RESEARCH ARTICLE

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Addition of bevacizumab to preoperative chemotherapy for colorectal liver metastases does not increase perioperative morbidity and mortality

Hepatic Oncology

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Summary points

- Bevacizumab administration in neoadjuvant setting for patients with colorectal liver metastases is a well established clinical practice.
- The patients with colorectal liver metastases that receive bevacizumab as part of neoadjuvant systemic therapy usually have been diagnosed with more advanced liver disease.
- An interval of 6–8 weeks between termination of neoadjuvant bevacizumab and hepatectomy is followed by most surgical teams worldwide.
- Neoadjuvant bevacizumab does not have an impact on perioperative complications after hepatectomy.
- There does not seem to be a statistically significant difference in overall and specific complications between patients that receive either oxaliplatin-based neoadjuvant chemotherapy or irinotecan-based neoadjuvant chemotherapy, both combined with bevacizumab.
- The patients who received more than eight cycles of chemotherapy demonstrate a higher rate of perioperative complications.

SUMMARY: **Aim:** Patients with colorectal liver metastases (CRLM) benefit from liver resection. Bevacizumab is commonly used in these patients resulting in a greater number of patients receiving an operation for a potentially curative liver resection, with initially unresectable liver metastases. Our purpose was to evaluate the effect of preoperative bevacizumab administration on perioperative complications in patients undergoing hepatic resection for CRLM. **Methods:** A retrospective analysis of patients undergoing hepatic resection for CRLM who received only neoadjuvant chemotherapy (chemotherapy group, $n = 133$), or neoadjuvant chemotherapy and bevacizumab (chemotherapy and bevacizumab group, $n = 103$). We compared surgical characteristics, perioperative complications and postoperative liver function. **Results:** The type of liver resection (minor vs major liver resection) was comparable in the two groups (major liver resection 52.6 vs 62.1%, $p = 0.144$). The addition of bevacizumab to preoperative chemotherapy does not affect the frequency (chemotherapy group vs chemotherapy and bevacizumab group, 35.3 vs 38.8%, $p = 0.581$), severity (major complications, 20.3 vs 19.4%, $p = 0.487$) and type of perioperative complications. Preoperative administration of bevacizumab was associated with a higher peak of postoperative alanine aminotransferase levels but did not affect functional recovery of the liver. **Conclusion:** Neoadjuvant administration of bevacizumab was not associated with an increased risk of postoperative complications after hepatic resection and did not affect

KEYWORDS

- bevacizumab • colorectal
- liver metastases • surgical complications

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the liver's functional recovery. Patients receiving more than eight cycles of bevacizumab are at an increased risk to develop perioperative complications.

Colorectal cancer is the third most common cancer and the third leading cause of cancer-related deaths worldwide [1,2]. Approximately 50% of patients develop liver metastases during the course of colorectal cancer [3,4], with half of these categorized as synchronous, and the rest as metachronous colorectal liver metastases (CRLM) [5,6]. The median survival rate for nonsurgically treated CRLM ranges from 5.7 to 19 months and for patients receiving no treatment at all, the average survival rate is just 7.4 months [7].

Surgical resection of liver metastases greatly increases the life expectancy of these patients. The median 5-year survival rates for surgically treated CRLM approach 35–40%, indicating the surgical removal of CRLM as the 'gold standard' treatment approach for these patients [8]. Unfortunately, despite the great advances in liver surgery in recent years, only 10–15% of patients present with resectable liver disease [9,10].

Several retrospective studies demonstrate the beneficial effects of neoadjuvant chemotherapy in the treatment of patients with CRLM, thus being a part of the therapeutic approach of these patients more and more often [11,12]. One of the main objectives of preoperative chemotherapy is to increase the number of patients that may be eligible for liver resection by downsizing the liver metastases [13]. If liver disease in patients with unresectable CRLM becomes resectable after preoperative chemotherapy, 5-year survival rates can reach up to 30% [14].

Bevacizumab is an antiangiogenic agent. It is a humanized monoclonal antibody targeting VEGF. More specifically, it targets and binds VEGF-A isoform, inhibiting in this way the interaction of this growth factor with its receptor VEGFR. Disruption of this important pathway deprives malignancies an essential component of their further development, neo-angiogenesis.

In patients with CRLM, bevacizumab can be given in combination with other chemotherapeutic agents (5-fluorouracyl, irinotecan, oxaliplatin) in the context of preoperative chemotherapy, and it has been shown to increase the response to liver metastases leading to possibly a greater number of patients with initially unresectable liver metastases to receive a potentially curative liver resection [15]. The addition of bevacizumab has been shown to improve the progression-free survival in

patients with unresectable CRLM [16,17]. As mentioned above, bevacizumab is administered in combination with cytotoxic chemotherapy. Out of these chemotherapeutic regimens, the most frequently administered are the oxaliplatin-based regimens and irinotecan-based regimens. It has been reported that irinotecan induced steatosis and steatohepatitis [18] as well as an oxaliplatin-induced sinusoidal injury [19] can potentially lead to an increased morbidity and mortality following hepatectomy [18,20].

The addition of bevacizumab to preoperative chemotherapy for CRLM, has raised concerns regarding the safety of hepatectomy in patients treated with this biological agent preoperatively because of its reported complications when administered [21–24]. Additionally another reason of concern was the fact that VEGF in addition to angiogenesis, has been found to be involved in many physiological processes, particularly important after hepatectomy, such as hepatocyte proliferation, hepatic recovery and wound healing [25–27].

The studies reported so far on patients receiving bevacizumab have demonstrated conflicting results, indicating in some cases a difference in complication rates between patients who received or did not receive preoperative bevacizumab, but in other cases no difference was recorded [28–31]. The primary objective of this study was to assess the effect of preoperative bevacizumab on perioperative morbidity and mortality in patients undergoing hepatic resection for CRLM.

Materials & methods

The electronic patient records of patients who had liver resection at the Royal Marsden Hospital and at The London Clinic for CRLM from January 2005 to December 2012 were evaluated and a retrospective liver resection database was created. In this database were included patients who underwent liver resection for CRLM and who received preoperative chemotherapy with or without bevacizumab. Patients who underwent liver resection without having received preoperative chemotherapy were excluded from this study.

For each patient, demographic characteristics were collected (sex, age at diagnosis of primary tumor and metastatic disease, age at hepatectomy) and data on the primary colorectal tumor

(primary site, stage, time and type of surgical removal). Regarding CRLM, characteristics such as: the number and distribution of metastases at the time of diagnosis, the time elapsed between the diagnosis of primary tumor and the diagnosis of CRLM were collected. Synchronous CRLM were defined as those diagnosed over a period up to 3 months after the diagnosis of the primary tumor, and the rest were defined as metachronous CRLM. With regards to the preoperative chemotherapy, the type of preoperative chemotherapy received, the number of cycles of chemotherapy received and the time elapsed between discontinuation of chemotherapy and hepatectomy were recorded. The type of hepatectomy, the postoperative complications and their management and the hospitalization time of patients were also collected. Liver functional parameters including serum total bilirubin, albumin level, international normalized ratio (INR) values and serum levels like alanine aminotransferase (ALT) were also documented.

The extent of liver disease in all patients was determined using magnetic resonance imaging. Computed tomography of the chest, abdomen and pelvis was performed to exclude extrahepatic metastases. For the same reason most of the patients additionally underwent fluorodeoxyglucose-positron emission tomography. Tumor response to chemotherapy was assessed using magnetic resonance imaging and according to Response Evaluation Criteria in Solid Tumors. Resectability was evaluated by interdisciplinary review which included a surgical expertise. Both the presence of progression of disease under chemotherapy and the presence of extrahepatic disease were not absolute contraindications for hepatectomy.

• Groups

Patients were divided into two groups. Patients of both groups received preoperative chemotherapy. The first group included patients receiving only chemotherapy (chemotherapy group) while the second group comprised patients receiving chemotherapy and bevacizumab (chemotherapy and bevacizumab group). Subgroups were created based on the cytotoxic chemotherapeutic regimens, which included either oxaliplatin-based chemotherapy or irinotecan-based chemotherapy. The creation of these subgroups aimed at finding any synergistic effect of bevacizumab with oxaliplatin or irinotecan in causing perioperative complications.

• Liver resection

All resections were initiated with curative intent. The type and extent of liver resection were determined by the liver surgeon within the multidisciplinary meeting. However these decisions were not binding for the liver surgeon who could modify the surgical plan depending on intra-operative findings and mainly according to the findings of intra-operative ultrasound which was performed on all patients. Intra-operative ultrasound aimed to detect occult tumors and to plan appropriate resections.

Portal vein embolization was performed 4 weeks before surgery in cases and extended hepatectomy was planned if the future liver remnant was deemed inadequate (future liver remnant to whole liver volume ratios <30%). Pre-, intra- or post-operative radiofrequency ablation was not a criterion for exclusion from the study.

Major hepatectomy was defined as resection of three or more liver segments. Liver resections were classified as anatomical or nonanatomical resections according to the segmental anatomy of the liver. The purpose of a nonanatomic resection was to preserve as much as possible of liver parenchyma (parenchymal sparing surgery). Resections were defined as either complete with negative microscopic margins (R0) or incomplete with microscopically (R1) or macroscopically (R2) positive margins.

Both the technique of liver parenchymal transection and the systemic use of Pringle maneuver depended on the surgeon's preference.

In patients with a primary tumor *in situ*, the decision was taken by the multidisciplinary team whether the indicated approach should be the synchronous resection of the primary tumor and CRLM or the 'liver first' approach. Determinants of the above decision were the general health of the patient and the extent of necessary hepatectomy.

Complications

Postoperative complications were graded on a 1–5 scale according to the Clavien Classification of Surgical Complications [32]. Grade I and II complications were considered as minor complications, grade III and IV as major complications, and grade V were the postoperative deaths. Perioperative mortality was defined as deaths that occurred during the operation or in the same hospital admission as the surgery or within 30 days from the operation.

To quote complications and their management in both groups, complications were categorized

into: wound complications (dehiscence or infection), pulmonary complications (pleural effusion, pneumonia, respiratory failure), hepatobiliary complications (bile leak, liver insufficiency), postoperative bleeding, cardiovascular complications (arrhythmia, myocardial infarction, newly diagnosed hypertension requiring medication), bowel complications (ileus requiring re-operation, enteric anastomotic leak in case of synchronous resection of primary tumor and CRLM), intraperitoneal fluid collections (other than biloma), thromboembolic complications (pulmonary embolus, DVT), sepsis of unknown cause and others.

Based on the known complications of bevacizumab (wound healing complications, thrombotic events, bleeding, hematologic toxicity) and the known actions of VEGF in physiological processes (hepatocyte proliferation, hepatic recovery and wound healing) we also proceeded in a different categorization of complications. This second categorization aimed at a more targeted comparison of complications between the two main groups and the subgroups. So, complications were categorized into: healing complications (wound healing, bowel anastomosis healing), thromboembolic complications (pulmonary embolus, deep venous thrombosis, myocardial infarction), postoperative bleeding, hepatic failure, bile leak, infections (wound infections, pneumonia, sepsis of unknown cause, pseudomembranous colitis, urinary tract infection), pulmonary/cardiovascular complications (pleural effusion, respiratory failure, arrhythmia, hypertension) and others.

Statistical analysis

Statistical analyses were performed with the Statistical Package of the Social Sciences (SPSS), version 17.0. Categorical variables were compared with the chi-square or Fisher's exact test (in cases of low frequencies) and continuous variables were compared with the Mann–Whitney U test. A p-value of less than 0.05 was considered statistically significant.

Results

• Patient demographics & tumor characteristics

From January 2005 to December 2012, 236 patients who received preoperative chemotherapy with or without bevacizumab, underwent liver resection for CRLM at Royal Marsden Hospital and at The London Clinic. The chemotherapy

group comprised 133 patients and the chemotherapy and bevacizumab group comprised 103 patients. The demographic characteristics of the patients and the characteristics of CRLM at diagnosis are shown in **Table 1**. Patients who received bevacizumab were younger and displayed more advanced stages of the disease. The patients of this group showed a smaller interval between the diagnosis of primary tumor and the diagnosis of CRLM (11 vs 5 months, $p = 0.001$) and more often their metastases were synchronous (51.1–72.8%, $p = 0.001$). The number of metastases and the overall size of liver metastases were greater in patients treated with bevacizumab. Finally, the majority of patients in the chemotherapy and bevacizumab group manifested bilobar liver metastases (30.8 vs 55.3%, $p < 0.001$). All the above data suggest that patients receiving bevacizumab presented a more advanced liver disease as well as a worse long-term prognosis. At the time of hepatectomy, 48 patients had the primary tumor *in situ*. Thirty-nine of them underwent synchronous resection of the primary tumor and CRLM, and for the remaining nine patients there was a liver-first approach.

• Preoperative systemic therapy

The patient's primary oncologist decides to add or not bevacizumab in a patient's chemotherapy regimen. The dose at which the bevacizumab was administered was 5 mg/kg and it was given as an intravenous infusion every 2 weeks, except the patients who received CAPOX or CAPIRI and who received bevacizumab every 3 weeks.

The main cytotoxic chemotherapy regimens administered to patients were FOLFOX (oxaliplatin/5-FU), FOLFIRI (irinotecan/5-FU), CAPOX (oxaliplatin/capecitabine) and CAPIRI (irinotecan/capecitabine). These regimens were received by 92.4% of patients (**Table 2**).

Between the two groups, there was heterogeneity regarding the exact chemotherapeutic regimens received ($p < 0.001$; **Table 2**). However when we compared the two groups with regards to administration of the oxaliplatin-based chemotherapy or the irinotecan-based chemotherapy, although the percentage of patients receiving irinotecan-based chemotherapy was higher in the group that received bevacizumab, this difference did not reach the level of statistical significance (oxaliplatin-based chemotherapy 69.9 vs 61.2%, irinotecan-based chemotherapy 24.1 vs 35%, $p = 0.082$).

Table 1. Demographics and tumor characteristics.

Variable	Chemotherapy (n = 133)	Chemotherapy and bevacizumab (n = 103)	Total (n = 236)	p-value
Gender:				0.754 [†]
– Male	84 (63.2%)	63 (61.2%)	147	
– Female	49 (36.8%)	40 (38.8%)	89	
Age at hepatectomy median (range)	63.1 (30.9–82.9)	61 (29.3–85.2)	62.1 (29.3–85.2)	0.036 [‡]
Performance status prior to hepatectomy:				0.351 [†]
– 0	68 (51.1)	60 (58.3)	128 (54.2)	
– 1	58 (43.6)	35 (34)	93 (39.4)	
– 2	6 (4.5)	8 (7.7)	14 (6)	
– 3	1 (0.8)	0 (0)	1 (0.4)	
Age at diagnosis of liver metastases median (range)	62.7 (30.5–82.5)	59.9 (28.1–82.5)	61.5 (28.1–82.5)	0.042 [‡]
Interval between primary and CLM, mean (range), months	11 (0–89)	5 (0–67)	8 (0–89)	0.001 [‡]
Synchronous vs metachronous				0.001 [†]
– Synchronous	68 (51.1)	75 (72.8)	143 (60.6)	
– Metachronous	65 (48.9)	28 (27.2)	93 (39.4)	
Number of liver metastases median (range)	2 (1–11)	3 (1–18)	2 (1–18)	<0.001 [‡]
Distribution of lesions:				<0.001 [†]
– Unilobar	92 (69.2)	46 (44.7)	138 (58.5)	
– Bilobar	41 (30.8)	57 (55.3)	98 (41.5)	
Size of bigger lesion median (range), mm	25 (7–200)	30 (10–103)	27 (7–200)	0.207 [‡]
Overall size of lesions median (range), mm	34 (7–200)	60.5 (10–227)	41 (7–227)	0.003 [‡]
Extrahepatic disease:				0.591 [†]
– No	118 (88.7)	89 (86.4)	207 (87.7)	
– Yes	15 (11.3)	14 (13.6)	29 (12.3)	
Primary tumor <i>in situ</i> at hepatectomy [§] :				0.048 [†]
– Yes	21 (15.8)	27 (26.2)	48 (20.3)	
– No	112 (84.2)	76 (73.8)	188 (79.7)	

Synchronous: diagnoses of colorectal liver metastases within 3 months from the diagnosis of primary tumor overall size of lesions: sum of diameters of all liver lesions.

[†]Pearson chi-square test.[‡]Mann-Whitney U test.[§]'Liver first approach' or 'synchronous resection'.

In the total population of the study, patients receiving the irinotecan-based chemotherapy underwent more often major liver resection than patients receiving the oxaliplatin-based chemotherapy (69.1 vs 50%, respectively, $p = 0.008$). Specifically in the chemotherapy group 75% of patients receiving irinotecan-based chemotherapy underwent a major liver resection versus 43% of patients receiving oxaliplatin-based chemotherapy ($p = 0.002$). On the other hand, in the chemotherapy and bevacizumab group, the percentages were 63.9 versus 60.3%, respectively ($p = 0.725$).

The patients of chemotherapy and bevacizumab group received more cycles of chemotherapy (mean 7.8 vs 6.1, $p < 0.001$) and on an average received 7.8 cycles of bevacizumab. In both institutions where the patients were operated, the general policy is to wait 6–8 weeks from the last dose of bevacizumab to the time of surgery. After the

last dose of bevacizumab, some patients received another one or two cycles of cytotoxic chemotherapy before surgery in an attempt to control potential disease progress in that period of time. The median interval between the last administration of chemotherapy and surgery was 65.5 days for the chemotherapy group and 61.5 days for the chemotherapy and bevacizumab group ($p = 0.284$). The median interval between the last administration of bevacizumab and surgery was 65 days.

• Liver resection

The type of liver resection (minor vs major liver resection) was comparable in the two groups (Table 3). Also, the two groups were comparable regarding the intraoperative blood loss ($p = 0.255$) and the blood transfusion requirements ($p = 0.788$). In total, 39 patients (16.5%) underwent synchronous resection of primary

Table 2. Preoperative systemic therapy.

Variable	Chemotherapy (n = 133)	Chemotherapy and bevacizumab (n = 103)	Total (n = 236)	p-value
Types of preoperative chemotherapy [†] :				<0.001*
– Oxaliplatin/5-FU (FOLFOX)	25 (18.8)	42 (40.8)	67 (28.4)	
– Irinotecan/5-FU (FOLFIRI)	28 (21.1)	33 (32)	61 (25.8)	
– Oxaliplatin/capecitabine (CAPOX)	64 (48.1)	21 (20.4)	85 (36)	
– Irinotecan/capecitabine (CAPIRI)	2 (1.5)	3 (2.9)	5 (2.1)	
– Other regimens	7 (5.3)	3 (2.9)	10 (4.2)	
– Undetermined/unknown	7 (5.3)	1 (1)	8 (3.4)	
Oxaliplatin vs irinotecan:				0.082
– Oxaliplatin-based chemotherapy	93 (69.9)	63 (61.2)		
– Irinotecan-based chemotherapy	32 (24.1)	36 (35)		
Second- or third-line chemotherapy				0.758 [§]
– Yes	7	4	11	
– No	119	98	217	
– Undetermined/unknown	7	1	9	
Total number of chemotherapy cycles median (range), mean	5.5 (1–24), 6.1	6 (4–24), 7.8	6 (1–24), 6.8	<0.001 [¶]
Total number of bevacizumab cycles median (range), mean		6 (3–24), 7.3		
Time from last chemotherapy to surgery, median (range), mean, days	65.5 (27–195), 73.2	61.5 (23–154), 66	62.5 (23–195), 70.1	0.284 [¶]
Time from last bevacizumab dose to surgery, median (range), mean, days		65 (35–194), 75.9		

[†]For the patients who received second- or third-line neoadjuvant chemotherapy. The above table shows the last chemotherapy regimens before surgery.

[‡]Pearson chi-square test.

[§]Fisher's exact test.

[¶]Mann–Whitney U test.

tumor and CRLM (16.5%), 15 patients (11.3%) from the chemotherapy group and 24 patients (23.3%) from the chemotherapy and bevacizumab group ($p = 0.014$). The two groups did not differ regarding patients who underwent PVE before the surgery (8.3% [11/133] vs 11.7% [12/103], $p = 0.385$) but the use of pre-, intra- or post-operative radiofrequency ablation was more common in the chemotherapy and bevacizumab group (12% [16/133] vs 20.4% [21/103], $p = 0.08$). R0 resection was achieved in 202 patients (85.6%), 117 patients (88%) in the chemotherapy group and 85 patients (82.5%) in the chemotherapy and bevacizumab group (88 vs 82.5%, $p = 0.237$). From our data it is shown that from the 23 patients who underwent PVE 20 had R0 resection, 2 R1 and 1 R2 (CC 10 R0, 1 R1 vs Bev 10 R0, 1 R1, 1 R2).

Thirteen patients (5.5%) from both groups showed pathologic complete response (PCR). Six (4.5%) of them from the chemotherapy group and 7 (6.8%) from the chemotherapy and bevacizumab group ($p = 0.445$). These patients showed better disease-free survival (DFS) ($p = 0.013$) but not better overall survival (OS)

($p = 0.071$). Patients with radiological complete response (RCR) were more likely to show PCR compared with the rest of the patients (42.8% [3/7] vs 4.4% [10/229] $p = 0.004$) thus making the RCR an important predictor for the presence of PCR.

• Complications

From a total of 236 patients, 87 patients (36.9%) experienced 102 complications. The overall complication rate is presented in **Table 3** and their management is presented in **Table 4**. Forty-seven patients (19.9%) experienced major complications. There was no difference between the two groups either regarding the complication rate (34.6 vs 39.8%, $p = 0.410$) or regarding the severity of complications (major complications 20.3 vs 19.4%, $p = 0.487\%$). Also, there was no difference between the two groups on the kind of complications demonstrated (**Table 4**).

When we grouped related complications, in an attempt to do so based on the known complications of bevacizumab and analyzed the groups for differences, there were no statistically significant differences found (**Table 5**).

Table 5 demonstrates the complication distribution in patients that received the oxaliplatin-based chemotherapy and the irinotecan-based chemotherapy with or without bevacizumab. There was no statistically significant difference in overall and specific complications between these groups.

Our data show no difference in the occurrence of complications in patients who had received bevacizumab >8 weeks or in those who had taken bevacizumab <8 weeks before resection ($p = 0.266$). As far as the effect of the number of cycles of bevacizumab in perioperative complications was concerned, our data show that those who received more than eight cycles of bevacizumab exhibited complications more often (59.3 vs 31.6 respectively, $p = 0.011$). The above difference was maintained in multivariate analysis

(variables including cycles of bevacizumab, type of resection) ($p = 0.024$).

There was no difference in mortality between the two groups. There were three deaths during the hospital stay after surgery, one in the chemotherapy group and two in the chemotherapy and bevacizumab group ($p = 0.582$). The cause of death of the patient from within the chemotherapy group was sepsis because of an infected intra-abdominal collection. Regarding the chemotherapy and bevacizumab group, one death occurred due to a pneumonia which developed postoperatively and the other one due to liver insufficiency.

• Recovery of liver function

Pre-operative serum liver function parameters (bilirubin, albumin, INR) were comparable between

Table 3. Liver resection.

Variable	Chemotherapy (n = 133)	Chemotherapy and bevacizumab (n = 103)	Total (n = 236)	p-value
Types of liver resection:				0.144 [†]
– Major	70 (52.6)	64 (62.1)	134 (56.8)	
– Minor	63 (47.4)	39 (37.9)	102 (43.2)	
Synchronous resection of primary tumor:				0.014 [†]
– Yes	15 (11.3)	24 (23.3)	39 (16.5)	
– No	118 (88.7)	79 (76.7)	197 (83.5)	
Portal vein embolization:				0.385 [†]
– Yes	11 (8.3)	12 (11.7)	23 (9.7)	
– No	122 (91.7)	91 (88.3)	213 (90.3)	
RFA in addition to resection (pre-, intra-, post-operatively):				0.08 [†]
– Yes	16 (12)	21 (20.4)	37 (15.7)	
– No	117 (88)	82 (79.6)	199 (84.3)	
Resection margins:				0.376 [†]
– R0	117 (88)	85 (82.5)	202 (85.6)	
– R1	14 (10.5)	14 (13.6)	28 (11.9)	
– R2	2 (1.5)	4 (3.9)	6 (2.6)	
Resection margins for R0 resection, median (range), mm	9 (1–40), 11.6	10 (1–85), 14.7	10 (1–85), 12.8	0.502 [‡]
Estimated blood loss, ml, median (range)	600 (50–2000)	630 (100–1700)	630 (50–2000)	0.255 [‡]
Blood transfusion requirements, no	33 (24.8)	24 (23.3)	10 (2–92), 13.7	0.788 [†]
Postoperative complications:				0.581 [†]
– Yes	47 (35.3)	40 (38.8)	87 (36.9)	
– No	86 (64.7)	63 (61.2)	149 (63.1)	
Major vs minor complications:				0.487 [†]
– Minor	27 (20.3)	20 (19.4)	47 (19.9)	
– Major	20 (15)	20 (19.4)	40 (16.9)	
Mortality	1 (0.75)	2 (1.94)	3 (1.27)	0.582 [§]

Major complications: Grade 3–4 according to Clavien Classification of Surgical Complications.

Minor complications: Grade 1–2 according to Clavien Classification of Surgical Complications.

[†]Pearson chi-square test.

[‡]Mann–Whitney U test.

[§]Fisher's exact test.

RFA: Radiofrequency ablation.

Table 4. Postoperative complications and their management.

Variable		Chemotherapy (n = 133)		Chemotherapy and bevacizumab (n = 103)		p-value
Type of complication		n = 47	Management	n = 40	Management	0.581
Wound		10		7		0.831
	Infection	8	6: antibiotics, 2: debridement	5	4: antibiotics, 1: debridement	0.698
	Dehiscence	2	Conservatively	2	2: conservatively, 1: reoperation	0.999
Pulmonary		10		8		0.943
	Pleural effusion	4	3: conservatively, 1: drainage	6	4: conservatively, 2: drainage	0.339
	Pneumonia	5	3: antibiotics, 2: antibiotics plus mechanical ventilation	2	Antibiotics	0.473
	Respiratory failure	1	Mechanical ventilation	0		0.999
Liver/biliary tree		14		14		0.470
	Bile leak	11	4: conservatively* 7: stent insertion	7	1: conservatively* 6: stent insertion	0.672
	Liver insufficiency	3	Conservatively	7	Conservatively	0.108
Intra-abdominal bleeding/ hematoma		2	2: re-operation	4	1: re-operation, 2: transfusion, 1: drainage	0.408
Cardiovascular		8		6		0.951
	Arrhythmia	5	Cardiovascular medication	3	2: Cardiovascular medication 1: electrocardioversion	0.999
	Myocardial infarction	1	ICU/organ support	2	ICU/organ support	0.582
	Hypertension	2	Cardiovascular medication	0		0.506
	Pericarditis	0		1	Conservatively	0.436
Bowel		2		2		0.999
	Anastomotic leak	1	Re-operation	2	2: re-operation	0.582
	Ileus	1	Re-operation	0		0.999
Intra-abdominal collections		5	3: drainage, 2: conservatively	3	Drainage	0.999
Urinary tract infection		0		1	Antibiotics	0.436
DVT/PE		0		2	1: LMWH, 1: LMWH plus IVC filter	0.189
Urinary bladder injury		1	Re-operation	0		0.999
Pseudomembranous colitis		1	Antibiotics	0		0.999
Sepsis of unknown cause		2	Antibiotics	2	Antibiotics	0.999

DVT: Deep venous thrombosis; LMWH: Low molecular weight heparin; PE: Pulmonary embolus.

the groups. For the first seven postoperative days, ALT was higher in the chemotherapy and bevacizumab group compared with the chemotherapy group, and this difference was statistically significant (postoperative days 1–4 $p < 0.001$, day 5 $p = 0.002$, day 6 $p = 0.006$ and day 7 $p = 0.012$). However, there was no difference in functional recovery of liver parameters (bilirubin, albumin, INR) between the groups (Figure 1).

Discussion

The beneficial effects of neoadjuvant chemotherapy in the treatment of patients with CRLM

have strengthened the use of this strategy in these patients [11,12]. One of the main objectives of preoperative chemotherapy is to downsize the liver metastases in patients with unresectable CRLM, in an attempt to make them candidates for potential curative liver resection [33,34].

However, the use of neoadjuvant chemotherapy is not confined only to patients with unresectable CRLM. In patients with resectable CRLM, the administration of neoadjuvant chemotherapy has started to play an important role, and it has been reported that neoadjuvant chemotherapy improves DFS and OS. At the same time it can

be used to distinguish the patients who respond to chemotherapy from the patients who do not respond to chemotherapy. This information is particularly useful both for a better selection of candidates for liver resection and in predicting the survival of these patients as well [35].

In recent years, the monoclonal antibody bevacizumab, which inhibits angiogenesis by binding to VEGF, has been gaining ground as far as the preoperative therapy regimens of patients with CRLM are concerned. It has been administered in combination with various cytotoxic chemotherapeutic regimens and has been reported to increase the OS in that cohort of patients [16,17,21].

Particularly important is the role of bevacizumab in the process of downsizing of CRLM, especially in patients with unresectable CRLM at the time of the diagnosis. Wong *et al.* reported, in a prospective study, the efficacy of neoadjuvant CAPOX combined with bevacizumab resulting in a conversion rate of 40% in their cohort of patients from initially considered unresectable to resectable liver metastases [15].

Significant advances in liver surgery in the recent decades have resulted in an expansion of the indications for hepatectomy in patients with CRLM as a more extended and complex hepatectomy can be performed without however increasing the morbidity and mortality. In addition to this, a point of intense skepticism for liver surgeons has been the safety of hepatectomy in patients who had received preoperative chemotherapy, because, as it has been shown, this therapy can have several implications in healthy liver parenchyma [18,19].

Although this skepticism did not prevent the expansion of indications for hepatectomy in patients with CRLM, it was not unfounded. Today we know that both irinotecan-induced steatosis and steatohepatitis [18] and oxaliplatin-induced sinusoidal injury [19] can potentially increase morbidity and mortality after hepatectomy [18,20].

Further skepticism regarding the safety of hepatectomy after preoperative chemotherapy was caused by the addition of bevacizumab to cytotoxic chemotherapy, with adverse effects on processes such as hepatocyte proliferation, hepatic recovery and wound healing [25–27]. So far the published clinical studies have not confirmed the fears of increased morbidity and mortality after preoperative administration of this agent [36–38]. Support to the safety of preoperative bevacizumab administration though was given by reported data by our team as well [39]. The main disadvantage of both our previous study and other published series is the small number of cases presented.

In this study, we present a great number of patients who received bevacizumab (103 patients) and also analyze the safety of its preoperative administration. The results of our study add support to the already published reports, highlighting the safety of the preoperative administration of bevacizumab. Comparing the postoperative morbidity of these patients with the morbidity of 133 patients who did not receive preoperative bevacizumab but only cytotoxic chemotherapy, we found no difference in the rate, the severity or nature of these complications. Additionally there was no difference in mortality between the two groups.

Table 5. Postoperative complications according to the receiving of cytotoxic chemotherapy.

Variable	All patients			Patients receiving oxaliplatin-based chemotherapy			Patients receiving irinotecan-based chemotherapy		
	Bev(-), n = 133	Bev(+), n = 103	p-value	Bev(-), n = 93	Bev(+), n = 63	p-value	Bev(-), n = 32	Bev(+), n = 36	p-value
Overall complications	47	40	0.581	31	20	0.836	12	20	0.137
Major complications	27	20	0.487	13	6	0.518	5	13	0.198
Healing	3	4	0.702	2	3	0.364	1	1	0.999
Thromboembolic	1	4	0.171	1	2	0.566	0	2	0.494
Bleeding	2	4	0.408	2	1	0.999	0	3	0.241
Liver failure	3	7	0.108	3	5	0.270	0	2	0.494
Bile leak	11	7	0.672	5	2	0.702	5	5	0.999
Infections	16	11	0.747	11	6	0.650	3	4	0.999
Pulmonary/cardiovascular complications	12	9	0.939	7	2	0.314	4	7	0.438
Others	7	3	–	4	0	–	2	2	–

Figure 1. Comparing the postoperative liver function of patients who received with those who did not receive bevacizumab preoperatively. Liver function was measured by recording the median values of (A) ALT; (B) total bilirubin; (C) albumin; (D) INR. Although the rates of ALT, between the first and seventh postoperative days, were higher for the patients who received bevacizumab ($p = 0.001$), the values of total bilirubin, albumin and INR did not differ between the two groups. ALT: Alanine aminotransferase; Bev: Bevacizumab; INR: International normalized ratio.

Lubezky N *et al.* who also studied a large series of patients who received preoperative bevacizumab, expressed some concerns regarding the safety of a preoperative administration of bevacizumab in patients who undergo synchronous resection of the primary tumor [31], however as their number of patients who underwent a synchronous removal of primary tumor was small, this concern was not supported by a statistically significant difference between the two groups. Our data does not support the findings of Lubezky N *et al.* In our study 39 patients underwent synchronous resection of primary tumor. Enteric anastomotic leak occurred in one

patient (6.7%) from the chemotherapy group and in two patients (8.3%) from the chemotherapy and bevacizumab group ($p = 0.999$).

Postoperative recovery of liver function is particularly important especially after extended hepatectomy has taken place. As shown by Wicherts *et al.*, and also demonstrated in our series, the postoperative recovery of liver function was similar in the two groups [40]. The serum markers of liver function were comparable between the two groups both pre- and regarding the first seven post-operative days. A difference, which however did not reach statistical significance, was the fact that while the higher

bilirubin value in patients of the chemotherapy and bevacizumab group was observed on the first postoperative day, in patients of the chemotherapy group it was observed on the third postoperative day. The values of ALT, which were used as markers of cellular damage, were higher in patients treated with bevacizumab.

In studies addressing the effect of preoperative administration of bevacizumab on perioperative morbidity, most of the patients received bevacizumab in combination with oxaliplatin- or irinotecan-based chemotherapy [36–39]. A possible synergistic effect of some of these cytotoxic chemotherapeutic regimens with bevacizumab in increasing perioperative complications was investigated in this study. Our results indicate that the addition of the bevacizumab in preoperative chemotherapy does not affect perioperative complications regardless of the type of cytotoxic chemotherapy it is co-administered with. Both patients who received oxaliplatin-based chemotherapy as well as those who received irinotecan-based chemotherapy, showed no difference in the rate, the severity or type of perioperative complications that can be attributed to concurrent administration or not of bevacizumab.

Although there is no conclusive data on how much time should elapse between the discontinuation of bevacizumab and the hepatectomy, most teams wait 6–8 weeks before they proceed to hepatectomy. A similar tactic is also followed by our team. This strategy was outlined because of the relatively long half-life of bevacizumab, which is 21 days. The effect of this time in the frequency of perioperative complications is unknown. In the literature one can find data supporting that surgery sooner than 8 weeks following discontinuation of bevacizumab leads to increased complications [37], but on the other hand there are data supporting that this time interval does not affect perioperative complications [38]. Our data show no difference in the occurrence of complications in patients who had received bevacizumab <8 weeks or in those who had taken bevacizumab >8 weeks before resection ($p = 0.266$).

With regards to the effect of the number of cycles of bevacizumab in perioperative complications, our data show that among patients who received bevacizumab, those who received more than eight cycles of bevacizumab exhibit complications more often (59.3 vs 31.6 respectively, $p = 0.011$). This difference was maintained in multivariate analysis

(variables including cycles of bevacizumab, type of resection) ($p = 0.024$). Although we have made this observation, we cannot be certain if this was due to the bevacizumab or the cytotoxic chemotherapy.

Although it has been reported that the preoperative administration of bevacizumab may be associated with a decreased incidence of postoperative liver insufficiency [38], we did not verify this hypothesis, as the incidence of postoperative liver failure in our series of patients, without reaching statistically significant levels, was more common in patients who received bevacizumab (2.3 vs 6.8%, $p = 0.108$).

The limitations associated with a retrospective study are acknowledged. The main limitation of the study is the heterogeneity of the two groups regarding the severity of the liver disease. As discussed above, patients who received bevacizumab showed more extensive liver disease. This difference in the extent of liver disease could potentially affect complication rates between the two groups. Another important limitation of the study is the heterogeneity of the two groups regarding the administered cytotoxic chemotherapy. Although this difference did not reach statistical significance, there is a tendency for patients receiving bevacizumab to have taken more often irinotecan-based chemotherapy and those who did not receive bevacizumab would more frequently receive oxaliplatin-based chemotherapy. This difference could again potentially affect complication rates between the two groups. This was one of the main reasons we performed a further analysis of the impact of preoperative bevacizumab administration on perioperative complications depending on the cytotoxic chemotherapeutic regimen which was co-administered.

Conclusion & future perspective

This study adds to the literature data with regards to the safety of liver resection in patients who received preoperative bevacizumab for CRLM. The large number (103 patients) of patients receiving bevacizumab preoperatively in this study in combination with what has been published on the safety of this biological agent, allows us to reach reliable conclusions. The addition of bevacizumab to preoperative chemotherapy does not affect the frequency, severity and type of perioperative complications, regardless of whether the patient underwent oxaliplatin-based or irinotecan-based chemotherapy. Among patients

who received bevacizumab the time elapsed between the discontinuation of bevacizumab and the hepatectomy does not appear to influence the perioperative complications. In contrast, patients who received more than eight cycles of bevacizumab seem to be at increased risk to develop perioperative complications.

Neoadjuvant systemic therapy will play central role in the management of CRLM in the future, with an increasing number of patients of this group undergoing liver resection, the safety of which is important to be established. Results from studies such as this could guide clinicians regarding the safety of bevacizumab's administration.

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Ethical conduct

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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