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ORIGINAL REPORT

Preoperative Bevacizumab Does Not Significantly Increase Postoperative Complication Rates in Patients Undergoing Hepatic Surgery for Colorectal Cancer Liver Metastases

Susan B. Kesmodel, Lee M. Ellis, E. Lin, George J. Chang, Eddie K. Abdalla, Scott Kopetz, Jean-Nicolas Vauthey, Miguel A. Rodriguez-Bigas, Steven A. Curley, and Barry W. Feig

From the Departments of Surgical Oncology, Cancer Biology, Biostatistics, and Cancer Medicine, The University of Texas M. D. Anderson Cancer Center, Houston, TX.

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Corresponding author: Barry W. Feig, MD, Department of Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Unit 444, Houston, TX 77030; e-mail: bwfeig@mdanderson.org.

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ABSTRACT

Purpose
Although bevacizumab (BV) increases survival rates when used with chemotherapy (CTX) in patients who have metastatic colorectal cancer (CRC), an increase in wound complications has been observed in patients who undergo surgery while receiving BV. We therefore evaluated whether neoadjuvant BV is associated with an increase in postoperative complications in patients undergoing surgery for CRC liver metastases.

Patients and Methods
Two subgroups of patients who received neoadjuvant CTX + BV (n = 81) or CTX alone (n = 44) were identified from a database of patients who underwent surgery for CRC liver metastases. Univariate and multivariate logistic regression models were used to evaluate the association of patient and tumor characteristics, neoadjuvant therapy, and operative factors with postoperative complications.

Results
Postoperative complications developed in 40 patients (49%) who received CTX + BV and 19 patients (43%) who received CTX. The median time from BV discontinuation to surgery was 58 days (range, 31 to 117 days). No significant associations were identified between BV use and timing of BV discontinuation and postoperative complications. On multivariate analysis, lower serum albumin and concomitant surgical procedures were associated with an increased risk of developing any complication (P = .035 and .023, respectively), and lower serum albumin was associated with hepatobiliary complications (P = .016).

Conclusion
Neither the use of BV nor timing of BV administration was associated with an increase in complication rates. These data suggest that the combination of BV with neoadjuvant CTX in patients who have CRC liver metastases does not increase surgical complications. To determine the optimal timing of surgery in patients receiving neoadjuvant BV, confirmatory prospective studies are required.

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INTRODUCTION

Bevacizumab (BV), a monoclonal antibody to vascular endothelial growth factor (VEGF), is an important component of treatment for metastatic cancer. Multiple phase III, randomized clinical trials have demonstrated the efficacy of BV in combination with cytotoxic chemotherapy (CTX) for metastatic colorectal cancer (CRC),[1-3] and combined therapy improves progression-free survival and duration of response compared with CTX alone. These data led to the approval of BV by the US Food and Drug Administration for use in combination with cytotoxic CTX as first-line or second-line therapy for metastatic CRC.

The liver is the most common site of organ metastasis from CRC, and resection of liver metastases is an effective treatment in select patients. Because of the increased efficacy of systemic therapy for CRC, decreased mortality rates from hepatic resection, and new surgical approaches and techniques, more patients who have CRC liver metastases are being considered candidates for surgical resection. Neoadjuvant CTX is being used with increasing frequency in these patients to decrease tumor volume, assess tumor response to therapy, and potentially treat micrometastatic disease before surgery. Retrospective studies have demonstrated improvements in overall survival after hepatic resection in select patients with CRC liver metastases who

received neoadjuvant CTX.[4,5] In addition, 5-year overall survival rates of up to 38% have been reported after hepatic resection in patients who had initially unresectable disease that was downsized by neoadjuvant CTX.[6]

Given its efficacy in combination with CTX for metastatic CRC, BV is also being combined with neoadjuvant CTX in patients who have CRC liver metastases before surgical resection. However, the safety and optimal timing of surgery in patients who receive BV are still under investigation. BV inhibits the activity of VEGF, one of the key mediators of angiogenesis.[7,8] The importance of VEGF in hepatocyte proliferation, hepatic recovery, and wound healing has been demonstrated in multiple preclinical studies.[9-14] The combination of BV's antiangiogenic effects and its long half-life (median, 17 to median, approximately 21 days; range, 11 to 50 days)[7] has led to concern that the use of preoperative BV may affect liver regeneration and wound healing and potentially may increase postoperative morbidity after hepatic surgery.[15,16] Therefore, the purpose of this study was to evaluate the association between neoadjuvant BV and postoperative morbidity in patients undergoing hepatic surgery for CRC liver metastases.

PATIENTS AND METHODS

Patients

With the approval of our institutional review board, we reviewed a database of patients who underwent hepatic surgery at The University of Texas M. D. Anderson Cancer Center since November 1, 1990. Inclusion criteria for the study cohort included receipt of neoadjuvant CTX; surgery for CRC liver metastases; and date of treatment after January 1, 2004, because BV was not administered before hepatic surgery at our institution before this date. The type and duration of CTX and the decision to use BV were at the discretion of the treating medical oncologist. Therefore, treatment varied depending on response and timing of referral for surgical intervention. Patients who received neoadjuvant CTX and BV were compared with patients who received neoadjuvant CTX alone.

Clinical Variables

Data on patient and tumor characteristics, neoadjuvant treatment regimens, and operative factors were collected. Patient and tumor characteristics included age, sex, comorbidities, body mass index, preoperative serum albumin, CRC stage at diagnosis, number and distribution of metastases, and use of preoperative portal vein embolization. Neoadjuvant treatment regimens were evaluated for agents used, duration of therapy, number of regimens, and time from completion of CTX and BV to surgery. Surgical variables included extent of hepatic surgery, radiofrequency ablation, largest tumor resected, extrahepatic surgical procedures, duration, and estimated blood loss.

Operative Management

Patients were considered candidates for surgery if all liver metastases could be eliminated by resection and/or radiofrequency ablation. Preoperative imaging of the chest, abdomen, and pelvis was obtained to determine the number, size, and distribution of liver metastases and to identify extrahepatic disease. Additional preoperative testing was performed at the discretion of the surgeon on the basis of imaging findings and patient comorbidities.

Intraoperative ultrasonography and low central venous pressure anesthesia were utilized. Radiofrequency ablation was performed by using an RF 3000 generator with a 3.5- or 4.0-cm–diameter array needle electrode (Boston Scientific, Natick, MA). Hepatic resections were classified according to the segmental anatomy of the liver as defined by Couinaud.[17] Major hepatic resections were defined as removal of three or more liver segments.

BV-Related Complications

Complications associated with BV, including hypertension, proteinuria, bleeding, gastrointestinal perforations, and arterial thromboembolic events, were evaluated and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Postoperative Complications

Postoperative complications were defined as those that occurred within 90 days of liver surgery, and they were graded by using a previously defined grading system for surgical complications.[18,19] Complications were classified as follows: wound complication, infection or collection that required partial wound opening and local wound care, wound complication that required surgery, or cellulitis that required antibiotics; hepatobiliary complication, biliary collection that required percutaneous drainage, or liver insufficiency (peak bilirubin level > 7 mg/dL)[20]; cardiovascular complication, arrhythmia, myocardial ischemia, or hemodynamic instability that required intensive care unit (ICU) monitoring; pulmonary complication, requirement of invasive or noninvasive ventilatory support, pleural effusion that required drainage, or pneumonia that required antibiotics; renal complication, increase in serum creatinine level ≥ 0.5 mg/dL during a 24-hour period, or need for hemodialysis; anastomotic complication, or radiographically documented or clinically evident leak; infectious complication, or documented blood, gastrointestinal/abdominal, or urinary tract infection that required antibiotics/drainage (wound and pulmonary infectious complications excluded); or other complication, readmission, re-operation, or need for ICU monitoring.

Statistical Analysis

Descriptive statistics, including frequency, median, range, and percentage, were calculated separately for the two treatment groups. Wilcoxon rank sum tests were performed to assess differences between continuous variables. The χ^2 test or (if there were five or fewer observations in a group) the Fisher's exact test was applied to assess the association between categoric variables. Univariate and multivariate logistic regression models were used to evaluate the association of clinical variables with postoperative complications and to determine the odds ratios and 95% CIs. A backward selection method was utilized in the multivariate model. A P value of less than .05 was considered statistically significant. All computations were carried out by using SAS software, version 9.1 (SAS Institute, Cary, NC).

RESULTS

Patient and Tumor Characteristics

Between January 1, 2004, and May 1, 2006, 125 patients who received neoadjuvant CTX underwent surgery for CRC liver metastases. Forty-four patients received CTX alone (CTX group), and 81 patients received CTX and BV (CTX + BV group). The majority of patient and tumor characteristics were similar in the two groups (Table 1).

Neoadjuvant Treatment Regimens

Other than BV administration, neoadjuvant treatment regimens were comparable between the two groups (Table 1). Oxaliplatin-based regimens were most commonly used. Among patients who received BV, the median time from discontinuation of BV to surgery was 58 days (range, 31 to 117 days).

Surgical Data

Factors related to surgery also were similar in the two groups (Table 1). Major hepatic resections were performed in greater than half of the patients. Twenty-two extrahepatic procedures were performed in 20 patients; these included bowel resection (n = 7), ostomy reversal (n = 4), lung resection (n = 3), adjacent organ resection (n = 1), bile duct reconstruction (n = 1), myocutaneous flap (n = 1), abdominal wall resection (n = 1), portal vein thrombectomy (n = 1), and additional extra-abdominal procedures (n = 3). The duration of

Table 1. Clinical Variables

Variable	Treatment				P
	CTX (n = 44)		CTX + BV (n = 81)		
	No.	%	No.	%	
Patient and tumor characteristics					
Age, years					.34
Median	58		57		
Range	31-80		29-84		
Sex					.33
Male	30	68	48	59	
Female	14	32	33	41	
Comorbidities					
Cardiovascular	5	11	12	15	.60
Hypertension	9	20	32	40	.03
Pulmonary	2	5	1	1	.28
Renal	3	7	2	2	.34
Hepatobiliary	0	0	2	2	.54
Diabetes mellitus	4	9	10	12	.77
BMI					.94
Median	28.4		28.4		
Range	20.4-40.1		18.0-48.9		
Preoperative serum albumin*					.86
Median	4.2		4.1		
Range	3.5-4.9		3.3-5.1		
Stage at initial diagnosis					.93
I	2	5	5	6	
II	9	20	13	16	
III	8	18	16	20	
IV	25	57	47	58	
Metastatic liver lesions					.04
1	16	36	17	21	
2	9	20	20	25	
3	10	23	10	12	
≥ 4	9	20	34	42	
No. of lesions					.02
Median	2		3		
Range	1-9		1-21		
Distribution of liver metastases					.20
Unilobar	27	61	40	49	
Bilobar	17	39	41	51	
Portal vein embolization	5	11	4	5	.28
Neoadjuvant treatment regimens					
No. of different CTX regimens received					.53
1	38	86	71	88	
2	6	14	8	10	
3	0	0	2	2	
Type of CTX					
FU or capecitabine† alone	2	5	7	9	.49
Oxaliplatin + leucovorin + either infusional FU or capecitabine	32	73	57	70	.78
Irinotecan + leucovorin + either infusional FU or capecitabine	10	23	24	30	.41
IFL	4	9	4	5	.45
Irinotecan alone	2	5	1	1	.28
Duration of CTX, days					.22
Median	97		105		
Range	15-441		29-513		
Time from last CTX dose to surgery, days					.08
Median	43		49		
Range	11-99		21-106		
Duration of BV, days					
Median	—		84		—
Range	—		14-513		
Time from last BV dose to surgery, days					
Median	—		58		—
Range	—		31-117		

(continued on following page)

Table 1. Clinical Variables (continued)

Variable	Treatment				
	CTX (n = 44)		CTX + BV (n = 81)		
	No.	%	No.	%	*P*
Operative factors					
Procedure					.45
Extended hepatectomy (≥ 5 segs)	8	18	17	21	
Hemihepatectomy (3 or 4 segs)	22	50	30	37	
Biseg/segmentectomy	6	14	12	15	
Wedge resection	8	18	17	21	
Radiofrequency ablation only	0	0	5	6	
Size of largest tumor resected, cm					.56
Median	2.5		2.5		
Range	0.5-11.5		0.5-12.0		
Radiofrequency ablation in addition to resection	12	27	20	25	.76
Extrahepatic procedure	8	18	12	15	.62
Duration of surgery, mins					.85
Median	134		139		
Range	69-408		67-675		
Estimated blood loss, mL					.77
Median	200		250		
Range	50-1,750		1,950		

Abbreviations: CTX, neoadjuvant chemotherapy alone; CTX + BV, neoadjuvant chemotherapy + bevacizumab; FU, fluorouracil (SP Pharmaceuticals, Albuquerque, NM); IFL, irinotecan (Pfizer Inc, New York, NY), bolus fluorouracil, and leucovorin (Ben Venue Laboratories Incm Bedford, OH); Biseg, bisegmentectomy; seg, hepatic segment.

*Normal preoperative serum albumin range, 3.5 to 4.7 g/dL.

†Capecitabine (Roche Pharmaceuticals, Nutley, NJ).

surgery and the estimated blood loss varied greatly depending on the surgical procedure performed.

BV-Related Complications

Ten patients (12%) experienced preoperative adverse events related to BV therapy. Nine patients developed hypertension (two, grade 1; one, grade 2; and six, grade 3); two had proteinuria (one, grade 1; one, grade 2); and one had minor bleeding (grade 1). There were no arterial thromboembolic events or gastrointestinal perforations.

Postoperative Complications

A total of 23 postoperative complications developed in 19 patients (43%) in the CTX group, and 58 postoperative complications developed in 40 patients (49%) in the CTX + BV group (Table 2). Of the patients with complications, 95% in the CTX group and 90% in the CTX + BV group had only one or two complications, and most of these were grade 1 or 2 (74% in the CTX group and 71% in the CTX + BV group; Table 3). There was no significant difference in the total number of complications that each patient developed between the two groups ($P = .22$). Of those patients who underwent major hepatic resections, complications developed in 49% overall, 43% in the CTX group, and 53% in the CTX + BV group ($P = .40$).

Wound complications were the most common complication observed, and they occurred in 27% of patients. Most were minor and were managed with local wound care or antibiotics. Four patients (one, CTX group; three, CTX + BV group) developed a superficial wound dehiscence treated with a vacuum-assisted wound closure device (VAC; Kinetic Concepts Inc, San Antonio, TX). Two patients in the CTX + BV group required operative management of wound dehiscence/infection. The initial surgery in one patient included an abdominoperineal resection and vertical rectus abdominis myocutaneous flap that resulted in an abdominal wall abscess. The second patient had persistent wound drainage and underwent debridement and tertiary wound closure approximately 2 months postoperatively.

Hepatobiliary complications developed in 7% of patients overall, in 11% of patients in the CTX group, and in 5% of patients in the CTX + BV group. Four patients developed bilomas that required percutaneous drainage (one, CTX group; three, CTX + BV group), and one patient in the CTX group developed a biliary stricture

Table 2. Postoperative Complications

Complication	Treatment Group				
	CTX (n = 44)		CTX + BV (n = 81)		
	No.	%	No.	%	*P*
Wound	11	25	23	28	.68
Hepatobiliary	5	11	4	5	.28
Cardiovascular	1	2	3	4	1.0
Pulmonary	2	5	11	14	.14
Renal	1	2	0	0	.35
Anastomotic	0	0	1	1	1.0
Infectious	1	2	7	9	.26
Death	1	2	1	1	1.0
Other	1	2	8	10	.1

NOTE. Some patients had more than one complication, as follows: CTX group—one patient with two complications and one patient with four complications; CTX + BV group—10 patients with two complications, three patients with three complications, and one patient with four complications.

Abbreviations: CTX, neoadjuvant chemotherapy alone; CTX + BV, neoadjuvant chemotherapy + bevacizumab.

Table 3. Grade of Surgical Complications

Complication	No. of Patients by Complication Grade per Treatment Group					
	CTX (n = 44)			CTX + BV (n = 81)		
	1-2	3-4	5	1-2	3-4	5
Wound	11	0	0	21	2	0
Hepatobiliary	0	4	1	0	4	0
Cardiovascular	1	0	0	3	0	0
Pulmonary	2	0	0	10	1	0
Renal	1	0	0	0	0	0
Anastomotic	0	0	0	0	1	0
Infectious	1	0	0	4	3	0
Other	1	0	0	3	5	0

Abbreviations: CTX, neoadjuvant chemotherapy alone; CTX + BV, neoadjuvant chemotherapy + bevacizumab.

that required percutaneous transhepatic cholangiography and stent placement. Reversible hepatic insufficiency developed in two patients in the CTX group and in one patient in the CTX + BV group. Chronic liver insufficiency developed in one patient in the CTX group.

Cardiovascular complications included atrial fibrillation in three patients (one, CTX group; two, CTX + BV group) and uncontrolled hypertension in one patient (CTX + BV group). Pulmonary complications included pneumonia in six patients (two, CTX group; four, CTX + BV group), pleural effusions that required drainage in two patients (both, CTX + BV group), and respiratory insufficiency that required noninvasive ventilatory support in four patients (all, CTX + BV group). One patient in the CTX + BV group developed acute respiratory distress syndrome that required intubation and temporary tracheostomy. The patient eventually recovered completely.

Infectious complications included intra-abdominal collections in three patients (all, CTX + BV group), two of whom underwent concomitant ileostomy reversal; line sepsis/bacteremia in four patients (one, CTX group; three, CTX + BV group); and *Clostridium difficile* colitis in one patient (CTX + BV group). Other complications in the CTX + BV group included one small bowel obstruction that required re-operation, one traumatic Foley catheter removal that required continuous bladder irrigation, ICU monitoring in three patients, and three hospital readmissions for dehydration. In the CTX group, one patient required readmission for dehydration.

There was one death in each group within 90 days of surgery. In the CTX group, one patient died as a result of progressive liver failure. In the CTX + BV group, one patient was readmitted to an outside hospital with septic physiology and developed multisystem organ failure within 24 hours. The source of sepsis was not identified before the patient's death.

Association of Clinical Variables With Postoperative Complications

On univariate analysis, only three clinical variables were associated with postoperative complications: lower preoperative serum albumin level, concomitant extrahepatic surgical procedures, and greater estimated blood loss (Table 4). On multivariate analysis, serum albumin level and extrahepatic surgical procedures remained significant risk factors for the development of any postoperative complication, and serum albumin level also was associated with the development of hepatobiliary complications (Table 4). Although there was a trend toward an increase in wound complications in patients who received a longer duration of chemotherapy ($P = .06$) or who had a greater body mass index ($P = .06$), neither reached statistical significance.

No significant association was identified between the use of BV and postoperative complications (Table 2). In addition, the time interval from discontinuation of BV to surgery, whether considered as a continuous variable ($P = .99$) or a categoric variable (Table 5), was not associated with an increased likelihood of developing complications. A subgroup analysis of patients who received BV also demonstrated no significant difference in complication rates between patients who received BV 31 to 45 days (n = 13), 46 to 60 days (n = 27), and greater than 60 days (n = 36) before surgery ($P = .21$).

DISCUSSION

Neoadjuvant BV is being used with increasing frequency in combination with cytotoxic CTX before surgical resection in patients who have

Table 4. Association Between Clinical Variables and Postoperative Complications on Univariate and Multivariate Logistic Regression Analyses

Complication or Clinical Variable	Analyses			
	Univariate *P*	Multivariate *P*	Odds Ratio	95% CI
Any complication	.046	.035	3.72	1.10 to 12.66
Lower serum albumin	.031	.023	3.45	1.18 to 10.1
Extrahepatic procedure	.048	NS	—	—
Greater estimated blood loss				
Wound complication	.299	—	—	—
Lower serum albumin	.056	NS	—	—
Extrahepatic procedure	.147	—	—	—
Greater estimated blood loss				
Hepatobiliary complication	.016	.016	20.41	1.76 to 250
Lower serum albumin	.680	—	—	—
Extrahepatic procedure	.030	NS	—	—
Greater estimated blood loss	.046	.035	3.72	1.10 to 12.66

Abbreviation: NS, not significant.

Table 5. Association Between Postoperative Complications and Time From Discontinuation of BV to Surgery

	Patients by Days From Last BV Dose to Surgery				
	≤60 Days (n = 40)*		> 60 Days (n = 36)†		
Complication	No.	%	No.	%	*P*
Any	22	55	16	44	.43
Wound	13	33	10	28	.70
Hepatobiliary	3	8	1	3	.39

NOTE. Discontinuation measured as last dose of BV known in 76 patients.
Abbreviation: BV, bevacizumab.
*Median, 49 days.
†Median, 74 days.

CRC liver metastases. However, given the antiangiogenic effects of BV, there has been concern that postoperative morbidity may be increased because of potential effects on liver regeneration and wound healing. In this study, we investigated clinical variables that may affect postoperative outcomes in patients undergoing hepatic surgery. These included factors that have been previously reported to increase postoperative morbidity and mortality after hepatic resection[21-26] as well as the use of neoadjuvant BV. Postoperative complications developed in 47% of the patients overall, in 43% of patients who received CTX alone, and in 49% of patients who received CTX and BV. Greater than 70% of these complications were minor (ie, grade 1 or 2). On univariate analysis, we found no significant differences in the number and types of postoperative complications between the two groups (Table 2). Importantly, there was no significant increase in hepatobiliary or wound complications or postoperative deaths in patients who received BV.

Currently, there are limited data on surgical outcomes in patients who have received BV. The largest reported study, from Scappaticci et al,[27] was a pooled analysis that evaluated surgical complications in patients from two randomized clinical trials that investigated the efficacy of BV.[2,28] This analysis demonstrated a three-fold increase in wound healing complications in patients who underwent surgery while receiving BV, although this did not reach statistical significance because of the relatively small number of patients. Two recent publications from D'Angelica et al[29] and Reddy et al[30] focused on morbidity in patients who received perioperative or preoperative BV, respectively, and who underwent partial hepatectomy. In the data reported by D'Angelica et al,[29] no significant difference in overall morbidity was demonstrated between patients who received CTX and BV compared with those who received CTX alone (40.6% *v* 37.5%; $P = 1.00$). Reddy et al[30] also demonstrated no significant difference in overall complications in those patients treated with and without preoperative BV (43.6 *v* 38.6%; $P = .78$). However, the investigators found that, in patients treated with BV, overall complications were more common in patients who received BV within 8 weeks of surgery (62.5% *v* 30.4%; $P = .06$). This did not reach statistical significance, and the small number of patients in this study makes it difficult to draw conclusions about the timing of BV discontinuation before surgery.

Because one of the primary concerns for surgical oncologists is the optimal timing of surgery in patients who receive BV, we evaluated the association between postoperative complications and the time from BV discontinuation to surgery. When this time interval was considered as either a continuous variable or a categoric variable (≤ 60 or > 60 days), no significant association with postoperative morbidity was identified. In patients who underwent surgery within 60 days of receiving BV (n = 40), the median time interval was 7 weeks, which suggests that this may be a safe time after which to consider surgery. In addition, when complication rates were compared between patients who received BV 31 to 45 days (n = 13), 46 to 60 days (n = 27), and greater than 60 days (n = 36) before surgery, there was still no significant difference ($P = .21$). These data imply that surgery may be performed even closer to BV administration without increasing postoperative morbidity. However, given the small number of patients in each group, definitive conclusions regarding the safety of surgery in patients who receive BV and the timing of BV discontinuation require additional investigation.

In addition to exploring the effects of preoperative BV, we were able to contribute data on the effects of neoadjuvant CTX on postoperative complications. Several recent studies reported increased postoperative morbidity and mortality in patients who received neoadjuvant CTX before hepatic resection. The duration of preoperative CTX was found to have a significant impact on postoperative morbidity in multiple studies.[21-23] In addition, a recent study from Vauthey et al[26] demonstrated an increase in postoperative mortality rates in patients who developed steatohepatitis. In this study, although there was a trend toward increased postoperative morbidity in patients who received a longer duration of CTX, this did not reach statistical significance ($P = .06$). In addition, there was no association between the type of CTX and postoperative complications, although the number of patients who received only non–oxaliplatin-based CTX regimens was small (n = 36).

Because this study is a retrospective analysis of a single institution experience with small patient numbers, definitive conclusions about the safety of neoadjuvant BV and timing of BV discontinuation cannot be made. The type of CTX, the decision to use BV, the duration of CTX and BV administration, and the timing of surgical consultation were at the discretion of the treating physician. Therefore, it is difficult to know what criteria were utilized for treatment and referral, which likely leads to selection bias. In addition, it is often difficult to assess the number and severity of complications in a retrospective manner. However, this is the largest study to date to evaluate the association between neoadjuvant BV and postoperative morbidity in patients undergoing hepatic surgery for CRC liver metastases; therefore, it provides important information that may be used for future prospective studies.

In summary, in this study, the addition of BV to neoadjuvant cytotoxic CTX in patients who have CRC liver metastases was not associated with an increase in postoperative complications. In addition, there was no association between postoperative complications and the time interval from BV discontinuation to surgery, although all patients underwent surgery at least 30 days after the last BV dose. These data suggest that BV may be administered in combination with neoadjuvant CTX before resection of CRC liver metastases without increasing postoperative morbidity. Although the optimal timing of surgery in patients who receive BV requires additional investigation, in this study there was no statistically significant increase in complication rates in patients who received BV within 31 to 60 days (n = 40) of surgery. Therefore, on the basis of these results, we still recommend waiting at least 6 weeks from discontinuation of BV to surgery.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Conception and design: Susan B. Kesmodel, Miguel A. Rodriguez-Bigas, Barry W. Feig

Provision of study materials or patients: George J. Chang, Eddie K. Abdalla, Scott Kopetz, Jean-Nicolas Vauthey, Miguel A. Rodriguez-Bigas, Steven A. Curley, Barry W. Feig

Collection and assembly of data: Susan B. Kesmodel

Data analysis and interpretation: Susan B. Kesmodel, Lee M. Ellis, E. Lin, George J. Chang, Miguel A. Rodriguez-Bigas, Steven A. Curley, Barry W. Feig

Manuscript writing: Susan B. Kesmodel, Lee M. Ellis, Steven A. Curley, Barry W. Feig

Final approval of manuscript: Susan B. Kesmodel, Lee M. Ellis, George J. Chang, Eddie K. Abdalla, Scott Kopetz, Jean-Nicolas Vauthey, Miguel A. Rodriguez-Bigas, Steven A. Curley, Barry W. Feig

REFERENCES

1. Giantonio BJ, Catalano PJ, Meropol NJ, et al: Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: Results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol 25:1539-1544, 2007

2. Hurwitz H, Fehrenbacher L, Novotny W, et al: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 350:2335-2342, 2004

3. Saltz L, Clarke S, Diaz-Rubio E, et al: Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: A randomized phase III study. J Clin Oncol 26:2013-2019, 2008

4. Allen PJ, Kemeny N, Jarnagin W, et al: Importance of response to neoadjuvant chemotherapy in patients undergoing resection of synchronous colorectal liver metastases. J Gastrointest Surg 7:109-115, 2003

5. Tanaka K, Adam R, Shimada H, et al: Role of neoadjuvant chemotherapy in the treatment of multiple colorectal metastases to the liver. Br J Surg 90:963-969, 2003

6. Adam R, Delvart V, Pascal G, et al: Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: A model to predict long-term survival. Ann Surg 240:644-657, 2004

7. Gordon MS, Margolin K, Talpaz M, et al: Phase I safety and pharmacokinetic study of recombinant human anti-vascular endothelial growth factor in patients with advanced cancer. J Clin Oncol 19:843-850, 2001

8. Hicklin DJ, Ellis LM: Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. J Clin Oncol 23:1011-1027, 2005

9. Donahower B, McCullough SS, Kurten R, et al: Vascular endothelial growth factor and hepatocyte regeneration in acetaminophen toxicity. Am J Physiol Gastrointest Liver Physiol 291:G102-G109, 2006

10. Howdieshell TR, Callaway D, Webb WL, et al: Antibody neutralization of vascular endothelial growth factor inhibits wound granulation tissue formation. J Surg Res 96:173-182, 2001

11. Mochida S, Ishikawa K, Inao M, et al: Increased expressions of vascular endothelial growth factor and its receptors, flt-1 and KDR/flk-1, in regenerating rat liver. Biochem Biophys Res Commun 226:176-179, 1996

12. Redaelli CA, Semela D, Carrick FE, et al: Effect of vascular endothelial growth factor on functional recovery after hepatectomy in lean and obese mice. J Hepatol 40:305-312, 2004

13. Taniguchi E, Sakisaka S, Matsuo K, et al: Expression and role of vascular endothelial growth factor in liver regeneration after partial hepatectomy in rats. J Histochem Cytochem 49:121-130, 2001

14. Zhang F, Lei MP, Oswald TM, et al: The effect of vascular endothelial growth factor on the healing of ischaemic skin wounds. Br J Plast Surg 56:334-341, 2003

15. Bilchik AJ, Poston G, Curley SA, et al: Neoadjuvant chemotherapy for metastatic colon cancer: A cautionary note. J Clin Oncol 23:9073-9078, 2005

16. Ellis LM, Curley SA, Grothey A: Surgical resection after downsizing of colorectal liver metastasis in the era of bevacizumab. J Clin Oncol 23:4853-4855, 2005

17. Couinaud C: Anatomic principles of left and right regulated hepatectomy: Technics. [in French] J Chir (Paris) 70:933-966, 1954

18. Martin RC, Jaques DP, Brennan MF, et al: Extended local resection for advanced gastric cancer: Increased survival versus increased morbidity. Ann Surg 236:159-165, 2002

19. Martin RC, Brennan MF, Jaques DP: Quality of complication reporting in the surgical literature. Ann Surg 235:803-813, 2002

20. Mullen JT, Ribero D, Reddy SK, et al: Hepatic insufficiency and mortality in 1,059 noncirrhotic patients undergoing major hepatectomy. J Am Coll Surg 204:854-862, 2007

21. Adam R, Pascal G, Castaing D, et al: Tumor progression while on chemotherapy: A contraindication to liver resection for multiple colorectal metastases? Ann Surg 240:1052-1061, 2004

22. Aloia T, Sebagh M, Plasse M, et al: Liver histology and surgical outcomes after preoperative chemotherapy with fluorouracil plus oxaliplatin in colorectal cancer liver metastases. J Clin Oncol 24:4983-4990, 2006

23. Karoui M, Penna C, min-Hashem M, et al: Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. Ann Surg 243:1-7, 2006

24. Kooby DA, Fong Y, Suriawinata A, et al: Impact of steatosis on perioperative outcome following hepatic resection. J Gastrointest Surg 7:1034-1044, 2003

25. Kooby DA, Stockman J, Ben-Porat L, et al: Influence of transfusions on perioperative and long-term outcome in patients following hepatic resection for colorectal metastases. Ann Surg 237:860-869, 2003

26. Vauthey JN, Pawlik TM, Ribero D, et al: Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol 24:2065-2072, 2006

27. Scappaticci FA, Fehrenbacher L, Cartwright T, et al: Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab. J Surg Oncol 91:173-180, 2005

28. Kabbinavar F, Hurwitz HI, Fehrenbacher L, et al: Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol 21:60-65, 2003

29. D'Angelica M, Kornprat P, Gonen M, et al: Lack of evidence for increased operative morbidity after hepatectomy with perioperative use of bevacizumab: A matched case-control study. Ann Surg Oncol 14:759-765, 2007

30. Reddy SK, Morse MA, Hurwitz HI, et al: Addition of bevacizumab to irinotecan- and oxaliplatin-based preoperative chemotherapy regimens does not increase morbidity after resection of colorectal liver metastases. J Am Coll Surg 206:96-106, 2008

