Liver Resection Remains a Safe Procedure After Neoadjuvant Chemotherapy Including Bevacizumab

A Case-Controlled Study

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Objective: This study was conducted to analyze if the combination of Bevacizumab with standard chemotherapy increases postoperative morbidity and mortality after resection of colorectal liver metastases as compared with resection after chemotherapy alone. Parameters contributing to an increased morbidity were evaluated.

Summary Background Data: Most patients referred for colorectal liver metastases are treated with neoadjuvant chemotherapy before hepatic surgery. Targeted agents like the vascular endothelial growth factor—antagonist Bevacizumab are increasingly added to standard therapy to prolong survival; however, little is known about the consequences of this policy in the perioperative period.

Methods: One hundred-two patients treated between 2005 and 2009, who received neoadjuvant chemotherapy combined with Bevacizumab (CHT + B) were identified. A cohort of 112 patients treated without chemotherapy alone before resection served as the control group (CHT). Complications were graded within an established staging system and the therapeutic consequences were laid down. Uni- and multivariate analysis of factors contributing to postoperative complications in the CHT + B group was performed using a logistic regression model.

Results: Postoperative complications occurred in 45 (44%, CHT + B) and 38 (34%, CHT) patients, respectively ($P = 0.216$). The incidence of severe complications requiring surgical or radiologic intervention or leading to organ failure was 10.8% in the CHT + B group and 7.1% in the CHT group ($P = 0.350$). Increased age, low serum albumin, resection of more than 3 liver segments and synchronous bowel procedures requiring an anastomosis were associated with an increased morbidity rate in the multivariate regression analysis. No patient died in either group.

Conclusions: The addition of Bevacizumab to standard chemotherapy before resection of colorectal liver metastases does not seem to increase postoperative morbidity. Caution should be given to extended resections >3 liver segments and synchronous bowel anastomoses.

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Potential curative surgery after neoadjuvant chemotherapy seems to prolong overall (OS) and progression-free survival (PFS) in patients with metastatic colorectal cancer (mCRC) confined to the liver.[1–3] Under optimal conditions, previously reported 5-year survival rates of 30% to 40%[4] can now exceed 70% in selected patients.[5] Standard chemotherapeutic regimens combine fluoropyrimidines with Oxaliplatin[6] or Irinotecan,[7] which have significantly prolonged median survival figures in patients treated in palliative intent. The addition of the human vascular endothelial growth factor (VEGF) antibody Bevacizumab has shown further improvement in the pivotal trial by Hurwitz et al[8] and has since become the standard of care for the majority of metastatic colorectal cancer patients[9] including some promising results in the neoadjuvant setting.[10] Furthermore, beneficial effects of Bevacizumab on chemotherapy-associated liver damage were reported, reducing the level and incidence of sinusoidal lesions after Oxaliplatin-containing chemotherapy.[11,12]

The use of targeted therapies in the treatment of metastatic colorectal cancer leads to new chances but also potential harms, which have to be anticipated and counteracted when surgery is intended. Experimental data have indicated increased incidence of bleeding events after anti-VEGF therapy[13] and have underlined the importance of VEGF in wound healing[14] and liver regeneration.[15] Phase IV data from nearly 2000 patients treated with palliative chemotherapy in combination with Bevacizumab reported severe bleeding events in 3% and gastrointestinal perforations in 2% of patients.[16] The evidence for the safety of a combination of Bevacizumab and cytotoxic chemotherapy prior to hepatic surgery for colorectal liver metastases is still scarce and limited to small retrospective series.[17–19] The optimal timing of discontinuing anti-VEGF therapy is not well defined and the severity of complications associated with liver surgery and their therapeutic consequences under these circumstances are hardly ever reported.

In our article, we will answer emerging questions: Does the addition of Bevacizumab to standard chemotherapy increase perioperative morbidity and mortality after resection of colorectal liver metastases? Morbidity will be described using a validated staging system in over 100 patients treated prospectively at our institution. Second, we analyzed factors associated with postoperative morbidity in these patients to identify high-risk subjects in the future.

PATIENTS AND METHODS

Between January 2005 and February 2009, 235 patients underwent potentially curative surgery for colorectal liver metastases at our institution. Of these, 102 patients received neoadjuvant chemotherapy in combination with Bevacizumab prior to liver resection. All patients who completed chemotherapy combined with Bevacizumab within 6 months prior to surgery were included (CHT + B group). All patient data were prospectively entered into a database; information was retrieved from medical charts, clinic notes, personal contact or the hospital information system (KIS). These data included demographic variables, characteristics of primary and metastatic colorectal cancer, details on pre- and postoperative chemotherapy and biologicals applied, preoperative indocyanine green (ICG) clearance, type and duration of surgery, intra- and postoperative blood transfusion, analysis of postoperative complications, and length of stay. For comparison of postoperative morbidity, a cohort of 112 patients treated with neoadjuvant

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chemotherapy and surgery without Bevacizumab between 2001 and 2004 was selected (CHT group).[20]

Preoperative Workup

All patients received a multidetector CT scan of the liver, abdomen, and thorax to stage metastatic colorectal cancer and to rule out unresectable extrahepatic disease. Routine preoperative MRT using 1.5 T or 3 T devices was applied in a recently started protocol. All patients were discussed in a weekly multidisciplinary board and resectability was judged by experienced hepatobiliary surgeons. Our policy is to resect only patients who benefited from preoperative chemotherapy (partial response or stable disease)[21,22]; patients with progression under chemotherapy are switched to another regimen until chemo-sensitivity is established. As a consequence of this concept, the rate of responding patients (CR/PR/SD) undergoing surgery was exceptionally high in this series (99 of 102 patients = 97.0%, CHT + B group).

Surgery

All resections were performed or assisted by experienced hepatobiliary surgeons. After resectability has been secured by using a small laparotomy, a bicostal incision was used to fully explore and mobilize the liver. All patients underwent intraoperative ultrasound (B&K Panther 2002 ADI unit; B&K Medical, Gentofte, Denmark); all resections were performed using CUSA (Cavitron ultrasonic aspirator; Valleylab, Boulder, CO) and bipolar forceps in a two-surgeon technique. For classification of liver resections, the IHPBA Brisbane 2000 nomenclature was used.[23] The type of liver resections and additional procedures are illustrated in Table 1.

Chemotherapy

All 102 patients (CHT + B) received cytotoxic combination chemotherapy and Bevacizumab within 6 months of liver surgery. Fifty-three patients (52.0%) were treated at our institution, the remaining 49 patients were referred after neoadjuvant chemotherapy at other centers. The treating medical or surgical oncologist determined the indication for chemotherapy and the regimen used. Chemotherapy usually consisted of a fluoropyrimidine (either 5-FU or Capecitabine) or Raltitrexed (n = 2) together with Oxaliplatin or Irinotecan. Most commonly, patients were treated with a 2- or 3-weekly XELOX regimen (n = 76),[10] or received FOLFOX4 (n = 8).[2] Other regimens used were XELIRI (n = 7) oder FOLFIRI (n = 7), 4 patients received both Oxaliplatin and Irinotecan due to initial therapy failure of the respective other drug. Chemotherapy was usually administered for 6 cycles before liver resection, the sixth cycle was given without Bevacizumab to establish a gap of 5 weeks between last Bevacizumab and surgery.[10] Adjuvant chemotherapy after resection was applied to 77 patients (75.4%) and was usually restarted 5 weeks after surgery.

Assessment of Postoperative Complications

For the purpose of postoperative morbidity, we used a classification proposed by Clavien and coworkers,[24] which was validated in several surgical cohorts including pancreatic surgery[25] or living donor liver transplantation.[26] Briefly, minor complications (Grade I or II) can be discriminated from major complications (grade III or IV) by the therapeutic measures necessary to treat those conditions. Grade I and II complications can be managed exclusively by medical means (eg, antiemetics, antipyretics, analgesics, diuretics and electrolytes for Grade I, antibiotics, blood products, all types of cardiovascular drugs or parenteral nutrition for Grade II). Grade III complications comprise interventions without (Grade IIIa) or with general anesthesia (Grade IIIb) and include percutaneous drainage of an abscess, endoscopy or reoperation. Grade IV complications include single- (Grade IVa) or multiorgan dysfunction (Grade IVb), requiring ICU admission with mechanical ventilation, hemodialysis, hemofiltration, or any kind of organ support. Liver dysfunction was defined as proposed by Belghiti and coworkers.[27] Grade V complication equals death of the patient. Death was counted as any mortality during the hospital stay or within 30 days of surgery. For the purpose of this analysis, the most severe complication was counted for each patient, although some patients had more than one complication.

TABLE 1. Type of Hepatic Surgery and Extrahepatic Procedures

	Chemotherapy + Bevacizumab	Chemotherapy
Hepatic resection		
Trisectionectomy		
Right	9	4
Left		1
Hemihepatectomy		
Right	16	6
Left	3	6
Left lateral sectionectomy	8	2
Bisegmentectomy	7	9
Segmentectomy		
Solitary	21	44
Multiple	38	40
Total	102	112
Additional procedure		
Cholecystectomy	57	63
Lymph node biopsy	7	2
Wedge resection stomach	1	
Right adrenalectomy	1	
Appendectomy	2	1
Partial nephrectomy	1	1
Bowel resection	20	3
Right colectomy	8	
Left colectomy	1	
Anterior resection	3	
Low anterior resection	4	1
Reversal of Hartmann's	1	
Ostomy closure/segmental resection	3	2

Statistical Analysis

For the analysis of continuous variables, a Mann-Whitney U Test was used because of the nonlinear distribution of most parameters. A χ^2 test was used to compare categorical variables. For the analysis of factors associated with postoperative complications, a uni- and multivariate logistic regression model was used; odds ratios and 95% confidence intervals were calculated. *P* values of less that 0.05 were considered statistically significant. All calculations were preformed using SPSS 17.0 (SPSS, Inc, Chicago, IL).

Role of the Funding Source, Ethical Considerations

The study was supported and sponsored by the Association of Research on the Biology of Liver Tumors. The database and statistical analysis are under the responsibility of the sponsor. The manuscript was written by DT and TG. The study was conducted in accordance with the Declaration of Helsinki and according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice and approved by the local institutional review board.

TABLE 2. Patient Characteristics According to Neoadjuvant Therapy Before Surgery

	Chemotherapy + Bevacizumab (n = 102)	Chemotherapy (n = 112)	*P*
Median age (range), yr	63.3 (31.4–81.6)	63.6 (28.9–84.2)	0.732
Gender, no. (%)			
Female	39 (38.2)	35 (31.3)	0.283
Male	63 (62.8)	77 (68.7)	
UICC stage primary, no. (%)			
I	5 (4.9)	5 (4.5)	0.279
II	12 (11.8)	16 (14.3)	
III	20 (19.6)	18 (16.1)	
IV	59 (57.8)	72 (64.3)	
n.a.	6 (5.9)	1 (0.9)	
Lab values, median (range)			
Albumin, mg/dL	41.5 (22.2–49.4)	38.3 (21.5–49.9)	<0.001
Alkaline phosphatase, U/L	95 (42–703)	111 (54–852)	0.003
Gamma glutamyl transferase, U/L	26 (7–605)	20 (2–579)	0.203
Aspartate aminotransferase, U/L	32 (12–1114)	23 (5–561)	<0.001
Alanine aminotransferase, U/L	26 (7–605)	20 (2–579)	0.024
ICG clearance, median (range)			
R15, %	6.4 (0.8–28.0)	5.2 (1.4–59.2)	0.382
Median number of tumors (range)	2 (1–10)	2 (1–10)	0.755
Largest median diameter, cm (range)	1.9 (0.2–13)	2.9 (0.3–15)	0.001
Type of resection, no. (%)			
Major	28 (27.4)	17 (15.2)	0.043
Minor	36 (35.3)	55 (49.1)	
Multiple	38 (37.3)	40 (35.7)	
Median resected segments (range)	3 (1–6)	3 (1–5)	0.127
Intraoperative transfusion of RBCs, no. (%)			
Yes	5 (4.9)	31 (27.7)	<0.001
No	95 (93.1)	70 (62.5)	
n.a	2 (2.0)	11 (9.8)	
Median length of stay (range), days	8 (4–77)	9 (5–47)	0.064
Type of cytotoxic chemotherapy, no. (%)			
Fluoropyrimidine + oxaliplatin	84 (82.3)	72 (64.2)	0.148
Fluoropyrimidine + irinotecan	13 (12.7)	11 (9.8)	
Fluoropyrimidine alone	0 (0)	15 (13.4)	
Other	4 (3.9)	14 (12.5)	
Median cycles of Bevacizumab (range)	6 (1–20)		
Median days between Bevacizumab and surgery (range)	34 (17–99)		

P values are derived from χ^2 test for categorical and from Mann-Whitney *U* test for continuous variables.
UICC indicates union international contre cancer; ICG R15, indocyanine green retention at 15 min; RBC, red blood cells; n.a., not applicable.

RESULTS

Comparison of the 2 Patient Groups—Demographics

In Table 2, the cohort receiving chemotherapy with Bevacizumab (CHT + B) is compared with 112 patients who were resected after combination chemotherapy without Bevacizumab (CHT). The 2 groups were well comparable in age, gender, tumor stage and postoperative values including length of stay. There were more major resections in the CHT + B group (27.4% vs. 15.2%). Although the 2 groups differed in several preoperative laboratory values, those differences were numerically only of minimal value. Interestingly, the use of blood products was significantly diminished in the cohort receiving neoadjuvant chemotherapy including Bevacizumab.

Data on Chemotherapy

The predominant chemotherapy regimen consisted of a fluoropyrimidine + Oxaliplatin in both groups. Further details on chemotherapy and Bevacizumab are given in Table 2. There was no significant difference in regimens apart from the use of Bevacizumab.

Bevacizumab and Postoperative Complications

The overall complication rate is presented in Table 3. There were no deaths (Grade V complication) during the hospital stay or within 30 days post liver resection in both groups. Compared with the CHT cohort, there was no significant difference in the rate of complications in the CHT + B group (34% vs. 44%, $P = 0.216$). There were 11 (10.8%) complications of Grade III or IV in the CHT + B cohort, which was similar to the control group (8 complications or

TABLE 3. Complications After Hepatic Surgery According to Severity and Associated Length of Stay

Grade, No. Patients (%)	Chemotherapy + Bevacizumab (n = 102)	Chemotherapy (n = 112)	*P*	Length of Stay, d*	*P*
0	57 (55.9)	74 (66.1)	0.216	7 (4–13)	
I	13 (12.7)	7 (6.3)		10 (5–15)	0.546
II	21 (20.6)	23 (20.5)		10 (5–18)	
IIIa	4 (3.9)	4 (3.6)		19 (13–54)	<0.001
IIIb	5 (4.9)	1 (0.9)			
IVa	1 (1.0)	3 (2.7)		49 (21–77)	<0.001
IVb	1 (1.0)	0 (0)			
V	0 (0)	0 (0)		NA	
Total	45 (44%)	38 (34%)			

*Length of stay is for the Chemo+Bevacizumab group only and is depicted as median days (range). *P* values are derived from χ^2 test (Grade) and Mann-Whitney *U* test (Length of Stay).
For grading of complications please refer to METHODS and Ref 24.

TABLE 4. Complications Grade III or IV and Therapeutic Consequences in Patients Treated With Chemotherapy and Bevacizumab Prior to Hepatic Resection

Complication (No. Patients)	Therapy	Grade
Bile leak/biloma (4)	Percutaneous drainage	IIIa
Bile leak/biloma (1)	Open drainage	IIIb
Wound dehiscence sc (1)	Revision in OR	IIIb
Anastomotic dehiscence after right colectomy (1)	Revision in OR, diversion	IIIb
Serosal tear, fistula (1)	Revision in OR, stitched	IIIb
Ileus, herniation of intestine after diaphragmatic resection (1)	Revision in OR, diaphragm sutured, no bowel resection	IIIb
Gram negative sepsis, source not identified, renal failure (1)	ICU, hemofiltration	IVa
Dehiscence after low anterior resection, peritonitis, consecutive multiorgan dysfunction (liver, kidney, respiratory) (1)	ICU, multiple revisions, abdominal dressing	IVb

For grading of complications please refer to METHODS and Ref 24.
sc indicates subcutaneous; OR, Operating room; ICU, Intensive care unit.

TABLE 5. Type and Severity of Complications in Patients Treated With Chemotherapy and Bevacizumab Prior to Hepatic Resection

	Grade						
Type of Complication (n)	I	II	IIIa	IIIb	IVa	IVb	Total (%)
Infectious	7	11		1	1		20 (19.6)
Cardio-pulmonary		4					4 (3.9)
Bile leak/retention		2	4	1			7 (6.9)
Perforation/dehiscence		1		2		1	4 (3.9)
Paralysis/ileus		2		1			3 (2.9)
Liver dysfunction	1	1					2 (2.0)
Other	5						5 (4.9)
Total (%)	13 (12.7)	21 (20.6)	4 (3.9)	5 (4.9)	1 (1.0)	1 (1.0)	45 (44.1)

For grading of complications please refer to METHODS and Ref 24.

7.1%, $P = 0.350$, χ^2 test). In Table 4, the high-grade complications of the CHT + B group are depicted and the therapeutic consequences are referenced. The grade of complication correlated well with the length of postoperative stay, Table 3. There was no difference in patients with major resections >3 segments to develop general complications (14/28 vs. 6/17, $P = 0.336$, χ^2 test) or high-grade complications (6/28 vs. 3/17, $P = 0.758$, χ^2 test) with respect to Bevacizumab administration.

Factors Associated With Postoperative Complications in Patients Receiving Chemotherapy and Bevacizumab

Table 5 shows the distribution of all morbidities in the CHT + B group stratified by type of affected organ system and grade of complication. There was no association between the chemotherapeutic regimen used and the occurrence of postoperative

TABLE 6. Uni- and Multivariate Regression Analysis of Factors Associated With Perioperative Morbidity in Patients Receiving Chemotherapy and Bevacizumab Prior to Hepatic Resection

	Univariate				Multivariate			
Factor	**B**	**Exp(B)**	**95% CI**	***P***	**B**	**Exp(B)**	**95% CI**	***P***
Age	0.065	1.07	1.02–1.12	0.005	0.130	1.14	1.05–1.24	0.003
BMI	−0.013	0.99	0.90–1.09	0.789				
ICG R15	0.116	1.12	1.03–1.22	0.008	0.090	1.09	1.00–1.20	0.058
Albumin	−0.112	0.89	0.81–0.99	0.031	−0.144	0.87	0.75–1.00	0.049
Alkaline phosphatase	0.004	1.01	0.99–1.01	0.213				
Gamma glutamyltransferase	0.001	1.00	0.99–1.00	0.551				
Aspartate aminotransferase	0.006	1.01	0.99–1.01	0.160				
Alanine aminotransferase	0.005	1.00	0.99–1.01	0.154				
No. chemotherapy cycles	0.015	1.02	0.90–1.15	0.811				
Days since last Bev. dose	0.001	1.00	0.98–1.03	0.934				
Resection >3 segments	1.266	3.55	1.50–8.38	0.004	2.39	10.94	2.46–48.70	0.002
Synchronous bowel procedure	1.117	3.06	1.10–8.49	0.032	2.78	16.11	2.93–88.57	0.001

B indicates regression coefficient; Exp(B), Odds ratio; CI, confidence interval; BMI, body mass index; ICG R15, indocyanine retention at 15 min; Bev., Bevacizumab.

TABLE 7. Published Series Dealing With the use of Bevacizumab and Hepatic Surgery

Author	**Journal**	**Year**	**No. Patients***	**Morbidity†**	**Mortality†**	**Risk Factors for Morbidity**
Kesmodel, SB	J Clin Oncol	2008	81	49% vs. 43%	1% vs. 2%	low serum albumin, extrahepatic procedure
Reddy, SK	J Am Coll Surg	2008	39	44% vs. 39%	2.6% vs. 3.5%	Age ≥70 yr, extrahepatic procedure
D'Angelica, M	Ann Surg Oncol	2006	16	41% vs. 38%	0%	n.a.
Current series			102	44% vs. 34%	0%	Major resection, sync colon, albumin, age

*treated with Chemotherapy + Bevacizumab preoperatively.
†Chemotherapy + Bevacizumab vurses chemotherapy alone.
n.a. indicates not applicable.

complications (data not shown). Univariate logistic regression analysis of factors associated with morbidity revealed that age, lower preoperative serum albumin, increased Indocyanine green retention at 15 minutes (ICG R15), resection of more than 3 segments and a synchronous bowel procedure was correlated to an increased rate of any postoperative complications. With the exception of ICG R15, all these variables remained significant risk factors for morbidity in the multivariate analysis (Table 6). When only severe complications of Grade III or IV were analyzed, resection of more than 3 segments was the only factor remaining significant in multivariate analysis (odds ratio, 12.8; $P = 0.010$; data not shown).

DISCUSSION

We were able to demonstrate in this analysis that postoperative morbidity after liver resection for colorectal metastases is not increased in patients receiving chemotherapy in combination with Bevacizumab compared with chemotherapy alone. To our knowledge, this is currently the largest series dealing with this topic (Table 7). To benefit from the established advantages of VEGF inhibition in combination with cytotoxic chemotherapy,[8–12] it has to be proven that no compromise in perioperative safety is attained by this therapy.

A central point of debate is the possible detrimental effect of VEGF-blockade and decreased liver regeneration in subjects undergoing surgery after treatment with one of these agents.[15] Decreased hepatic function will predispose to infections, bleeding, and wound healing impairment, hence postoperative complication rate is expected to be higher after a therapy that included a VEGF blocking antibody.

All available although small series to date[17–19] report comparable morbidity and mortality after hepatic resection with and without preoperative therapy using Bevacizumab. No increase in hepatobiliary complications are reported in 2 of those studies.[18,19] The rate of liver insufficiency is reported to be even lower in patients treated with chemotherapy plus Bevacizumab in a recent unpublished series (4% vs. 11% with chemo only).[28] When assessing liver regeneration after resection in patients treated with Bevacizumab, an equivalent situation can be observed after portal vein embolization (PVE) prior to extended resection to increase the future remnant liver volume (FRLV). PVE mimics the situation after resection leading to hypertrophy of the remnant lobe due to nonperfusion of the embolized segments.[29] In the largest recent analysis, Covey et al[30] showed that the treatment with neoadjuvant chemotherapy itself had no negative influence on liver regeneration before intended resection. Zorzi et al[31] have found no difference in the absolute increase of FRLV after PVE in patients treated with chemotherapy and Bevacizumab (8.8%) compared with patients with chemotherapy and resection (6.8%) or resection after PVE alone (10.1%). However, Belghiti and coworkers[32] have recently published their findings that hypertrophy was impaired in patients additionally receiving Bevacizumab and PVE (relative increase in FRLV: 15% Bev+ vs. 40% Bev−). These contradictory results could partly be explained by the different durations of cytotoxic chemotherapies in these patients, since recent unpublished data suspect an increase in postoperative liver insufficiency rates in patients receiving more

than 9 cycles of Oxaliplatin. This effect was not linked to the administration of Bevacizumab in this respective series.[28] In our analysis, severe liver dysfunction occurred only in 1 patient suffering from multiorgan dysfunction due to peritonitis after dehiscence of his rectal anastomosis.

The finding that major liver resections are associated with increased postoperative complications is trivial and has been described many times before, especially in the light of preoperative chemotherapy.[33] An interesting finding is the correlation of increased anastomotic complications when hepatic resection is synchronously performed with bowel surgery after treatment with Bevacizumab. Although it has been shown before that synchronous resection of liver metastases and the colorectal primary tumor can be safely performed under certain circumstances,[34,35] the constellation of major liver resections and colorectal surgery should be avoided.[36] Of note, most series dealing with synchronous hepatic and colorectal resections contain only a small proportion of patients pretreated with chemotherapy or do not report the use of chemotherapy at all. In our series, some of the most severe complications occurred in patients in which a synchronous bowel anastomosis was performed. The only patient with a Grade IVb complication requiring ICU care for more than 2 months had undergone synchronous low anterior resection together with a minor liver resection; dehiscence of the rectal anastomosis and subsequent peritonitis lead to this adverse outcome. He was eventually discharged home 77 days after surgery. Another severe complication associated to a bowel resection (Grade IIIb) was encountered in a patient with right colectomy combined with an extended right hemihepatectomy. This patient had an almost complete dehiscence of the colonic anastomosis although there was no anatomic or vascular compromise evident upon revision.

In spite of the small number, the correlation of complications and synchronous bowel procedures cannot be neglected. There are only few reports of anastomotic complications attributable to Bevacizumab therapy[16,37] and the few cases reported here will not change our treatment policy entirely. However, a word of caution is indicated with the combination of hepatic surgery and bowel anastomosis in the background of anti-VEGF therapy.

In the original report by Dindo et al[24] the definition of mortality was any death related to a complication. We have adapted this definition as suggested before to include patients who have died during the hospital stay or within 30 days after surgery.[25] Since the critical period after surgery can extend beyond 30 days, some authors have advocated to report the 90-day mortality instead, since this might better reflect any sequelae attributable to the operation. One patient in each group died within 90 days after surgery after being discharged from hospital (1% vs. 0.9%, P = NS).

One point of criticism is the retrospective nature of half of this series and the inherent bias that is always encountered with this type of analyses. Possible flaws could be selection of patients for treatments according to their medical fitness or other confounding factors, especially when a new treatment modality emerges. We therefore decided to compare the results from recent patients treated with chemotherapy and Bevacizumab with a cohort of patients treated in a time period when the addition of targeted therapies was not an option. Besides some minor disparities in laboratory values, we found differences in those 2 cohorts, which could be understood as influencing the outcome of our analysis. There were more major resections in the CHT + B cohort, although the median tumor size had decreased compared with earlier patients. This underlines the fact that the extent of liver surgery for mCRC is most often not dictated by the size but by the distribution of the metastases, which is bilobar in the majority of cases. However, since resection of more than 3 segments was also a risk factor for postoperative complications, the disparity observed here does not negatively influence our conclusions. The decline in tumor size might reflect the strict adherence to our response evaluation protocol described earlier; 97% of resected patients had either response or stabilization of disease during neoadjuvant therapy. The decreased use of blood products during surgery (lower estimated blood loss) has also been described in 2 of the previous series dealing with the safety of Bevacizumab in liver surgery.[17,18] We do however think, that this finding might also be due to our emerging policy to avoid the use of blood products perioperatively in the light of adverse oncological outcomes that have been described before.[38,39]

CONCLUSION

In this article, we add evidence to the observation that surgery for colorectal liver metastases can be safely performed without increased morbidity or mortality after neoadjuvant chemotherapy including Bevacizumab. We found an association of increased morbidity with larger resections of 4 or more segments and with synchronous bowel procedures involving an anastomosis. Avoidance of such treatment combinations should further improve potential cure in mCRC. Prospective surgical trials are necessary to fully confirm our findings.

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