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Article Sub-Title		
Article CopyRight	Société Internationale de Chirurgie (This will be the copyright line in the final PDF)	
Journal Name	World Journal of Surgery	
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Schedule	Received	
	Revised	
	Accepted	
Abstract	<p><i>Background:</i> 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.</p> <p><i>Methods:</i> 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 on between 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 bevacizumab, and group B had it without bevacizumab.</p> <p><i>Results:</i> 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%, $p = 0.03$).</p> <p><i>Conclusions:</i> 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.</p>	
Footnote Information	Mahfud Mahfud and Stefan Breitenstein contributed equally to this work. Dr. Mahfud is a Henri Bismuth fellow who spent 4 months at each of the centers involved in the study.	

Journal: 268
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1

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

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7 **Santiago Lopez-Ben · Daniel Jaeck · Joan Figueras · Pierre Alain-Clavien**

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10 **Abstract**

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20 in the Swiss HPB Center of the University Hospital
21 Zurich (CH), the Department of Digestive Surgery and

A1 Mahfud Mahfud and Stefan Breitenstein contributed equally to this
A2 work. Dr. Mahfud is a Henri Bismuth fellow who spent 4 months at
A3 each of the centers involved in the study.

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22 Transplantation Strasbourg (F), and the Division of Hepato-
23 biliary-pancreatic surgery of “Josep Tureta” Hospital
24 Girona (E). Consecutive patients operated on between July
25 2005 and December 2007 due to CRLMs who received
26 neoadjuvant chemotherapy were assessed. Patients were
27 divided in two groups: group A had neoadjuvant chemo-
28 therapy with bevacizumab, and group B had it without
29 bevacizumab.

30 *Results* No differences in overall morbidity (56 vs. 40%
31 in the bevacizumab and control groups, respectively,
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33 incidence of severe postoperative complications was not
34 statistically different between the bevacizumab and control
35 groups (31 and 18%, respectively, $p = 0.31$). Wound
36 complications were comparable (11% in the bevacizumab
37 group compared and 9% in the control group, $p = 1.00$).
38 However, bevacizumab was associated with a significantly
39 decreased incidence of postoperative hepatic insufficiency
40 (7 vs. 20%, $p = 0.03$).

41 *Conclusions* No impact on the incidence or severity of
42 complications by bevacizumab could be shown. Bev-
43 acizumab may even reduce the incidence of liver failure
44 after liver surgery.

45
46 **Introduction**

47 Systemic chemotherapy prior to resection of colorectal
48 liver metastases (CRLMs) is increasingly advocated by
49 modern interdisciplinary teams in many countries. How-
50 ever, the benefit and safety of this strategy remains con-
51 troversial [1–5].

52 Bevacizumab (Bev) is a monoclonal antibody against vas-
53 cular endothelial growth factor (VEGF) with antiangiogenic

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

65 Chemotherapeutic agents that inhibit tumor growth also
66 have inherent side effects on healthy tissue. For instance,
67 oxaliplatin and irinotecan may alter the histomorphologic
68 characteristics of the liver [14–19], and Bev has been
69 associated with bleeding, thrombosis, impaired wound
70 healing, and liver regeneration [20]. The effect of preop-
71 erative Bev with chemotherapeutic agents (particularly
72 oxaliplatin and irinotecan) on posthepatectomy complica-
73 tions remains under debate [17, 21]. Three studies from
74 North America failed to show an increase in postoperative
75 complications upon adding Bev to preoperative chemo-
76 therapy [22–24]. However, the study by D’Angelica et al.
77 [22] included only 16 patients treated with Bev; and the
78 studies by Reddy et al. [23] and Kesmodel et al. [24] had
79 relevant methodologic shortcomings due to lack of statisti-
80 cal adjustments and matching of patient groups. Also, all
81 studies were carried out in the United States, where the
82 chemotherapy is predominantly oxaliplatin-based.

83 To address a putative negative impact of the use of Bev
84 on postoperative outcome, we designed a European mul-
85 ticentric study in three established surgical centers that
86 maintained well documented databases. We evaluated
87 consecutive patients treated with an oxaliplatin- or irino-
88 tecan-based chemotherapy regimen, with and without Bev,
89 regarding the incidence and severity of postoperative
90 complications including evidence of hepatic insufficiency.
91 Owing to the relatively long half-life of Bev (~20 days)
92 [8, 25], we also focused on the interval between the last
93 dose of Bev and the initiation of surgery—what we called
94 the “drug holiday”—on postoperative outcome.

95 Methods

96 Study design

97 Patients who underwent liver resection owing to CRLMs
98 from three European hepatopancreatobiliary centers
99 (Girona, Spain; Strasburg, France; Zurich, Switzerland)
100 between July 2005 and December 2007 were retrospec-
101 tively assessed for eligibility using well established

databases in each respective center. Forty-five consecutive
102 patients treated with neoadjuvant chemotherapy with Bev
103 were identified. An independent reviewer (M.P.) matched
104 these patients manually by screening a database from 2007
105 one-by-one against patients who had received neoadjuvant
106 chemotherapy without Bev. Matching criteria were age,
107 number of chemotherapeutic cycles, number of metastases,
108 size of metastases, bilobularity of the disease, synchronous
109 or metachronous metastases, presence of extrahepatic dis-
110 ease, simultaneous or staged hepatectomy, and associated
111 extrahepatic procedures. Results were statistically adjusted
112 according to potential confounders (<ClinicalTrials.gov>
113 NCT 00875147).
114

Outcome measures

115
116 Data on outcome parameters were reviewed and extracted
117 from the prospective database at each center. The primary
118 endpoint was the occurrence of postoperative complica-
119 tions, graded according to a validated therapy-oriented
120 complication score on a five-point scale [26]. Severe
121 complications were defined as events requiring interven-
122 tion under local or general anesthesia or treatment in the
123 intensive care unit (ICU) (complication grade $\geq 3a$). Spe-
124 cific hepatic complications (e.g., subphrenic abscess, bile
125 leak, bilioma, liver insufficiency) were recorded in detail.
126 Postoperative liver insufficiency was defined according to
127 the 50–50 criterion—prothrombin time $<50\%$ of normal
128 and serum bilirubin $>50 \mu\text{mol/l}$ —on postoperative day 5 or
129 thereafter [27] independent of ascites or encephalopathy.

Preoperative chemotherapy

130
131 Preoperative chemotherapy was based on various combi-
132 nations of chemotherapeutic drugs such as oxaliplatin, iri-
133 notecan, leucovorin, and 5-FU or capecitabine with or
134 without Bev. Usually, Bev was given in addition to standard
135 chemotherapy regimens such as FOLFOX (5-FU/leucov-
136 orin/oxaliplatin) and FOLFIRI (5-FU/leucovorin/irinote-
137 can). The number of cycles of neoadjuvant chemotherapy
138 and the duration of the “drug holiday” were recorded.

Surgical procedure

139
140 An R0 resection was targeted in all patients. Pringle’s
141 maneuver was not applied on a routine basis but was used
142 selectively according to criteria available at each center.
143 Intraoperative ultrasonography was performed on a regular
144 basis in each patient to detect occult tumors and to confirm
145 the anatomic relations between the tumor and vascular
146 structures. During major hepatectomy—defined as a resec-
147 tion of ≥ 3 segments [28, 29]—a selective devascularization

148 technique was used at the three centers consisting of selec-
149 tive ligation of the hepatic artery and the portal system prior
150 to transection of the parenchyma, with the hepatic vein
151 usually being closed after transection. Liver resection was
152 carried out using either an ultrasonic surgical dissector
153 (Girona and Strasbourg) or the crush clamp technique and
154 bipolar irrigated cautery (Zurich). Biliary and vascular
155 structures were secured by sutures and clips during hepatic
156 parenchymal transection.

157 Statistical analysis (comparability of the groups)

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

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

170 Because this study was not a randomized trial, we paid
171 attention to potential confounders that might influence the
172 association between complications and Bev treatment. We
173 compared the groups in terms of their mean propensity
174 (probability) of developing a severe complication. We used
175 a logistic backward-selection regression model, entering
176 factors associated with complications as independent
177 variables and major complications (grade $\geq 3a$) as a
178 dependent variable. The variables considered were age,
179 extrahepatic disease, extrahepatic procedure, major/minor
180 surgery, type of neoadjuvant chemotherapy, and the need
181 for perioperative transfusion. All variables in the logistic
182 regression model with an association of $p \leq 0.3$ in the
183 multivariable model were retained. Based on the resulting
184 regression equation, we calculated the probability of a
185 severe complication for each patient and the mean proba-
186 bility for the two groups. The mean \pm SD propensity for
187 developing a severe complication was $28.6 \pm 17.2\%$ for
188 the Bev group and $20.5 \pm 16.2\%$ for the control group.
189 The difference of 8.1% [95% confidence interval (CI) 1.1–
190 15.1%] was statistically significant ($p = 0.024$). With this
191 evidence showing that the two groups were not entirely
192 comparable (because of not being a randomized trial), we
193 adjusted the main analysis for the propensity of getting a
194 severe complication to adjust for this imbalance between
195 groups [30]. All statistical analyses were performed using
196 SPSS version 12 software (SPSS, Chicago, IL, USA) and
197 Windows version 10 software (Stata, College Station, TX,
198 USA) [31].

Results

Were the two groups comparable? 200

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

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

216 Did adding preoperative Bev affect postoperative
217 morbidity and mortality?

218 Occurrence of complications in both groups was adjusted
219 for propensity, and showed no significant difference
220 (Tables 2, 3). Overall morbidity rate was 56% (Bev) versus
221 40% (control); adjusted OR 1.74, 95% CI 0.71–4.28;
222 $p = 0.23$. Severe complications showed no significant
223 increase in Bev compared with the control group: 31 vs.
224 18%, respectively; adjusted OR 1.76, 95% CI 0.60–5.18;
225 $p = 0.31$. Likewise, no difference was noted with respect
226 to hospital stay (15 days in the Bev group versus 13 days in
227 the control group). Mortality was 0 versus 2 in the Bev and
228 control groups, respectively. Causes of death entailed
229 hepatic insufficiency with multiorgan failure.

230 Did Bev influence postoperative liver insufficiency
231 or wound complications?

232 Surprisingly, the incidence of postoperative hepatic insuf-
233 ficiency was significantly lower in the Bev group. Post-
234 operative hepatic insufficiency was documented in only
235 three patients (7%) in the Bev group compared with nine
236 (20%) in the control group (adjusted OR 0.19, 95% CI
237 0.04–0.83, $p = 0.03$). Wound complications were similar
238 in the two groups (11% in the Bev group vs. 9% in the
239 control group, $p = 1.00$) (Table 2).

240 Did the Bev drug holiday affect postoperative
241 complications?

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

Table 1 Patients' characteristics

Parameter	Bev group	Control group	<i>p</i>
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. \geq 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. \geq 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 bevacizumab, 5-FU 5-fluorouracil, CEA carcinoembryonic antigen, RBC red blood cell, PRBCs packed red blood cells

^a Only data from the Bev group are recorded

operated on \geq 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 \geq 6 weeks before surgery ($p = 0.06$). Overall postoperative complications were similar in the two subgroups. Moreover, the occurrence of severe

complications (grade \geq 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	<i>p</i>
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), <i>p</i> = 0.14	1.74 (0.71–4.28), <i>p</i> = 0.23
Complications grade $\geq 3^a$	14 (31%)	8 (18%)	2.09 (0.78–5.63), <i>p</i> = 0.15	1.76 (0.60–5.18), <i>p</i> = 0.31
Hepatobiliary complications	10 (22%)	12 (27%)	0.59 (0.22–1.63), <i>p</i> = 0.31	0.52 (0.18–1.49), <i>p</i> = 0.22
Hepatic insufficiency	3 (7%)	9 (20%)	0.29 (0.07–1.14), <i>p</i> = 0.08	0.19 (0.04–0.83), <i>p</i> = 0.03

Results are the number of patients

CI confidence interval

^a Adjusted for propensity of getting complication

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

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

274 The correlation between the type of chemotherapeutic
275 agent, liver injury, and clinical outcome after liver resec-
276 tion for CRLM is currently under intense debate [32–34].
277 Oxaliplatin has been shown to cause sinusoidal obstructive
278 syndrome, or blue liver syndrome [35], and irinotecan
279 contributes to the development of chemotherapy-associated
280 steatohepatitis (CASH), which manifests as liver steatosis,
281 lobular inflammation, and ballooning of hepatocytes [15,

36]. However, the recently published largest randomized
282 controlled trial reported no increase in morbidity upon
283 application of perioperative chemotherapy prior to liver
284 resection for resectable metastatic colorectal cancer [37].
285 Whether the addition of Bev to those regimens adds tox-
286 icity has remained unclear.
287

288 Platelets play a primary role in hemostasis and angio-
289 genesis as they are the major transporter of VEGF [38].
290 Blocking VEGF in platelets by a new chemotherapeutic
291 drug such as Bev may impair wound healing and promote
292 gastrointestinal perforations, hemorrhage, and thrombo-
293 embolic adverse effects [11, 39, 40]. However, the avail-
294 able clinical data have not convincingly demonstrated
295 enhancement of postoperative complications by Bev after
296 either colorectal or liver surgery [40, 41]. Chemotherapy-
297 associated hepatotoxicity has been mostly linked to the
298 dose and/or number of treatment cycles [5, 16].

299 Patient survival has been shown to be markedly
300 improved when Bev is added to 5-FU-based chemotherapy
301 regimens (FOLFOX or FOLFIRI) as first-line treatment of
302 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	<i>p</i>
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 ≥3 ^a	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), <i>p</i> = 0.22	1.74 (0.70-4.31), <i>p</i> = 0.23
Bev subgroup: drug holiday ≥6 weeks	8 (32%)	1.91 (0.73-4.99), <i>p</i> = 0.19	1.52 (0.52-4.48), <i>p</i> = 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

303 failed to show an increased incidence of wound healing [40]
 304 after primary colorectal cancer resection. Similarly, after
 305 hepatic resection we found no significant difference in
 306 overall wound complications in the Bev group (11%)
 307 compared with the control group (9%). Three studies have
 308 looked at the effects of irinotecan- or oxaliplatin-based
 309 chemotherapy prior to resection of colorectal liver metas-
 310 tases with and without Bev [22–24]. The first study by

D’Angelica et al. [22] was a case-matched study, comparing 311
 patients who received Bev or not preoperatively. This study, 312
 however, suffers from a low number of patients (only 16 313
 patients received Bev preoperatively), a lack of information 314
 regarding the type of chemotherapy used in the control 315
 group, and a lack of data regarding the severity of the 316
 complications. Finally, the outcome values were not 317
 adjusted statistically according to potential confounders. 318

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

319 The second study, by Reddy et al. [23], enrolled 39 patients
320 treated with Bev, but the results were not statistically
321 adjusted to confounders. The third study, by Kesmodel et al.
322 [24], was the largest study with 81 patients included in the
323 Bev group. However they did not match the control group,
324 nor did they adjust for confounders. In all three studies
325 [22–24], Bev was added predominantly to oxaliplatin, as
326 this is the standard regimen in North America (Table 6).

327 In the current study, Bev-treated patients had a higher
328 rate of overall complications and severe complications.
329 However, the differences did not reach statistical signifi-
330 cance. We observed a potential advantage in the use of Bev
331 with the significantly reduced incidence of postoperative
332 hepatic insufficiency in patients receiving Bev prior to
333 surgery. The explanation for this benefit is yet unclear, but
334 we speculate that Bev decreases the sinusoidal injury
335 induced by oxaliplatin. The observation by others that Bev
336 decreases the incidence of sinusoidal obstruction syndrome
337 [17] supports this idea. The exact mechanism of this find-
338 ing is still unknown, but the VEGF blockade may act by
339 down-regulating metalloproteinases and thereby decrease
340 the rate of apoptosis in endothelial cells.

341 It is currently recommended and accepted by many
342 groups [19] that liver surgery should be delayed for
343 6 weeks after the last dose of Bev. The basis of this rec-
344 ommendation lies in the long half-life (~20 days) of the
345 drug [8, 43]. Some groups have looked at this more care-
346 fully. For example, Gruenberger et al. [41] reported that
347 Bev can be safely administered up to 5 weeks before liver
348 resection [41], whereas recently Reddy et al. [23] recom-
349 mended discontinuation of Bev at least 8 weeks prior to
350 surgery [23]. In our study, we failed to identify any sig-
351 nificant impact on the occurrence of postoperative com-
352 plications in patients who had received Bev <6 weeks or in
353 those who had taken Bev ≥6 weeks before liver resection.
354 However, caution must be applied because of the relatively
355 small number of patients ($n = 20$) who had received Bev
356 shortly prior to surgery. Until confirmation of these data,

we still discontinue Bev at least 4 weeks prior to surgery in 357
each of our centers. 358

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

374 Conclusions

375 This study provides evidence that Bev, in combination with
376 modern neoadjuvant chemotherapies, does not significantly
377 increase the number or the severity of postoperative com-
378 plications. The discontinuation of Bev therapy ≥6 weeks
379 prior to surgery may not confer any reduction in morbidity
380 after liver resection. If the potential benefit of Bev in pre-
381 venting postoperative liver failure is confirmed, Bev may
382 enjoy an increased interest in its use as neoadjuvant che-
383 motherapy prior to resection for colorectal liver metastasis.
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