ORIGINAL CONTRIBUTION

A Population-Based Study of Complications After Colorectal Surgery in Patients Who Have Received Bevacizumab

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BACKGROUND: Patients receiving Bevacizumab, a vascular endothelial growth factor inhibitor used to treat metastatic colorectal cancer, may be at greater risk of complications after colorectal surgery because of impaired healing.

OBJECTIVE: The purpose of this study was to describe population-based rates of complications of colorectal surgery after Bevacizumab treatment and evaluate the relationship between time since last treatment and risk of complications.

DESIGN: This was a population-based retrospective cohort study using administrative and cancer registry data.

SETTINGS: The study was conducted in Ontario, Canada.

PATIENTS: Patients with metastatic colorectal cancer receiving Bevacizumab between January 2008 and December 2011 were followed for a year after treatment or until death.

MAIN OUTCOME MEASURES: Administrative data were used to identify patients who underwent colorectal surgery after initiation of Bevacizumab and to determine whether they experienced a complicated postoperative course. The relationship between time since last Bevacizumab treatment (≤28 d, 29 d to 3 mo, and >3 mo) and risk of postoperative complications was evaluated using logistic regression.

RESULTS: Of the 2759 patients who received Bevacizumab for the treatment of metastatic colorectal cancer, 265 underwent a colorectal procedure after exposure. The majority had a bowel resection or repair with no stoma (47.5%) and had emergency surgery (61.1%). Overall, 96 (36.2%) had a complicated postoperative course, including 20.4% readmission, 12.5% wound complications, and 7.9% mortality rate within 30 days of surgery. Adjusted multivariate analysis showed no difference in the likelihood of a complicated postoperative course among patients undergoing surgery within 28 days of receiving their last Bevacizumab dose compared with 29 days to 3 months (OR = 1.23 (95% CI, 0.53–2.84), or 3 to 12 months (OR = 0.98 (95% CI, 0.46–2.09) after receiving Bevacizumab.

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LIMITATIONS: Reliance on administrative data to measure complications limited the scope of this study.

CONCLUSIONS: Patients with metastatic colorectal cancer requiring colorectal surgery after exposure to Bevacizumab experience substantial morbidity and mortality. The risk of complications is not detectably associated with time since exposure. See **Video Abstract** at http://links.lww.com/DCR/A474.

KEY WORDS: Bevacizumab; Cohort study; Colorectal cancer; Population based; Postoperative complications.

Bevacizumab (BV), a partially humanized monoclonal antibody that binds to vascular endothelial growth factor (VEGF), improves progression-free and overall survival when used in combination with other chemotherapy agents in patients with metastatic colorectal cancer (CRC).[1–3] BV is now part of first-line treatment in the management of metastatic CRC, and >65% of patients treated for advanced CRC are exposed to BV.[4] The actions of BV have a potential to inhibit wound healing[5]; pooled data from 2 randomized trials[2,3] revealed wound complications in 13.0% of patients who received BV with chemotherapy before undergoing surgery compared with 3.4% in patients undergoing surgery who were exposed to chemotherapy alone. In addition, GI perforation was an uncommon but serious adverse event in phase 3 trials of BV in metastatic CRC[1,2] and occurred in 1.9% of patients treated with BV in a large, community-based cohort.[6] Consequently, the BV product monograph states that BV should be discontinued ≥28 days before elective surgery and should not be initiated for ≥28 days after surgery.

Most studies that have evaluated the effect of BV on postoperative complications have not found worse outcomes in patients who received perioperative BV as compared with those who did not.[7–12] However, many of these studies have been conducted in single centers and included only patients undergoing elective liver surgery for metastatic CRC. Furthermore, the effects of this drug on postoperative complications in a more urgent setting have not been studied other than the few patients requiring such surgery enrolled in randomized control studies. Moreover, patients selected for clinical trials often differ from the general population of patients with metastatic CRC, and currently there are no population-based assessments of the outcomes and postoperative complications of colorectal surgery after BV treatment. This is important because some patients with metastatic CRC will unexpectedly require urgent colorectal surgery during or shortly after discontinuing BV therapy, for example, for bowel obstruction if a primary tumor progresses on systemic therapy.[13] The aim of this study was to provide a population-based description of the risk of complications from colorectal surgery in patients who received BV treatment for metastatic CRC and to explore the relationship between this risk and the time since BV exposure.

PATIENTS AND METHODS

This study was approved by the institutional review board at Sunnybrook Health Sciences Centre (Toronto, Ontario, Canada).

Identification of Cohort

We conducted a population-based, retrospective cohort study in Ontario using information from multiple linked administrative health databases. We identified all persons in the province, aged 18 to 90 years, who received BV for the indication of first-line treatment of metastatic cancer from January 1, 2008, through December 31, 2011, using the publicly funded drug database. We linked these persons to the Ontario Cancer Registry (OCR) to identify patients who had a history of CRC (see Supplementary Table S1, http://links.lww.com/DCR/A570). The OCR includes information on all incident cancers (except nonmelanoma skin cancers) diagnosed since 1964 in Ontario. Reporting is provincially mandated and >95% complete.[14] The OCR does not maintain information on tumor recurrence. Demographic information and vital status were obtained from the Registered Persons Database, a roster of all Ontario Health Insurance (OHIP) beneficiaries (virtually all individuals living in Ontario). OHIP includes information on claims billed by physicians for services, permitting identification of medical procedures occurring in Ontario.

We identified persons from this group who underwent a colorectal surgical procedure while on therapy or within 1 year of their last BV treatment with Canadian Classification of Health Interventions (CCI) codes for colorectal surgery from the Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD) database (see Supplementary Table S2, http://links.lww.com/DCR/A570). The DAD contains information on every patient discharged from a hospital in Ontario. Surgeries were classified as bowel resection or repair without stoma, bowel resection or repair with stoma, and bypass or diversion only. Surgery urgency (elective vs emergent) was determined based on hospital admission category. The time from the last BV treatment to the date of surgery was categorized as ≤28 days, 29 days to 3 months, and >3 months.

Outcomes

The primary outcome was a complicated postoperative course (a composite outcome including death, readmission, or surgical complication). We identified death and complications within 30 days of the surgical procedure. We identified readmission to any hospital during the 30 days after index discharge. Surgical complications were identi-

fied through CCI and International Statistical Classification of Diseases, 10th Revision, codes in CIHI-DAD; the National Ambulatory Care Reporting System (NACRS); or OHIP fee codes using methods consistent with previous studies.[15,16] The NACRS includes data for all hospital- and community-based ambulatory care, including emergency department visits. Surgical complications included reoperation for intra-abdominal complications after the index surgery (drainage, resection, or stoma creation), wound complications (percutaneous drainage of abdominal abscess, wound infection, major wound disruption, or fistula formation), venous thromboembolism or pulmonary embolism, sepsis, hemorrhage, cardiovascular events (acute myocardial infarction or congestive heart failure), stroke, or transient ischemic attack (see Supplementary Table S3, http://links.lww.com/DCR/A570).

Covariates

Baseline characteristics were described including age at date of surgery, sex, neighborhood income quintile, Charlson comorbidity score (0 or ≥1 based on 5 y preceding surgery date), and number of cycles of BV before surgery date. Primary tumor location was classified as colon, rectum, or not otherwise specified. We also determined whether the primary tumor had been resected before initiation of BV therapy by identifying nonpalliative colorectal surgical interventions through CCI codes in CIHI-DAD for patients who were diagnosed 5 years before the date of first BV treatment. Patients who were diagnosed >5 years before first BV treatment were assumed to have had surgical resection as part of curative therapy at presentation. Receipt of radiation therapy ever received (yes or no) was identified based on OHIP and CIHI codes (see Supplementary Table S4, http://links.lww.com/DCR/A570).

Statistical Analysis

We calculated descriptive statistics for study variables measured at time of surgery, stratified by timing of surgery since last BV treatment (≤28 d, 29 d to 3 mo, and >3 mo). We calculated the proportion experiencing a complicated postoperative course and compared those undergoing surgery within 28 days, 29 days to 3 months, and those >3 months since last BV therapy with Cochran–Mantel–Haenszel tests. A logistic regression model was developed to evaluate the relationship between time since last BV treatment (≤28 d, 29 d to 3 mo, and >3 mo) and the occurrence of a complicated postoperative course. Covariates included in the model were age (continuous), sex, Charlson comorbidity (0 or ≥1), neighborhood income quintile, previous resection of primary (yes or no), previous radiation (yes or no), emergency procedure (yes or no), and type of surgery (repair or resection without stoma, repair or resection with stoma, bypass only, and bypass or diversion only). A second model evaluated the relationship between time since last BV treatment and any complication (including death) excluding readmissions.

Data were analyzed data using SAS Enterprise Guide 6.1 (SAS Institute, Cary, NC). All of the statistical tests were 2 sided, and p values <0.05 were considered statistically significant. Data sets were linked using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences. To reduce the risk of reidentification of patients, standard Institute for Clinical Evaluative Sciences policy requires suppression of direct or indirect reporting of any group of ≤5 patients. To comply with this policy, table cells with ≤5 patients were suppressed, and in some cases to prevent calculation of these results, aggregated table cells were presented.

RESULTS

We identified 2759 patients aged 18 to 90 years who received BV for the treatment of metastatic CRC between January 1, 2008, and December 31, 2011. Of these patients, a total of 265 patients (9.6%) underwent a colorectal surgical procedure within 1 year of BV treatment and were included in this study (Fig. 1). Of these patients, 55 (20.8%) had surgery ≤28 days after last treatment, 85 (32.1%) had surgery between 29 days and 3 months after last treatment, and 125 (47.2%) had surgery >3 months after their last BV treatment (Fig. 2). The average age of patients was 61 years, 44% of patients were women, most (68%) had a colonic primary, and 40.8% had an intact primary. Patients included in the study received an average of 13 BV cycles (Table 1).

The majority of patients having surgery underwent bowel resection or repair with no stoma (47.5%), and most (61.1%) had surgery in an emergent setting (Table 2). Patients who had their last BV treatment within 28 days of surgery were more likely to have emergent surgery (92.7%) than patients who underwent surgery ≥29 days after last BV ($p < 0.001$; Table 2). Overall, 36.2% (n = 96) of patients had a complicated postoperative course (the composite outcome including death, readmission, or surgical complication within 30 days); there was no difference in the likelihood of a complicated postoperative course between patients receiving surgery ≤28 days after BV treatment (40.0%), 29 days to 3 months after BV treatment (32.9%), and >3 months after BV treatment (36.8%; $p = 0.82$; Table 2). The risk of death within 30 days was found to be 7.9% overall. A total of 20% of patients in the cohort required readmission within 30 days of discharge, and many experienced wound complications (12.5%) postoperation.

In multivariate analysis, compared with patients undergoing surgery within 28 days of treatment with BV, there was no difference in the likelihood of a complicated postoperative course among patients undergoing sur-

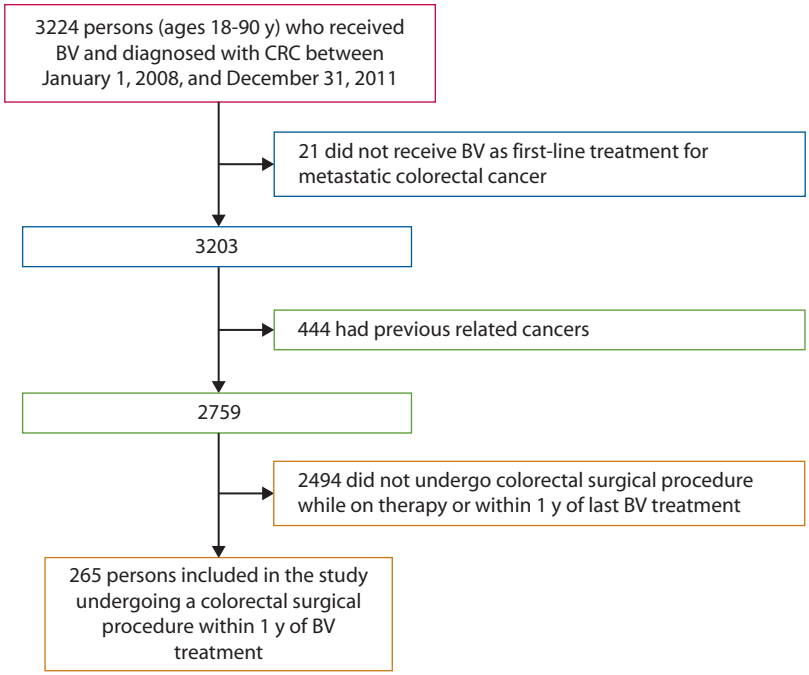

FIGURE 1. Cohort with persons diagnosed with metastatic colorectal cancer (CRC) receiving Bevacizumab (BV) treatment from January 1, 2008, through December 31, 2011, who received surgery within 1 year of BV treatment.

gery 29 days to 3 months after receiving BV (OR = 1.23 (95% CI, 0.53–2.84)) or >3 months after BV (OR = 0.98 (95% CI, 0.46–2.09); Table 3). The only covariate associated with a complicated postoperative course was the emergency nature of the procedure: compared with those undergoing elective surgery, patients undergoing emergency surgery had a markedly higher risk of a complicated course (OR = 2.16 (95% CI, 1.13–4.12)). Age, sex, neighborhood income quintile, intact primary, receipt of radiation, and surgery type were not found to have a statistically significant association with the likelihood of patients having a complicated postoperative course. When readmissions within 30 days were excluded, compared with those undergoing surgery within 28 days of receiving BV, there was still no difference in the likelihood of complications among patients undergoing surgery 29 days to 3 months

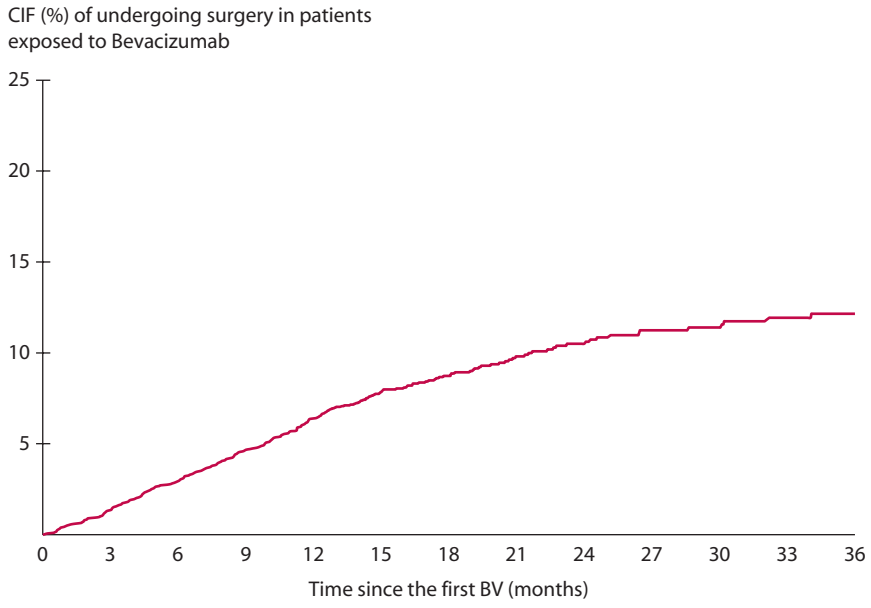

FIGURE 2. Cumulative incidence (CIF) of undergoing colorectal surgery by months since last Bevacizumab (BV) treatment in entire group exposed to BV.

TABLE 1. Characteristics of patients who received surgery for metastatic colorectal cancer after Bevacizumab treatment, by time since last Bevacizumab

Characteristic	Total (N = 265)	Time since surgery: ≤28 d (N = 55)	29 d to ≤3 mo (N = 85)	>3 mo (N = 125)	p
Age at surgery date, mean ± SD, y	61.18 ± 10.71	61.71 ± 10.97	60.59 ± 10.74	61.34 ± 10.65	0.81
Women	116 (43.8)	25 (45.5)	37 (43.5)	54 (43.2)	0.80
Charlson score[a]					
0	194 (73.2)	38 (69.1)	60 (70.6)	96 (76.8)	0.45
≥1	52 (19.6)	14 (25.5)	14 (16.5)	24 (19.2)	
Neighborhood income quintile[b]					0.20
1	47 (17.7)				
2	55 (20.8)	19 (34.6)[c]	36 (42.4)[c]	47 (37.6)[c]	
3	54 (20.4)	14 (25.5)	18 (21.2)	22 (17.6)	
4	55 (20.8)	10 (18.2)	15 (17.6)	30 (24.0)	
5	52 (19.6)	11 (20.0)	15 (17.6)	26 (20.8)	
Primary cancer					
Colon/other[d]	183 (69.1)	47 (85.5)	58 (68.2)	80 (64.0)	0.02
Rectum	82 (30.9)	9 (16.4)	28 (32.9)	45 (36.0)	
Intact primary	108 (40.8)	22 (40.0)	45 (52.9)	41 (32.8)	0.13
Receipt of radiation[e]	90 (34.0)	12 (21.8)	28 (32.9)	50 (40.0)	0.02
Bevacizumab cycles received, mean ± SD	13.09 ± 8.81	11.82 ± 9.34	12.78 ± 9.02	13.86 ± 8.40	0.33

Data are presented as number of patients (%) unless otherwise stated. Cells with <6 persons are suppressed.
[a]Charlson score is missing for 19 patients.
[b]Neighborhood income quintile is missing for 2 patients.
[c]Neighborhood income quintile categories 1 and 2 were collapsed to suppress cells with <6 persons.
[d]Location was *other* in <6 patients.
[e]Data include the receipt of radiation at any time in the observation period.

after receiving BV (OR = 0.87 (95% CI, 0.32 – 2.41)) or >3 months after BV (OR = 0.67 (95% CI, 0.26 – 1.68); see Supplementary Table S5, http://links.lww.com/DCR/A570).

To evaluate the validity of time since last BV treatment, we compared the dates of BV administration in our cohort determined from the publicly funded drug database with dates of chemotherapy drug administration in OHIP and NACRS within 2 days. We found a 99% concordance between data sources for date of administration, indicating a high degree of confidence in our estimation of the time since last BV treatment (data not shown).

DISCUSSION

Our study found that a high proportion (36.2%) of patients with metastatic CRC who undergo colorectal surgery within 1 year of treatment with BV experienced a complicated postoperative course. Our patients were

TABLE 2. Characteristics of colorectal surgery and complications, by time since Bevacizumab

Variable	Total (N = 265)	Time since surgery: ≤28 d (N = 55)	29 d to <3 mo (N = 85)	≥3 mo (N = 125)	p
Emergency procedure	162 (61.1)	>90%[a]	48% to 50%[a]	55% to 57%[a]	<.001
Type of surgery					
Bowel resection/repair, no stoma	126 (47.5)	24 (43.6)	39 (45.9)	63 (50.4)	0.41
Bowel resection/repair, with stoma	107 (40.4)	31(56.4)[b]	46 (54.1)[b]	62 (49.6)[b]	
Bypass or diversion only	32 (12.1)				
Complications					
Overall	96 (36.2)	22 (40.0)	28 (32.9)	46 (36.8)	0.82
Death within 30 days	21 (7.9)	6 (10.9)	6 (7.1)	9 (7.2)	0.46
Readmission	54 (20.4)	13 (23.6)	14 (16.5)	27 (21.6)	0.96
Wound complications	33 (12.5)	8 (14.5)	11 (12.9)	14 (11.2)	0.52
Infection	12 (4.5)	↔	↔	↔	0.75
Abscess drainage	21 (7.9)	↔	↔	↔	0.65

Data are n (%) unless otherwise stated. For arrows (↔), the number was suppressed because of small cells.
[a]Ranges were given to prevent calculation of suppressed cells.
[b]Bowel resection/repair with stoma and bypass or diversion-only categories were combined for table reporting to suppress presentation of small cells.

TABLE 3. Logistic regression model evaluating effect of time since BV on overall complication outcome

Variable	*OR*	*95% CI*	*p*
Time since BV			
≤28 d	ref	–	
29 d to 3 mo	1.23	0.53–2.84	0.51
>3 mo	0.98	0.46–2.09	0.67
Age at surgery date	0.98	0.96–1.01	0.22
Sex			
Women	0.79	0.44–1.42	0.43
Men	ref	–	
Charlson score			
0	0.78	0.38–1.59	0.49
≥1	ref	–	
Neighborhood income quintile			
1	0.34	0.13–0.88	0.59
2	0.28	0.11–0.68	0.18
3	0.20	0.08–0.52	0.02
4	0.55	0.23–1.33	0.25
5	ref	–	
Intact primary			
No	1.75	0.95–3.21	0.07
Yes	ref	–	
Receipt of radiation			
Yes	1.65	0.91–2.99	0.10
No	ref	–	
Emergency procedure			
Yes	2.16	1.13–4.12	0.02
No	ref	–	
Type of surgery			
Bowel resection/repair, no stoma	0.82	0.34–1.96	0.44
Bowel resection/repair, stoma	1.08	0.45–2.60	0.58
Bypass or diversion only	ref	–	

BV = Bevacizumab; ref = reference.

at high risk of death within 30 days of surgery (7.9%), frequently experienced wound complications (12.5%), and often required readmission within 30 days of discharge (20.4%), indicating that surgery in this group was associated with significant morbidity and mortality. However, the overall proportion of patients experiencing complications did not vary with time since exposure to BV; patients having received BV therapy within 28 days of their surgery were not more likely to experience complications than those >3 months since treatment. The only variable associated with a complicated postoperative course was the emergency nature of the procedure.

A number of studies have assessed the impact of BV therapy on postoperative complications. A pooled analysis of 2 randomized controlled trials comparing standard chemotherapy with chemotherapy plus BV found a low rate of surgery in patients receiving BV; 12.0% (75/616 patients) of patients treated with BV underwent surgery after initiation of this drug compared with 5.6% (29/516 patients) in the control arm.[5] A smaller proportion of patients in these trials (n = 28; 4.5% of enrolled patients) underwent colorectal surgery after BV exposure. In these trials, the incidence of wound healing complications for patients undergoing any surgical procedure was 13.0% in the BV treatment group compared with 3.4% in the control arm; however, this difference was not statistically significant.[5] Two systematic reviews have evaluated the effect of BV on postoperative complications[12,17]; among the studies reviewed, including 2 large prospective cohorts,[18,19] surgery was not a rare event after BV exposure. Most patients who had major abdominal surgery in the studies underwent liver resection and had a relatively low incidence of postoperative wound complications. Major liver resections are generally performed in an elective setting, and mandatory wait times from last dose of BV are standard.[8,12,20] In addition, liver resections are associated with a lower risk of complications than colorectal resections.[21] Because of the small numbers of patients undergoing colorectal surgery included in these studies, it is difficult to compare our findings with the existing literature.

Although a small proportion of patients (9.6% in our study) undergo colorectal surgery after treatment with BV, because BV is the standard of care for management of patients with metastatic CRC, a large number of patients treated with BV each year will require such surgery. Understanding the impact of BV on surgical morbidity and mortality is therefore important, yet few studies evaluate the postoperative outcomes of such patients. Of note, exposure to BV has a prolonged impact on angiogenesis: the half-life of BV is 20 days (range, 11–50 d), and even low circulating levels can effectively inhibit the actions of VEGF.[22] Because VEGF is a key regulator of angiogenesis with an important role in wound healing,[23] exposure to BV theoretically may have a negative effect on surgical outcome for some time after the last dose. In a study of 32 patients with preoperative exposure to BV who underwent surgery a median of 6 weeks after exposure to BV, VEGF was entirely inactivated in the plasma and wound fluid at the time of surgery.[24] In fact, with administration of 5 mg/kg of BV every 2 weeks, VEGF may be measurably inactivated for <12 weeks after the last dose.[25]

Our study included a relatively large sample of patients undergoing colorectal surgery after exposure to BV and provides results that are generalizable to patients in the community setting. Importantly, our patients were treated by medical oncologists and surgeons throughout Ontario, and their care does not represent treatment given solely at tertiary centers. All of the patients with advanced CRC in Ontario treated with BV who underwent colorectal surgery were included, and because administrative data were used to evaluate outcomes, there was no loss of patients to follow-up; 30-day outcomes were captured irrespective of where patients presented or received care. However, our study has limitations. We relied on administrative data to identify the occurrence of complications, and this may have resulted in an underestimation of the risk. Administrative databases are widely used in the literature to identify surgical complication rates[15,26,27] and, because our overall rate of complications was relatively high compared with previous studies,[5] it is unlikely

that major morbidity was missed. We did not collect information on exposure to other chemotherapeutic agents; the high incidence of surgical complications months after exposure to BV may be secondary to other treatments for metastatic disease. Our study was restricted to evaluating the outcomes of colorectal surgery; however, this is a common type of surgery in these patients and is also high risk for postoperative complications in the setting of BV.[5] Although ours is the only population-based study of postoperative complications after colorectal surgery in patients treated with BV, the number of patients who required surgery in our study was relatively small. In addition, although a complicated postoperative course occurred frequently in these patients (36%), the small number of events overall (n = 96) limits the power of our study to detect a difference between groups and increases the risk of model overfitting in multivariate analysis, particularly in our analysis excluding 30-day readmissions. Notably, surgeons likely approached patients requiring surgery within 28 days of BV differently than those requiring surgery with a greater time since exposure. Although our failure to detect a relationship between time since last BV dose and surgical morbidity and mortality may be because of factors such as surgical selection, we found that patients remained at substantial risk of complications even with a long time interval since drug exposure.

CONCLUSION

A minority of metastatic patients with CRC require colorectal surgery after exposure to BV. Although this is a group at high risk of postoperative complications, we could not detect an association between time since last BV dose and the odds of a complicated postoperative course. Consequently, whereas BV exposure should be taken into account in surgical decision-making, it is not a contraindication to surgery when surgery is otherwise indicated.

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