (4)
N1/2	80% (36)
Nx	11,1% (5)
Differentiation (%): well; intermediate; undifferentiated	20% (9); 51,1% (23); 28,9% (13)
Previous to liver surgery primary resection	88,9% (40)
Liver metastases	
Synchronous	73,3% (33)
Metachronous	26,7% (12)
Bilobar	62,2% (28)
Number of LM* ≥ 4	71,1% (32)
Size of largest LM ≥ 5 cm	35,5% (16)
Downsizing chemotherapy	100%
Number of cycles, median (ranges)	8 (3 – 68)
Chemotherapy regimens Folfox / Folfiri / Folfirinox	42,2% (19) / 44,4% (20) / 11,1% (5)
Targeted Biotherapy**	71,1% (32)
Two-step hepatectomy,	68,9% (31)
Completed two-step	80.6% (25)
Failed two-step	19.4% (6)
Clearance of the FLR at 1st stage	71% (22)
One-step hepatectomy	31,1% (14)
Surgery of one-step	100%
Wedge / RFA / extended right hepatectomy	78.6%(11) /35.7 %(5) /14.3 %(2)
Major hepatectomy (one- or two-step)	55% (25)
Right hepatectomy	68% (17)
Right hepatectomy extended to segment 4 or 1	28% (7)
Left hepatectomy extended to segment 5 and 8	4% (1)

*LM superior to one centimeter in size
**Bevacizumab n=21, Cetuximab n=11
BMI: body mass index, LM: liver metastases, PS: performance status, ASA: American score of anesthesiology, FLR: future liver remnant

To bring to surgery, unresectable LM from CRC, tools are used including preoperative downsizing bio-chemotherapy or less often hepatic arterial infusion, followed by one- or two-step hepatectomies after portal vein occlusion (i.e. ligation or embolization) [10-12]. Adjunction of targeted biotherapies such as cetuximab and bevacizumab or tri-regimen chemotherapies enhance the response rate and can help to increase the number of patients who can benefit from radical surgery [10,11].

The principal aim of this study was to analyze, among selected patients with initially not easily resectable (hardly or non-resectable) LM from CRC, factors associated to chemotherapy response, to occurrence of postoperative morbi-mortality, and actuarial overall survival.

Table 2: Results upon morphologic responses after downsizing bio-chemotherapy comparing responder (partial/complete) vs not responder (stable/progressive) patients (RESICT and/or Choi criteria).

	Partial/complete response N=31	Stability/progression N=14	Univariate p< 0.05	Multivariate p< 0.05
Age, mean ± SD	59.19 ± 1.941	61.14 ± 1.325	0,524	ns
Sex ratio M:F	1.2	3.6	0,188	ns
BMI ≥ 25 (kg/cm^2)	48% (15)	86% (12)	0,023	0.025
Differentiation (%): intermediate/undifferentiated	52% (16)	79% (11)	0,11	ns
CEA before liver surgery, mean	707.9 ± 446.4	121.3 ± 46.92	0,254	ns
Number of LM*, mean	6.323 ± 0.4646	5.000 ± 0.8581	0,153	ns
Size of largest LM (cm), mean	4.448 ± 0.4447	4.892 ± 0.7175	0,595	ns
Number of cycles, mean	11.61 ± 2.311	8.692 ± 1.303	0,432	ns
Targeted (bio) therapies**	81% (25)	50% (7)	0,035	ns

*LM superior to one centimeter in size
**Bevacizumab n=21, Cetuximab n=11
BMI: body mass index, CEA: carcinoma embryogenic antigen, LM: liver metastases

Table 3: Results comparing patient who failed to complete two-stage hepatectomy to those who completed all stapes strategy.

·	Failed group (6)	Completed group (25)	Univariate p<0.05	Multivariate p<0.05
Age, mean ± SD	62.33 ± 3.94	60.52 ± 1.55	0,626	ns
Sex male	100%	52% (13)	0,058	ns
BMI (kg/cm^2) mean ± SD	29.21 ± 2.54	26.39 ± 0.97	0,282	ns
ASA ≥ 3	30% (2)	20% (5)	0,595	ns
PS 0-1	100%	88% (22)	0.745	ns
Number of LM*, mean ± SD	6.17 ± 1.40	5.68 ± 0.55	0,801	ns
Number of LM* ≥ 5	67%(4)	60% (15)	0.763	ns
Size of largest LM ≥ 5 cm	67% (4)	36% (9)	0,067	0.046
Number of LM ≥ 5 * and size ≥ 5 cm	67% (4)	12% (3)	0.01	0.012
Number of cycles, mean	18.83 ± 9.90	10.88 ± 1.74	0,619	ns
Biotherapy	67% (4)	44% (11)	0,394	ns
Morbidity at 1st stage	50% (3)	8% (2)	0,037	ns
1st stage combined to primitive surgery	0%	12% (3)	1,000	ns
Invaded hepatic lymph nodes	30% (2)	4% (1)	0,087	ns

*LM superior to one centimeter in size
BMI: body mass index, PS: performance status, ASA: American score of anesthesiology, LM: liver metastases

Material and Methods

Between November 2004 and June 2013, 63 patients presenting with initially hardly resectable or unresectable LM from CRC were selected for liver surgery after multidisciplinary discussions including hepatobiliary surgeons, oncologists, gastroenterologists and radiologists. The study was conducted in two French university-hospitals having the same politics for the treatment of LM from CRC according to current recommendations. All studied patients underwent a downsizing preoperative systemic bio-chemotherapy. RECIST, and when available, Choi's criteria were used to evaluate the morphological responses to preoperative bio-chemotherapy [13,14].

One or two-step hepatectomies were planned according to tumor size, localization, relation to hepatic vessels and FLR volumes. Different group of patients were compared upon following patients characteristics and/or variables: (i) presence or absence of significant morphological responses to down-sizing bio-chemotherapy (RESICT and/or Choi), (ii) completion or not of the two-step hepatectomy, (iii) presence or absence of postoperative ≥ grade II Dindo-Clavien scale complications [1,15], (iv) presence or absence of mortality up to 90 postoperative days. Finally, actuarial overall survivals were assessed according to Kaplan-Meier analyze in patients who underwent complete surgical treatment, incomplete surgery (failure of two-step surgery) and those who underwent no surgery and treated exclusively by bio-chemotherapy.

Statistical analyzes

Statistical analyzes were performed using IBM SPSS statistics software version 20.0. Univariate analyzes were done for continuous variables using non-parametric Mann-Whitney test and for qualitative variables using chi-square or two-tailed Fisher's exact tests when necessary. Multivariate analyzes were done using the logistic regression modeling. The most covariate factors were chosen by fitting a logistic regression model using a backward stepwise selection procedure (p< 0.05 for entry, p< 0.10 for removal) with adjusted Odds Ratio (OR).

Omnibus test of model coefficients is associated with p value that was used to assess significant effect for the combined predictors on the outcome variables. The Goodness of fit and appropriateness of the logistic regression model were evaluated using the Nagelkerke R

Table 4: Results comparing factors upon occurrence or not of postoperative morbidity for patients who underwent complete surgical procedures (one- or two-stage).

	No morbidity N=25	Morbidity N=14	Univariate p< 0.05	Multivariate p< 0.05
Age, mean	59.14 ± 1.767	61.00 ± 2.317	0,529	ns
Sex ratio M:F	1.9	1.3	0,748	ns
PS ≥ 1	20% (5)	42.8% (6)	0,249	ns
ASA ≥ 3	36% (9)	21% (3)	0,491	ns
BMI (kg/cm^2), mean	26.63 ± 0.83	26.50 ± 1.55	0,937	ns
Chemotherapy				
Cycles number, mean	8.143 ± 0.71	15.31 ± 4.28	0,037	ns
More than 8 cycles	48 % (12)	85.7% (12)	0,03	ns
Major hepatectomy	64% (16)	85.7% (12)	0,373	ns
Major hepatectomy + CT> 8 cycles	24% (6)	42.8% (6)	*	0.05
Perioperative transfusion	4% (1)	14.2% (2)	*	0.04
Hepatic parenchyma				
Steatosis > 5%	52% (13)	71.4% (10)	0,353	ns
Sinusoidal obstruction syndrome	20% (5)	7.1% (1)	0,398	ns

*These two factors were not significant in univariate analyzes, however, in multivariate analyze modeling the two factors were stable and showed significant results (see method section).

BMI: body mass index, PS: performance status, ASA: American score of anesthesiology, LM: liver metastases

squared values and Hosmer-Lemeshow value and finally by the overall correct percentage of prediction. Multicollinearity was checked for all analyzes and the Wald test was used for hypothesis testing. To assess discriminatory performance of a Binary Logistic Model, a receiver operating curve (ROC) and calculated areas under the ROC curves (AUCs) were performed.

The association between factors that could be predictors such as sex, age, Body Mass Index (BMI) ≥25 kg/m², American Society Anaesthesiology ASA ≥3, performance statute ≥3 (world health organization), number of supra centimeter LM ≥5, LM size ≥5 cm (diameter of the largest tumor), number of chemotherapy cycles, use of associated biotherapy to chemotherapy, RECIST and/or Choi morphological tumor response rates, presence of invaded hepatic lymph nodes and binary outcomes as completion of two-step hepatectomy strategy were used as well as the performance or not of a major hepatectomy (≥3 segments), necessity of per-operative blood transfusion and binary outcomes as morbidity (Dindo-Clavien scale ≥II) or mortality (during 90 postoperative days) were used.

Overall survival analyzes included all patients (including those who died during ninety postoperative days). Kaplan-Meier analyzes with log-rank test were used. In case of multiple testing, Bonferroni correction was applied. All p values were two-tailed, with statistical significance indicated by a value of p< 0.05.

Results

Among 63 patients with initially hardly resectable or unresectable LM, 18 (28.5%) were not illegible for a curative intent surgery after bio-chemotherapy for following reasons: presence of unresectable extrahepatic metastases (n=11), other medical contraindications to major surgery (n=7). Forty-five patients were finally illegible and enrolled a curative intent surgical strategy. Patient's characteristics and details of procedures are summarized in Table 1.

Primaries were removed previously to liver surgery in 40/45 (88.8%) of patients. The liver resection defined the principal type of surgery for patients who had associated procedures. Seventy liver procedures were realized (1.55 hepatectomy per patient). Extra-hepatic resectable metastases were present in 11% of patients and removed at the same operative time (right inferior pulmonary metastases n=1, complete cytoreduction surgery with HIPEC of peritoneal carcinomatosis n=4). Sixty per cent of patients underwent preoperatively more than 6 cycle's bio-chemotherapy (Table 1).

Four patients died postoperatively (up to 90 days), with a per patient mortality rate of 9% and per procedure mortality rate of 5.7%. The causes of deaths were major portal thrombosis (n=2), uncontrolled septic shock (n=1) and diffuse arterial mesenteric infarction (n=1). Overall postoperative morbidity rate (≥Dindo-Clavien II) was 35.5% per patient and 24.3% per procedure. More than 3 days intensive-care unit stay was needed for 20% of patients (n=9). Detail of postoperative complications included grade IV peritonitis (n=1); grade III biliary fistulae (n=1), biliary stenosis (n=1), intra-abdominal collection (n=1), evisceration (n=1), myocardial infarction (n=1) and pleural effusion (n=1); grade II pulmonary emboli (n=1), bowel fistulae (n=1), gastric ulcer (n=1) and pulmonary effusion (n=2). The overall mean hospital stay for all procedures was 12.9 ± 9 days.

Table 2 reports the results of uni- and multivariate analyzes after comparison between sub-group of patients who presented or not significant morphological responses following downsizing bio-chemotherapy. Univariate analyzes found two associated factors: (i) body mass index ≥25 kg/m² concerned 86% of patients in not responder sub-group vs. 48% of patients in responder sub-group (p= 0.023, OR= 6.400, 95%CI = 1.223 to 33.49) and (ii) targeted biotherapy was associated to chemotherapy in 81% of patients in responder sub-group vs. 50% of patient in not responder sub-group (p=0.036, OR= 4.167, 95%CI= 1.053 to 16.49). Multivariate analyzes found the body mass index ≥25 kg/m² as being the associated factor of non-response to bio-chemotherapy (p= 0.025, OR= 0.073, 95%CI= 0.007 to 0.712).

Two-step hepatectomy was used to achieve macroscopic (R0/R1) clearance of LM in 31/45 (68.8%) patients. Six patients failed to reach the second-step for one or multiple following reasons: disease progression (n=2), tumor recurrence inside FLR (n=4), insufficient

Table 5: Results comparing factors upon occurrence or not of postoperative mortality for patients who underwent complete surgical procedures (one- or two-stage).

39 patients	Dead N=4	Alive N=35	Univariate p< 0.05	Multivariate p< 0.05
Age, mean	61.75 ± 4.42	59.14 ± 1.61	0.667	ns
BMI (kg/cm^2), mean	22.92 ± 2.95	26.55 ± 0.7	0.131	ns
ASA ≥ 2	75% (3)	86% (30)	0.202	ns
PS ≥ 1	25% (1)	26% (9)	0.874	ns
Largest LM size ≥ 5 cm	75% (3)	40% (14)	0.10	ns
Number of chemotherapy cycles, mean	16.50 ± 5.56	8.647 ± 1.09	0,037	ns
Major hepatectomy	75% (3)	26% (9)	0,045	ns
Major hepatectomy + Chemotherapy > 8 cycles	50% (2)	37% (13)	0,798	ns
Perioperative transfusion	75% (3)	6% (2)	0,004	0.013
Hepatic parenchyma				
Steatosis > 5%	50% (2)	77% (27)	0,736	ns
Sinusoidal obstruction syndrome	0	17% (6)	0,691	ns

increase of FLR volume (n=2) and severe morbidity following the first-step (n=1). Table 3 reports the results of comparison between the two sub-groups of patients who completed (or not) the two-step hepatectomy. Univariate analyzes reported the occurrence of major complications after the first hepatectomy as a negative associated factor for completion of the second-step hepatectomy (failure of second step 50% vs. 8% in the absence of major complication, p= 0.037, OR= 11.50, 95% CI = 1.33 to 99.38). Multivariate analyze found the size of LM ≥5 cm (p= 0.046, OR = 0.093, 95%CI = 0.009 to 0.956) as the only independent associated factor of failure of the two-step hepatectomy. However, the failure of the second-step surgery was significantly higher after multivariate analyzes when both the largest tumor size ≥5 cm and the number of supra centimeter LM ≥5 were pooled (p= 0.012).

Postoperative morbi-mortality rates were analyzed for 39/45 (86.7%) of patients who completed radical resection. Table 4 reports the results of comparison between the sub-groups of patients presenting or not one or more Dindo-Clavien ≥II postoperative complication(s). The mean number of preoperative chemotherapy cycles was significantly higher in patients who presented Dindo-Clavien ≥II postoperative complications (p< 0.037). Univariate analyzes showed that patients with ≥8 cycles of bio-chemotherapy had significant more complications vs. those who received less than 8 cycles, 85.7% vs. 48%, respectively (p=0.03, OR=4.25, 95%CI= 1.10 to 16.42, one tailed analyze). Multivariate analyze showed the necessity of perioperative transfusion as the sole associated factor of occurrence of postoperative complications (14.2% vs. 4%, p=0.04, OR=12, 95%CI=1.07 to 134.11). Furthermore, postoperative complications occurred more often in patients who underwent major hepatectomy after ≥8 chemotherapy cycles (p=0.05). Table 5, shows the results of comparison between post-surgery dead and alive patients. Univariate analyzes showed significant differences concerning the mean number of bio-chemotherapy cycles 16.5 ± 5.5 for dead patients vs. 8.6 ± 1.0 for alive patients (p= 0.037), a major vs. minor hepatectomy (75% vs. 26% respectively, p= 0.045, OR=12, 95%CI=1.07 to 133.70) and the need of perioperative transfusion (75% vs. 6% respectively, p=0.004, OR=49.50, 95%CI= 3.41 to 719.30). Multivariate analyze showed the perioperative transfusion as the sole associated factor of postoperative mortality (p=0.013, OR=23.25, 95% CI=1.925 to 280.77). In addition, when pooled, the need of perioperative transfusion and the largest LM size ≥5 cm were statistically associated to higher occurrence of postoperative mortality (p= 0.10, OR = 5.47, 95%CI = 0.39 to 76.39).

The mean number of liver metastases was significantly different between patients who underwent one- vs. two-step surgery (4.0 ± 0.44 vs. 6.0 ± 0.54 respectively, p=0.043). Univariate analyzes showed less postoperative morbidity after one- vs. two-step complete surgery (7% vs. 48% respectively, p=0.013).

Overall survival analyzes were performed for patients (i) who finalized the therapeutic macroscopic complete strategy (n=39), (ii) those who failed the second-step surgery (n=6) and (iii) those who were exclusively treated by bio-chemotherapy (n=18). For them, the 3-year overall survival rates were 65%, 0% and 0%, respectively. The median survival of patients who completed macroscopic surgery was 77 months vs. 24 and 17 for patients with incomplete surgery and patients who received exclusive bio-chemotherapy, respectively (p=0.0015, between first and second groups and p=0.001 between first and third groups).

Discussion

In this series curative intent surgery is possible in highly selected patients with initially hardly or unresectable LM from CRC with 9% mortality, 35.5% morbidity rates and an acceptable 3-year overall survival rate.

Down-sizing bio-chemotherapy is mostly proposed as the first line treatment to bring initially hardly or unresectable LM from CRC to surgery. This sequence provides the best long-term survival rates [5,8,16]. All of the patients in the present series had preoperative down-sizing chemotherapy either with bi-regimen (FolFox or FolFiri) or tri-regimen (Fol-Fox-Iri) drugs. For 71% of them, targeted biotherapies (21 bevacizumab and 11 cetuximab) were associated to chemotherapy regimens. The mean number of cycles was 8, that by necessity to observe significant morphological responses or at least to do not propose surgery in progressive patients. We observed that the adjunction of targeted biotherapie intensify the down-sizing action of chemotherapy. This was reported by other series in which patients with CRC LM were treated by bi-regimen chemotherapy with adjunction of either, cetuximab, bevacizumab or panitumumab [11,17-21]. However, tri-regimen chemotherapy without target therapies is associated to similar high response rates [16,22]. In the present series, patients with a BMI ≥25 were both in uni- and multivariate analyzes associated to a negative impact in terms of

morphological responses after bio-chemotherapy.

More than ¾ of patients in the present series had a two-step hepatectomy. For these patients, we considered that all in one-step extended liver surgery would be too risky. Patients who failed to reach the second-step procedure presented intrahepatic recurrence inside the FLR and absence of significant liver hypertrophy of the FLR. We observed two factors as being associated to failure of the two-step procedure. Firstly, the size-number of LM (≥5 in number and/or ≥5 cm). Secondly, the occurrence of significant morbidity after the first-step liver surgery. We did not opted to perform Associated Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) technique because we believe that this procedure needs "maturation" in terms of technical and medical aspects and could not be proposed routinely as a standard care in such patients [5,23-25].

When radical surgery (in one- or two-step) was planned, there was a negative impact in term of morbidity, after major hepatectomy in patients who received more than 8 cycles of bio-chemotherapy. Karoui et al. [26] reported a cut-off of 6 cycles of chemotherapy (without biotherapies) as increasing significantly the postoperative morbidity rates. Lehmann et al. [27] reported more contradictory results, especially when metastases were accessible for surgery. However, we observed that the performance of major hepatectomy with perioperative need of transfusion, especially in patients who received a long history of chemotherapy were significant associated factors of occurrence of higher rate postoperative complications. In the present series, the rate of histological liver injuries was not directly associated to the occurrence of major complications. For patients with more than 5 cm in size and 5 LM, for whom more than 6-8 cycles' chemotherapy are required with the need of major liver resection, we suggest to propose a two-step procedure.

Among the advantages of the two-step procedure is the selection of appropriate candidates to radical extensive surgery after the first-step. Indeed, left surgical or ablative clearance of the LM with performance of right portal vein occlusion are reversible steps that will not compromise further therapeutics. The first step surgery will allow, liver parenchyma histological analyzes, a better estimation of number and location of LM by intraoperative ultrasound, there contact to the venous inflow outflow system and presence of intrahepatic collateral vein, also detection of peritoneal carcinomatosis [28]. We also believe that serious postoperative morbidity may delay or avoid postoperative interval chemotherapy and may represent a "loss of chance" [29-33]. Interestingly, Muratore et al. [34] in a small series of patients with bilobar LM, reported that routine use of chemotherapy between the first and second-step hepatectomy (interval chemotherapy) did not guarantee lower progression disease or drop-out rates.

The negative impact of transfusions on perioperative and long-term outcome after liver resection reported by Kooby et al. [35] is in concordance with our results. Indeed, they reported that non-transfused patients had significantly fewer postoperative complications than those who received blood products (33% vs. 46%, $p< 0.0001$). Also, transfused patients had decreased survival compared to non-transfused patients with a median survival of 37 months vs. 49 months respectively, $p< 0.0004$. Multivariate analyze showed the perioperative transfusion as the sole predictive factor of postoperative mortality in our series (p=0.013, OR=23.25, 95% CI=1.925 to 280.77). In addition, when pooled, the need of perioperative transfusion and the largest LM size ≥5 cm were statistically associated to higher occurrence of postoperative mortality (p= 0.10, OR = 5.47, 95%CI = 0.39 to 76.39).

In the present series, patients who underwent one-step hepatectomy presented less postoperative complications. All in one-step strategy was not feasible for all of our patients especially those who presented with synchronous bilobar disease and/or diffuse peritoneal carcinomatosis [36-38]. In addition, the lowest morbidity after one-step surgery might be due to the fact that this was not proposed routinely to the majority of patients but to highly selected patients. Previously, series reported a higher rate of morbi-mortality after one-step surgery as soon as the majority of patient underwent one-step resection of all macroscopic bilobar liver disease and other major abdominal resections [5,39]. Yet, we believe that if the resection is not risky and technically possible in one-step, this should be proposed [28,40]. Furthermore, the recurrence rate following one-stage ultrasonically guided liver resection was reported to be similar to that reported after two-stage liver resection [28]. In a particular way, we always discuss a one-step hepatectomy with multiple radiofrequency ablations of all lesions each time when the patient did not received more than 6-8 cycles of chemotherapy.

Lam et al. [39] reported a systemic review of 459 patients with initially unresectable LM from CRC. The majority of patients had preoperative chemotherapy (88%). Postoperative morbidity and mortality after the first-step were 17% and 0.5%, respectively. Portal vein occlusion was used in 76% of patients. Ultimately, 352 of the initial 459 (77%) patients underwent the second-step of hepatectomy (major liver resection 84%). Postoperative morbidity and mortality after the second-hepatectomy were 40% and 3%, respectively. Median overall survival was 37 months (range: 24-44 months) in patients who completed both stages. In patients who did not complete both stages, median survival was 16 months (range: 10-29 months). The 3-year disease-free survival rate was 20% (range: 6-27%).

Concerning factors related to the occurrence of 90 days postoperative mortality, the small number of dead vs. alive patients (n= 4 vs. 35) did not allowed appropriate statistical analyzes. Thus, we observed more chemotherapy cycles in dead vs. alive patients (16.5 vs. 8.6, respectively), major liver resections were more observed in dead patients (75% vs. 26%, respectively) as well as the need of postoperative blood transfusions (75% vs. 6%, respectively). These 3 reported factors, when pooled together could increase the rate of mortality after major hepatectomy by 3 to 5 folds. Surprisingly, dead patients did not present with more severe histopathological liver parenchyma injuries related to bio-chemotherapy such as steatosis, steatohepatitis and/or sinusoidal lesions. Yet, we do not know whether this was due to the fact that most of the patients underwent a two-step surgery with a relatively long period of time of interruption of systemic chemotherapy.

Finally, a significant gain of survival rates in highly selected patients for whom radical surgery was performed compared to patients who had incomplete or no surgery. This is conform to several other reported series of hepatectomies for LM from CRC reporting a relatively high rate of 3 and 5-year survival after radical liver resection or re-resection in highly selected patients in specialized centers [5,30,39,41-43]. For these patients, the important point would be to determine the impact of initial aggressive oncological management by the most appropriate drugs that would induce the best response rate, rendering resectable, initially unresectable patients [8,11,12,38,39]. This emphasizes the importance of including patients in appropriate prospective trials to better determine the impact of multimodal

therapies in patients with CRC liver metastatic disease including tri-regimen chemotherapies associated to biotherapies [17].

In conclusion, initially hardly or unresectable patients with LM from CRC can be resected usually by two-step hepatectomy, after aggressive down-sizing bio-chemotherapy with acceptable morbi-mortality. Studying predictive factors of failure and complications by including such patients in prospective randomized trials may help us to find the best potentially curative therapies for them.

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