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Impact of Preoperative Bevacizumab on Complications After Resection of Colorectal Liver Metastases: Case-Matched Control Study

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Abstract
Background Chemotherapy may increase postoperative morbidity and mortality after liver surgery. Especially bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), could have a detrimental effect. To assess the impact of neoadjuvant bevacizumab on clinical outcome after hepatectomy for colorectal liver metastases (CRLMs) this case-matched control study was initiated.
Methods The multicentric data collection was performed in the Swiss HPB Center of the University Hospital Zurich (CH), the Department of Digestive Surgery and Transplantation Strasbourg (F), and the Division of Hepato-biliary-pancreatic surgery of "Josep Tureta" Hospital Girona (E). Consecutive patients operated onbetween July 2005 and December 2007 due to CRLMs who received neoadjuvant chemotherapy were assessed. Patients were divided in two groups: group A had neoadjuvant chemotherapy with bevacicumab, and group B had it without bevacizumab.
Results No differences in overall morbidity (56 vs. 40% in the bevacizumab and control groups, respectively, $p = 0.23$) or mortality could be documented. Similarly, the incidence of severe postoperative complications was not statistically different between the bevacizumab and control groups (31 and 18%, respectively, $p = 0.31$). Wound complications were comparable (11% in the bevacizumab group compared and 9% in the control group, $p = 1.00$). However, bevacizumab was associated with a significantly decreased incidence of postoperative hepatic insufficiency (7 vs. 20%, $p = 0.03$).
Conclusions No impact on the incidence or severity of complications by bevacizumab could be shown. Bevacizumab may even reduce the incidence of liver failure after liver surgery.

Mahfud Mahfud and Stefan Breitenstein contributed equally to this work. Dr. Mafhud is a Henri Bismuth fellow who spent 4 months at each of the centers involved in the study.

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Introduction

Systemic chemotherapy prior to resection of colorectal liver metastases (CRLMs) is increasingly advocated by modern interdisciplinary teams in many countries. However, the benefit and safety of this strategy remains controversial [1–5].

Bevacizumab (Bev) is a monoclonal antibody against vascular endothelial growth factor (VEGF) with antiangiogenic

properties. Bev is typically used in combination with other chemotherapeutic agents such as oxaliplatin, irinotecan, leucovorin, and 5-fluorouracil (5-FU) for treatment of patients with CRLMs [6–8]. In addition to its direct antiangiogenic effects, Bev may also improve the delivery of chemotherapy by altering tumor vasculature and decreasing the elevated interstitial pressure in tumors [6, 7, 9, 10]. It is therefore postulated that Bev treatment may result in a high rate of disease stability, with a substantial impact on survival and progression-free survival in the setting of metastatic colorectal cancer [11–13].

Chemotherapeutic agents that inhibit tumor growth also have inherent side effects on healthy tissue. For instance, oxaliplatin and irinotecan may alter the histomorphologic characteristics of the liver [14–19], and Bev has been associated with bleeding, thrombosis, impaired wound healing, and liver regeneration [20]. The effect of preoperative Bev with chemotherapeutic agents (particularly oxaliplatin and irinotecan) on posthepatectomy complications remains under debate [17, 21]. Three studies from North America failed to show an increase in postoperative complications upon adding Bev to preoperative chemotherapy [22–24]. However, the study by D'Angelica et al. [22] included only 16 patients treated with Bev; and the studies by Reddy et al. [23] and Kesmodel et al. [24] had relevant methodologic shortcomings due to lack of statistical adjustments and matching of patient groups. Also, all studies were carried out in the United States, where the chemotherapy is predominantly oxaliplatin-based.

To address a putative negative impact of the use of Bev on postoperative outcome, we designed a European multicentric study in three established surgical centers that maintained well documented databases. We evaluated consecutive patients treated with an oxaliplatin- or irinotecan-based chemotherapy regimen, with and without Bev, regarding the incidence and severity of postoperative complications including evidence of hepatic insufficiency. Owing to the relatively long half-life of Bev ($\sim$20 days) [8, 25], we also focused on the interval between the last dose of Bev and the initiation of surgery—what we called the "drug holiday"—on postoperative outcome.

Methods

Study design

Patients who underwent liver resection owing to CRLMs from three European hepatopancreatobiliary centers (Girona, Spain; Strasburg, France; Zurich, Switzerland) between July 2005 and December 2007 were retrospectively assessed for eligibility using well established databases in each respective center. Forty-five consecutive patients treated with neoadjuvant chemotherapy with Bev were identified. An independent reviewer (M.P.) matched these patients manually by screening a database from 2007 one-by-one against patients who had received neoadjuvant chemotherapy without Bev. Matching criteria were age, number of chemotherapeutic cycles, number of metastases, size of metastases, bilobularity of the disease, synchronous or metachronous metastases, presence of extrahepatic disease, simultaneous or staged hepatectomy, and associated extrahepatic procedures. Results were statistically adjusted according to potential confounders (<ClinicalTrials.gov> NCT 00875147).

Outcome measures

Data on outcome parameters were reviewed and extracted from the prospective database at each center. The primary endpoint was the occurrence of postoperative complications, graded according to a validated therapy-oriented complication score on a five-point scale [26]. Severe complications were defined as events requiring intervention under local or general anesthesia or treatment in the intensive care unit (ICU) (complication grade $\geq$ 3a). Specific hepatic complications (e.g., subphrenic abscess, bile leak, bilioma, liver insufficiency) were recorded in detail. Postoperative liver insufficiency was defined according to the 50–50 criterion—prothrombin time <50% of normal and serum bilirubin >50 μmol/l—on postoperative day 5 or thereafter [27] independent of ascites or encephalopathy.

Preoperative chemotherapy

Preoperative chemotherapy was based on various combinations of chemotherapeutic drugs such as oxaliplatin, irinotecan, leucovorin, and 5-FU or capecitabine with or without Bev. Usually, Bev was given in addition to standard chemotherapy regimens such as FOLFOX (5-FU/leucovorin/oxaliplatin) and FOLFIRI (5-FU/leucovorin/irinotecan). The number of cycles of neoadjuvant chemotherapy and the duration of the "drug holiday" were recorded.

Surgical procedure

An R0 resection was targeted in all patients. Pringle's maneuver was not applied on a routine basis but was used selectively according to criteria available at each center. Intraoperative ultrasonography was performed on a regular basis in each patient to detect occult tumors and to confirm the anatomic relations between the tumor and vascular structures. During major hepatectomy—defined as a resection of $\geq$3 segments [28, 29]—a selective devascularization

technique was used at the three centers consisting of selective ligature of the hepatic artery and the portal system prior to transection of the parenchyma, with the hepatic vein usually being closed after transection. Liver resection was carried out using either an ultrasonic surgical dissector (Girona and Strasbourg) or the crush clamp technique and bipolar irrigated cautery (Zurich). Biliary and vascular structures were secured by sutures and clips during hepatic parenchymal transection.

Statistical analysis (comparability of the groups)

Student's *t*-test and the Mann–Whitney test were used to compare continuous variables with normal and nonnormal distributions, respectively. The chi-squared test was applied for comparison between categoric variables.

We compared complication rates using a logistic regression analysis with complications as a dependent variable and neoadjuvant chemotherapy (with or without Bev) as an independent variable. We repeated the analysis for patients with and without a drug holiday (≥6 weeks or <6 weeks). Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were estimated; and $p < 0.05$ was considered statistically significant.

Because this study was not a randomized trial, we paid attention to potential confounders that might influence the association between complications and Bev treatment. We compared the groups in terms of their mean propensity (probability) of developing a severe complication. We used a logistic backward-selection regression model, entering factors associated with complications as independent variables and major complications (grade ≥ 3a) as a dependent variable. The variables considered were age, extrahepatic disease, extrahepatic procedure, major/minor surgery, type of neoadjuvant chemotherapy, and the need for perioperative transfusion. All variables in the logistic regression model with an association of $p \leq 0.3$ in the multivariable model were retained. Based on the resulting regression equation, we calculated the probability of a severe complication for each patient and the mean probability for the two groups. The mean ± SD propensity for developing a severe complication was 28.6 ± 17.2% for the Bev group and 20.5 ± 16.2% for the control group. The difference of 8.1% [95% confidence interval (CI) 1.1–15.1%] was statistically significant ($p = 0.024$). With this evidence showing that the two groups were not entirely comparable (because of not being a randomized trial), we adjusted the main analysis for the propensity of getting a severe complication to adjust for this imbalance between groups [30]. All statistical analyses were performed using SPSS version 12 software (SPSS, Chicago, IL, USA) and Windows version 10 software (Stata, College Station, TX, USA) [31].

Results

Were the two groups comparable?

Among the 478 consecutive patients treated for CRLMs in the three centers during the study period, 319 (66.7%) received preoperative chemotherapy. A total of 45 matched pairs (90 patients) were enrolled in the study. In 45 patients, chemotherapy was combined with Bev, and in the remaining 45 it was not (control group). Patients' demographics (Table 1) showed no significant differences between the groups except for sex distribution (42% male in the Bev group vs. 69% male in the control group, $p = 0.02$).

In the Bev group, irinotecan was used in 32 patients and oxaliplatin in 11 compared with 34 and 8 patients, respectively, in the control group. 5-FU-based chemotherapy without irinotecan or oxaliplatin was applied in five patients only (two in the Bev and three in the control group). Operative parameters (Table 1) were comparable in the two groups.

Did adding preoperative Bev affect postoperative morbidity and mortality?

Occurrence of complications in both groups was adjusted for propensity, and showed no significant difference (Tables 2, 3). Overall morbidity rate was 56% (Bev) versus 40% (control); adjusted OR 1.74, 95% CI 0.71–4.28; $p = 0.23$. Severe complications showed no significant increase in Bev compared with the control group: 31 vs. 18%, respectively; adjusted OR 1.76, 95% CI 0.60–5.18; $p = 0.31$). Likewise, no difference was noted with respect to hospital stay (15 days in the Bev group versus 13 days in the control group). Mortality was 0 versus 2 in the Bev and control groups, respectively. Causes of death entailed hepatic insufficiency with multiorgan failure.

Did Bev influence postoperative liver insufficiency or wound complications?

Surprisingly, the incidence of postoperative hepatic insufficiency was significantly lower in the Bev group. Postoperative hepatic insufficiency was documented in only three patients (7%) in the Bev group compared with nine (20%) in the control group (adjusted OR 0.19, 95% CI 0.04–0.83, $p = 0.03$). Wound complications were similar in the two groups (11% in the Bev group vs. 9% in the control group, $p = 1.00$) (Table 2).

Did the Bev drug holiday affect postoperative complications?

The drug holiday prior to hepatic resection was <6 weeks in 20 patients (44%), whereas 25 patients (56%) were

Table 1 Patients' characteristics

Parameter	Bev group	Control group	*p*
Demographic data			
No. of patients	45	45	
Age (years)	58 (54–61)	62 (59–65)	0.08
Male patients (no.)	19 (42%)	31 (69%)	0.02
Preoperative chemotherapy			
Duration (months)	4 (3.5–4.8)	3.7 (3.3–4.3)	0.38
Cycles (no.)	9 (7–10)	7 (6–8)	0.16
Cycles (no. ≥6)	30 (67)	22 (49)	0.13
Bev drug holiday (days)[a]	60 (47–73)		
Irinotecan-based	11 (24%)	8 (18%)	0.55
Oxaliplatin-based	32 (71%)	34 (76%)	
5-FU-based	2 (4%)	3 (7%)	
Metastases			
No.	4 (3–5)	6 (3–8)	0.24
Size (cm) (range)	3.3 (2.4–4.2)	3.2 (2.6–3.9)	0.93
Bilobar	29 (64%)	26 (58%)	0.33
Synchronous	15 (33%)	12 (27%)	0.65
CEA > 50 ng/ml	14 (31%)	21 (47%)	0.13
Extrahepatic disease	20 (44%)	16 (36%)	0.52
Primary tumor			
Colon/sigmoid	19 (42%)	12 (27%)	0.27
Rectum	25 (56%)	31(69%)	
Stage			
Duke A	2 (4%)	1 (2%)	0.38
Duke B	11 (24%)	7 (16%)	
Duke C	31 (69%)	32 (71%)	
Operative parameters			
Simultaneous surgery	8 (18%)	8 (18%)	1.00
Two-staged hepatectomy	6 (13%)	3 (7%)	0.48
Major hepatectomy (no. ≥3 segments	19 (42%)	25 (56%)	0.29
RF complementary	16 (36%)	14 (31%)	0.82
Pringle maneuver	34 (76%)	34 (76%)	1.00
Ischemia time (min)	27 (20–34)	34 (28–40)	0.10
Associated extrahepatic procedure	17 (38%)	15 (33%)	0.82
Negative hepatic resection margin (cm)	0.5 (0.30–0.81)	0.45 (0.27–0.63)	0.55
Intraoperative blood loss (ml)	523 (399–646)	658 (407–908)	0.33
Perioperative RBC transfusion	12 (27%)	12 (27%)	1.00
Units PRBCs transfused	1 (0–2)	1 (0–2)	0.94
Operating time (min)	248 (224–270)	270 (237–302)	0.26

Results, unless otherwise stated, are the number of patients. Continuous variables are reported with the median and interquartile range (25–75%), and categorical variables are reported with percentages

Bev bevacizimab, *5-FU* 5-fluorouracil, *CEA* carcinoembronic antigen, *RBC* red blood cell, *PRBCs* packed red blood cells

[a] Only data from the Bev group are recorded

operated on ≥6 weeks after the last dose of chemotherapy. Patient characteristics, postoperative outcome, and the analysis stratified for patients according to the drug holiday are summarized in Tables 4 and 5.

Patients in the subgroup that had received Bev <6 weeks before surgery were significantly younger. There was a trend toward more cycles in the subgroup that received chemotherapy ≥6 weeks before surgery ($p = 0.06$). Overall postoperative complications were similar in the two subgroups. Moreover, the occurrence of severe complications (grade ≥ 3a) was not significantly different. ORs were also overlapping (1.74 vs. 1.52), suggesting that the drug holiday did not have a strong effect on the incidence or severity of postoperative complications.

Discussion

This multicenter comparative study evaluated the influence of bevacizumab on postoperative outcome after liver

Table 2 Postoperative complications

Parameter	Bev group	Control group	*p*
No. of patients	45	45	
Outcome			
Mortality	0	2 (4%)	0.49
Morbidity	25 (56%)	18 (40%)	0.20
Severe complication (grade $\geq$ 3[a])	14 (31%)	8 (18%)	0.22
Hepatic insufficiency	3 (7%)	9 (20%)	0.03
Hepatobiliary complications	10 (22%)	12 (27%)	0.80
Wound complication	5 (11%)	4 (9%)	1.00
Bleeding/thromboembolic complication	3 (7%)	4 (9%)	1.00
Gastrointestinal complication[b]	1 (2%)	1 (2%)	1.00
Hospital stay (days) (range)	15 (11–20)	13 (8–18)	0.47

Unless otherwise stated, the results are the number of patients. Continuous variables are reported with medians and interquartile range (25–75%), and categorical variables are reported with percentages

[a] Complication category [26]

[b] Anastomotic dehiscence or leak

Table 3 Postoperative complications

Characteristics	Bev group	Control group	Unadjusted odds ratio (95% CI)	Adjusted odds ratio[a]
Overall complications	25 (56%)	18 (40%)	1.88 (0.81–4.36), $p = 0.14$	1.74 (0.71–4.28), $p = 0.23$
Complications grade $\geq$ 3[a]	14 (31%)	8 (18%)	2.09 (0.78–5.63), $p = 0.15$	1.76 (0.60–5.18), $p = 0.31$
Hepatobiliary complications	10 (22%)	12 (27%)	0.59 (0.22–1.63), $p = 0.31$	0.52 (0.18–1.49), $p = 0.22$
Hepatic insufficiency	3 (7%)	9 (20%)	0.29 (0.07–1.14), $p = 0.08$	0.19 (0.04–0.83), $p = 0.03$

Results are the number of patients

CI confidence interval

[a] Adjusted for propensity of getting complication

resection for CRLM. Overall morbidity and mortality were not significantly different between patients exposed or not to Bev, independent of the Bev "drug holiday" prior to surgery. Surprisingly, the incidence of postoperative liver insufficiency was significantly lower in the group of patients treated with Bev. The only two fatal outcomes occurred in the control group.

We selected a matched pair methodology based on on-secutive data collection, with adjustment for potential confounding using a propensity score [30]. Short of a randomized controlled trial, this methodology is the most convincing strategy to evaluate the impact of Bev in this surgical population.

The correlation between the type of chemotherapeutic agent, liver injury, and clinical outcome after liver resection for CRLM is currently under intense debate [32–34]. Oxaliplatin has been shown to cause sinusoidal obstructive syndrome, or blue liver syndrome [35], and irinotecan contributes to the development of chemotherapy-associated steatohepatitis (CASH), which manifests as liver steatosis, lobular inflammation, and ballooning of hepatocytes [15, 36]. However, the recently published largest randomized controlled trial reported no increase in morbidity upon application of perioperative chemotherapy prior to liver resection for resectable metastatic colorectal cancer [37]. Whether the addition of Bev to those regimens adds toxicity has remained unclear.

Platelets play a primary role in hemostasis and angiogenesis as they are the major transporter of VEGF [38]. Blocking VEGF in platelets by a new chemotherapeutic drug such as Bev may impair wound healing and promote gastrointestinal perforations, hemorrhage, and thromboembolic adverse effects [11, 39, 40]. However, the available clinical data have not convincingly demonstrated enhancement of postoperative complications by Bev after either colorectal or liver surgery [40, 41]. Chemotherapy-associated hepatotoxicity has been mostly linked to the dose and/or number of treatment cycles [5, 16].

Patient survival has been shown to be markedly improved when Bev is added to 5-FU-based chemotherapy regimens (FOLFOX or FOLFIRI) as first-line treatment of metastatic colorectal cancer [12, 42]. Scappaticci et al. [40]

Table 4 "Bevacizumab drug holiday": comparison of <6 weeks or ≥6 weeks between hepatectomy and last dose

Parameter	< 6 Weeks	≥6 Weeks	*p*
Demographic data			
No. of patients	20	25	
Age (years)	53 (48–58)	61(57–65)	0.012
No. with age > 70 years	2 (10%)	7 (28%)	0.26
Male patients	7 (35%)	12 (48)	0.54
Preoperative chemotherapy			
Duration (months)	3.6 (2.6–4.6)	4.5 (3.5–5.5)	0.17
Cycles ≥6	10 (50%)	20 (80%)	0.056
Preoperative irinotecan[a]	14 (70%)	18 (72%)	0.73
Metastases			
Hepatic metastasis ≥4	8 (40%)	9 (36%)	1.00
Bilobular presentation	13 (65%)	16 (64%)	1.00
Synchronous presentation	8 (40%)	7 (28%)	0.52
Extrahepatic disease	10 (50%)	10 (40%)	0.57
Operative parameters			
Simultaneous surgery	3 (15%)	5 (20%)	0.71
Two staged hepatectomy	4 (20%)	2 (8%)	0.38
Major hepatectomy (≥3 segments)	9 (45%)	10 (40%)	0.77
Associated extrahepatic procedure	8 (40%)	9 (45%)	1.00
Outcome			
Intraoperative blood loss (ml)	454 (226–642)	557 (404–750)	0.32
Perioperative RBC transfusions	5 (25%)	7 (28%)	1.00
Overall complications	11 (55%)	14 (56%)	1.00
Complication grade ≥3a[b]	6 (30%)	8 (32%)	1.00
All hepatic complications	6 (30%)	5 (20%)	0.50
Liver insufficiency	3 (15%)	3 (12%)	1.00
Wound complication	3 (15%)	2 (8%)	0.64
Bleeding/thromboembolic complications	0	3 (12%)	0.24
Gastrointestinal complications[c]	1 (5%)	0	0.44
Length of hospital stay (days)	14 (8-21)	15 (9-21)	0.90
Mortality	0	0	–

Unless otherwise stated, the results are the number of patients. Continuous variables are reported with medians and interquartile range (25–75%) and categorical variables are reported with percentages

[a] Two patients treated with capecitabine

[b] Complication category according to Dindo et al. [26]

[c] Anastomotic dehiscence or leak

Table 5 Impact of drug holiday on postoperative complications (complication grade ≥3[a])

Condition	No.	Unadjusted odds ratio (95% CI)	Adjusted odds ratio[a]
Bev subgroup: drug holiday <6 weeks	6 (30%)	1.68 (0.74-3.85), $p = 0.22$	1.74 (0.70-4.31), $p = 0.23$
Bev subgroup: drug holiday ≥6 weeks	8 (32%)	1.91 (0.73-4.99), $p = 0.19$	1.52 (0.52-4.48), $p = 0.44$
Control group	8 (18%)		

The control group was used for comparisons in both patient groups

[a] Adjusted for propensity of getting complication and control group

failed to show an increased incidence of wound healing [40] after primary colorectal cancer resection. Similarly, after hepatic resection we found no significant difference in overall wound complications in the Bev group (11%) compared with the control group (9%). Three studies have looked at the effects of irinotecan- or oxaliplatin-based chemotherapy prior to resection of colorectal liver metastases with and without Bev [22–24]. The first study by D'Angelica et al. [22] was a case-matched study, comparing patients who received Bev or not preoperatively. This study, however, suffers from a low number of patients (only 16 patients received Bev preoperatively), a lack of information regarding the type of chemotherapy used in the control group, and a lack of data regarding the severity of the complications. Finally, the outcome values were not adjusted statistically according to potential confounders.

Table 6 Available comparative studies evaluating impact of preoperative bevacizumab

Parameter	D'Angelica et al. [22]	Reddy et al. [23]	Kesmodel et al. [24]	Present study
Type of study	Matched controls	Not matched	Not matched	Matched controls
CTX alone/CTX + Bev (no.)	32/16	57/39	44/81	45/45
FOLFIRI/FOLFOX ratio	FOLFOX > FOLFIRI	FOLFOX > FOLFIRI	FOLFOX > FOLFIRI	FOLFIRI > FOLFOX
Overall complications	38% (6/16)	44% (17/39)	49% (40/81)	56% (25/45)
Hepatobiliary complications	6% (1/16)	18% (7/39)	5% (4/81)	24% (11/45)
Wound complications	19% (3/16)	10% (4/39)	28% (23/81)	11% (5/45)
Bleeding/thromboembolic complications	13% (2/16)	3% (1/39)	0% (0/81)	7% (3/45)
Gastrointestinal complications	–	–	1% (1/81)	2% (1/45)
Drug (Bev) holiday interval	Median 6.9 weeks	Median 10 weeks	Median 58 days	9 Weeks

CTX chemotherapy

The second study, by Reddy et al. [23], enrolled 39 patients treated with Bev, but the results were not statistically adjusted to confounders. The third study, by Kesmodel et al. [24], was the largest study with 81 patients included in the Bev group. However they did not match the control group, nor did they adjust for confounders. In all three studies [22–24], Bev was added predominantly to oxaliplatin, as this is the standard regimen in North America (Table 6).

In the current study, Bev-treated patients had a higher rate of overall complications and severe complications. However, the differences did not reach statistical significance. We observed a potential advantage in the use of Bev with the significantly reduced incidence of postoperative hepatic insufficiency in patients receiving Bev prior to surgery. The explanation for this benefit is yet unclear, but we speculate that Bev decreases the sinusoidal injury induced by oxaliplatin. The observation by others that Bev decreases the incidence of sinusoidal obstruction syndrome [17] supports this idea. The exact mechanism of this finding is still unknown, but the VEGF blockade may act by down-regulating metalloproteinases and thereby decrease the rate of apoptosis in endothelial cells.

It is currently recommended and accepted by many groups [19] that liver surgery should be delayed for 6 weeks after the last dose of Bev. The basis of this recommendation lies in the long half-life ($\sim$20 days) of the drug [8, 43]. Some groups have looked at this more carefully. For example, Gruenberger et al. [41] reported that Bev can be safely administered up to 5 weeks before liver resection [41], whereas recently Reddy et al. [23] recommended discontinuation of Bev at least 8 weeks prior to surgery [23]. In our study, we failed to identify any significant impact on the occurrence of postoperative complications in patients who had received Bev <6 weeks or in those who had taken Bev $\geq$6 weeks before liver resection. However, caution must be applied because of the relatively small number of patients ($n = 20$) who had received Bev shortly prior to surgery. Until confirmation of these data, we still discontinue Bev at least 4 weeks prior to surgery in each of our centers.

The main limitation of this study was the retrospective nature of the analysis. Despite the fact that unadjusted and carefully adjusted analyses did not differ markedly, we cannot exclude substantial residual confounding factors. A second limitation is the acquisition of data from three centers in Europe. Differences regarding technical details during surgery data collection may lead to heterogeneity of data. However, these three European centers have a large experience with and volume of liver surgery, and they use comparable liver resection techniques. These potential shortcomings were addressed by case matching and adjusting for the propensity to develop complications. As a final point, we cannot exclude the possibility that with a larger group of patients the slight differences in the complication rate might become significant.

Conclusions

This study provides evidence that Bev, in combination with modern neoadjuvant chemotherapies, does not significantly increase the number or the severity of postoperative complications. The discontinuation of Bev therapy $\geq$6 weeks prior to surgery may not confer any reduction in morbidity after liver resection. If the potential benefit of Bev in preventing postoperative liver failure is confirmed, Bev may enjoy an increased interest in its use as neoadjuvant chemotherapy prior to resection for colorectal liver metastasis.

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