DR FAHIMA DOSSA (Orcid ID : 0000-0002-4670-7445)

Article type : Original Article

Does the Presence of an Intact Primary Increase the Risk of Non-Elective Colorectal Surgery in Patients Treated with Bevacizumab?

Nancy N. Baxter, MD PhD^{1,2,3,4}; Rinku Sutradhar, PhD^{2,3,4}; Fahima Dossa, MD^{1,3}; Longdi Fu, MSc²; Paula Rochon, MD MPH^{3,4,7}; Alice C. Wei, MDCM MSc⁵; Erin D. Kennedy, MD PhD⁶; Craig C. Earle, MD MSc^{2,3,7}

Running Head: Emergency Colorectal Surgery after Bevacizumab

Authors Affiliations:

¹Department of Surgery, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Canada

²Institute for Clinical Evaluative Sciences, Toronto, Canada

³Institute of Health Policy, Management and Education, University of Toronto, Toronto, Canada

⁴Dalla Lana School of Public Health, University of Toronto, Toronto, Canada

⁵Memorial Sloan Kettering Cancer Center, New York, NY, USA

⁶Sinai Health System, Toronto, Canada

⁷Ontario Institute for Cancer Research, Toronto, Canada

Corresponding Author: Dr. Fahima Dossa, MD, Division of General Surgery, St. Michael's Hospital, 040-16 Cardinal Carter Wing, 30 Bond Street, Toronto, ON, M5B 1W8 Canada | fahima.dossa@mail.utoronto.ca

Funding source: This study was conducted with the support of the Ontario Institute for Cancer Research and Cancer Care Ontario through funding provided by the Government of Ontario and the Canadian Institutes of Health Research (CIHR) Foundation grant (148470).

Conflicts of Interest: There are no conflicts of interest to disclose.

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/codi.15294](https://doi.org/10.1111/codi.15294)

This article is protected by copyright. All rights reserved

Ethics Statement: This study was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre, Toronto, Canada.

Patient Consent Statement: ICES is a prescribed entity under section 45 of Ontario's Personal Health Information Protection Act. Section 45 authorizes ICES to collect personal health information, without consent, for the purpose of analysis or compiling statistical information with respect to the management of, evaluation or monitoring of, the allocation of resources to or planning for all or part of the health system.

Data Sharing Statement: The dataset from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS. The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

Word Count: Abstract = 246 | Body = 2,885 | Tables/Figures = 4 | Supplemental tables = 4

Abstract

Aim: In patients with incurable metastatic colorectal cancer (mCRC), primary tumour resection is debated; however, patients with intact primaries may be at higher risk of complications requiring surgery when receiving treatment with bevacizumab. We estimated the risk of non-elective colorectal surgery in patients undergoing bevacizumab therapy for mCRC and evaluated the association between intact primary tumours and risk of non-elective surgery

Methods: We designed a population-based, retrospective cohort study using administrative and cancer registry data in Ontario, Canada. We included patients with mCRC who received bevacizumab from Jan.1, 2008-Dec.31, 2014. The primary outcome was non-elective colorectal surgery after initiating bevacizumab. We determined the cumulative incidence of non-elective colorectal surgery among patients with previously resected and unresected primaries, accounting for the competing risk of death. We explored the relationship between previous resection of the primary and need for non-elective surgery using a cause-specific hazards model, controlling for patient, tumour, and treatment factors.

Results: We identified 1,840 (32.7 %) patients with intact primaries and 3,784 (67.3%) patients with prior resection. The cumulative incidence of non-elective surgery 1 year after initiating bevacizumab for all patients was 3.9% (95%CI: 3.4-4.5%). One-year cumulative incidence was higher in those with intact primaries vs. those with resected primaries (6.1% vs. 2.9%, $p<0.0001$). After adjustment, an intact primary remained strongly associated with non-elective colorectal surgery (HR = 2.89, 95% CI: 2.32-3.61, $p<0.0001$).

Conclusions: Bevacizumab is associated with a low but meaningful risk for serious gastrointestinal complications, necessitating vigilance, particularly among patients with an intact primary tumour.

What does this paper add to the literature?

Patients with metastatic colorectal cancer treated with bevacizumab are at risk for gastrointestinal complications. The association between an intact primary and complications is unclear. Using a risk-adjusted, population-based sample, we found patients with intact primaries were at a higher risk of requiring non-elective surgery than resected patients when treated with bevacizumab.

Introduction

Bevacizumab, a recombinant monoclonal antibody that blocks angiogenesis through inhibition of vascular endothelial growth factor, is standard of care in the management of many patients with metastatic colorectal cancer.^{1,2} Randomized clinical trials provide evidence of improved survival with use of bevacizumab in combination with cytotoxic chemotherapy.³⁻⁶ A large number of patients are therefore exposed to this agent worldwide. However, previous studies demonstrate that patients with colorectal cancer treated with bevacizumab are at a low but real risk of life-threatening gastrointestinal complications during therapy. Perforation occurs in approximately 2% of patients with colorectal cancer treated with bevacizumab^{7,8} and this complication is almost 4 times more common in patients treated with bevacizumab vs. those treated with chemotherapy alone.⁹ In fact, gastrointestinal perforation is one of the most common causes of fatal adverse events in patients treated with bevacizumab.^{10,11} Patients are also at risk of fistula formation,¹²⁻¹⁴ ischemic colitis, gastrointestinal bleeding,^{10,11} and delayed anastomotic complications, occurring well after initial surgical resection.¹⁵⁻¹⁷ Surgery performed to manage these complications is associated with a high risk of wound complications^{4,6,18,19} and a high mortality rate.^{13,18,20}

Although the mechanism underlying the risk of gastrointestinal complications with bevacizumab exposure is uncertain,⁷ a number of risk factors have been identified as potentially mediating the relationship, including an increased risk associated with the presence of an intact primary tumour.^{14,21,22} In previous retrospective cohort studies, patients with intact primary tumours were reported to have double the risk of gastrointestinal perforation as those with resected primaries.^{20,22,23} However, previous studies have had too few events to adjust for patient, tumour, and treatment factors. Additionally, these studies have not accounted for the competing risk of death in this population, which may have biased estimates.

Because the necessity of resecting the primary in patients with incurable Stage IV colorectal cancer has been called into question²⁴⁻²⁸ fewer patients are undergoing surgery prior to initiation of systemic therapy than in the past.²⁹⁻³² Understanding the relationship between the presence of an intact primary and GI complications requiring surgery in patients undergoing bevacizumab therapy is thus important.³³ The aim of this study was to provide a population-based description of the risk of non-elective colorectal surgery in patients undergoing bevacizumab therapy for metastatic colorectal cancer and to evaluate the association between an intact primary and the risk of non-elective surgery.

Methods

Identification of Cohort

We conducted a population-based, retrospective cohort study in Ontario, Canada using information from administrative health databases. The province of Ontario has a universal, publicly funded healthcare insurance program and residents of Ontario have a unique insurance number, which can be used to identify them in administrative health datasets. Population-based administrative health data are available for select researchers through ICES, an independent non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze healthcare and demographic data, without consent, for health system evaluation and improvement. Datasets held by ICES can be linked using unique encoded patient identifiers.

We identified all patients in Ontario, aged 18-90, who received bevacizumab for treatment of metastatic colorectal cancer from January 1, 2008 (first year of funding for bevacizumab) through December 31, 2014 through the New Drug Funding Program database, a publicly funded drug program database that records information, including disease eligibility and

drug treatments, for all patients receiving specific cancer drugs (including bevacizumab) delivered through the program. We identified patients with a history of colorectal cancer by linking these persons to the Ontario Cancer Registry (OCR) (Supplementary Table 1), a provincially mandated registry that includes information on all incident cancers (except non-melanoma skin cancers) diagnosed in Ontario since 1964 and is over 95% complete.³⁴ Vital status and demographic information were obtained from the Registered Persons Database (RPDB), a roster of all Ontario Health Insurance Program (OHIP) beneficiaries (virtually all persons residing in the province). The OHIP database includes information on physician claims for services, enabling identification of medical encounters and procedures.

Status of the Primary

For patients receiving their first dose of bevacizumab within 5 years of colorectal cancer diagnosis, we determined if persons had undergone resection of their primary from the Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD) and Same Day Surgery (SDS) databases – these databases contain information on every patient discharged from a hospital or same-day surgery unit in Ontario. We used Canadian Classification of Health Interventions (CCI) codes for colorectal surgery to determine if a resection had occurred (Supplementary Table 2). For patients diagnosed >5 years before the first bevacizumab cycle, we assumed the primary had been surgically resected as part of curative treatment at presentation.

Ascertainment of Outcome

The outcome of interest was the need for non-elective colorectal surgery, which was used as a surrogate for serious gastrointestinal complications. From the date of first exposure to bevacizumab, we determined if a colorectal procedure was performed using CCI codes and the DAD/SDS database (Supplementary Table 2). Surgery was deemed non-elective if associated with a non-elective hospital admission. For patients who underwent non-elective colorectal surgery, we also measured time from the last cycle of bevacizumab to surgery, in days, as a secondary outcome.

Covariates

Baseline characteristics for each individual were assessed at the initiation of bevacizumab. Characteristics included age, sex, primary tumour location (colon, rectum), comorbidities, and socioeconomic status. Information on the receipt of radiation therapy was

collected at baseline but we also determined if the individual received radiation at any point during their observation window. Comorbidity was determined using the Johns Hopkins ACG System ® (Version 10) Aggregated Diagnosis Groups (ADG) score (1-5, 6-9, 10+).

Socioeconomic status (SES) was determined from location of patient residence; persons were identified as living in a rural vs urban area based on RPDB data; for those residing in an urban area, patient SES was based on a household-size adjusted measure of household income in their area, using the 2006 census summary. Receipt of radiation was identified from OHIP fee codes (Supplementary Table 3).

Statistical Analysis

We calculated descriptive statistics for baseline characteristics measured at the first bevacizumab cycle overall and stratified by intact vs resected primary. We compared the distribution of baseline characteristics between those who had an intact vs. resected primary using a chi-squared test for categorical variables and a t-test or Mann-Whitney U test for continuous variables. We examined the relationship between the presence of an intact primary and the need for non-elective surgery. The index date was the date of bevacizumab initiation. We determined the risk of non-elective colorectal surgery over time among those with and without an intact primary using a cumulative incidence function approach, where death (occurring first) was handled as a competing event,³⁵ and compared groups using the Gray test.

To adjust for baseline differences between patients with and without an intact primary, we computed each patient's propensity of having an intact primary using information on characteristics available at initiation of bevacizumab.³⁶ Specifically, this was done by implementing a multivariable logistic regression model with intact primary (yes/no) as the dependent variable and the available covariates [age (continuous), sex, Johns Hopkins ADG score (continuous), SES, site of primary (colon, rectum), and previous radiation (yes/no)] as independent variables. For each patient, we then used the values of their measured characteristics and the regression parameter estimates from the logistic model to predict their probability (propensity) of having an intact primary.

To examine the association between status of the primary and the hazard of non-elective colorectal surgery, a multivariable cause-specific Cox regression model was implemented, where death was a competing risk.³⁷ The covariates included status of the primary (intact vs. resected), the propensity score (continuous) calculated above,³⁸ and receipt of radiation, treated as a binary

time-dependent covariate that turned “on” and remained “on” once the patient received radiation (either before or at any point during their follow-up). Patients were censored at the time of elective colorectal surgery, one year after their last bevacizumab cycle, or at study end (max date of administrative data follow-up, December 31, 2016), whichever occurred first. As sensitivity analyses, we examined alternative methods of adjusting for covariates, including adjusting for baseline covariates without propensity score adjustment and adjusting for both propensity score and baseline covariates.

Deidentified data were analyzed at ICES using SAS statistical software version 9.2 (SAS Institute, Cary, NC). Statistical tests were two-sided, and p-values < 0.05 were considered statistically significant.

Results

We identified 5,769 patients who received their first dose of bevacizumab therapy between January 1, 2008 and December 31, 2014 (Figure 1). Of these, we excluded 23 patients where the indication for bevacizumab was not treatment of metastatic colorectal cancer or patients were outside of the age range of 18-90 years, and 122 patients who were not identified as having colorectal cancer in OCR. After all exclusions, 5,624 patients remained, forming the cohort for analysis. Of these patients, 1,840 (32.7%) had an intact primary and 3,784 (67.3%) had their primary resected prior to initiating bevacizumab therapy (Table 1). Patients with an intact primary were more likely to have rectal cancer than those with a resected primary (29.8 % vs. 20.5%, $p < 0.001$). Within propensity score strata, the characteristics of patients with and without an intact primary were similarly distributed.

Patients in both groups received a similar number of bevacizumab cycles (mean 13.7, SD 11.9 for patients with resected primaries vs. mean 13.1, SD 12.2 for patients with intact primaries; $p = 0.13$); however, a greater proportion of patients with resected primaries received radiation therapy after initiating bevacizumab than patients with intact primaries ($n = 1,090$; 28.8% vs. $n = 419$; 22.8%, respectively; $p < 0.001$). Overall, 3,417 (60.8%) patients died within 1 year of their last cycle of bevacizumab, with a greater proportion dying in the intact versus resected primary groups ($n = 1,233$; 67.0% vs. $n = 2,184$; 57.7%, respectively; $p < 0.001$).

A total of 338 patients (6.0%) required non-elective colorectal surgery while on bevacizumab treatment or within 12 months of their last cycle, 165 (9.0%) of those with an intact primary and 173 (4.6%) of those who had undergone prior resection. The cumulative incidence

of non-elective surgery 1 year after initiating bevacizumab treatment for all patients in the cohort was 3.9% (95%CI: 3.4-4.5%). The 1-year cumulative incidence of non-elective colorectal surgery was higher in those with an intact primary vs. those with a resected primary (6.1% vs. 2.9%, $p < 0.0001$) (Figure 2). The secondary outcome, median time from last dose of bevacizumab to date of non-elective surgery, was shorter in the intact (52 days; IQR: 17-135) versus resected (76 days; IQR: 26-172) primary group ($p = 0.072$). After adjustment for propensity score and receipt of radiation, an intact primary remained strongly associated with undergoing non-elective colorectal surgery after initiating bevacizumab treatment (HR = 2.89, 95% CI: 2.32-3.61, $p < 0.0001$) (Table 2). In sensitivity analyses, the HRs found in the model adjusting for baseline covariates without propensity score adjustment (HR = 2.72, 95%CI: 2.19-3.39, $p < 0.0001$) and in the model adjusting for both propensity score and baseline covariates (HR = 2.94, 95%CI: 2.35-3.66, $p < 0.0001$) were very similar to our primary analysis (Table 2, Supplementary Table 4).

Discussion

This study of patients with metastatic colorectal cancer treated with bevacizumab found status of the primary tumor to be strongly associated with subsequent need for non-elective colorectal surgery; patients who had an intact primary cancer underwent non-elective surgery at a nearly 3 times greater rate as compared to patients with a resected primary. While most patients with colorectal cancer treated with bevacizumab did not require non-elective colorectal surgery, for the 33% of patients who initiated bevacizumab with an intact colorectal cancer primary, 9% required surgery while on treatment, or within 12 months of their last dose.

This study used non-elective colorectal surgery as a surrogate for serious gastrointestinal complications - patients undergoing bevacizumab treatment are known to be at higher risk of gastrointestinal complications than those treated with non-bevacizumab containing regimens. In a pooled analysis of 7 randomized trials⁸ of chemotherapy +/- bevacizumab, 44 of 1,990 patients receiving bevacizumab regimens developed a gastrointestinal perforation (2.2%) vs. 13 of 1,211 (0.7%) patients receiving non-bevacizumab containing regimens. In a pooled analysis of 2 trials,¹⁹ 28 (4.5%) patients of 616 receiving bevacizumab required colorectal surgery as compared to 16 of 516 (3.1%) patients receiving chemotherapy alone.

A few studies provide some insight into the effect of an intact primary on the risk of severe colorectal complications (gastrointestinal perforation, need for non-elective colorectal

surgery) in patients receiving bevacizumab containing regimens. Four large observational cohort studies followed patients with metastatic colorectal cancer exposed to bevacizumab therapy: the Bevacizumab Regimens' Investigation of Treatment Effects (BRiTE) study²² included 1,953 patients (15.6% with an intact primary) treated at 248 centers, the Bevacizumab Expanded Access Trial (BEAT)²⁰ included 1,914 patients (13% with an intact primary) treated at 376 centers, the Avastin Registry – Investigation of Effectiveness and Safety study (ARIES)³⁹ included 1,550 patients exposed to bevacizumab as first-line therapy (19.2% with intact primary) at 248 centers, and the Avastin ColOREctal Non-interventional study (ACORN)¹¹ included 714 patients (69.9% with an intact primary) treated at 42 centers. The overall incidence of gastrointestinal perforation appears similar in these studies (1.9% BRiTE, 1.9% BEAT, 1.2% ARIES, 2.2% ACORN). However, only two of these studies reported incidence stratified by primary tumour status. In these two studies, perforation was more common in those with an intact primary (3.0% BRiTE, 4.0% BEAT) versus those with a resected primary (1.7% BRiTE, 1.8% BEAT). In a smaller study by Lee et al.,²³ 4.5% of patients with intact primaries versus 1.7% of patients with resected primaries developed perforations. All three studies suggest a greater risk for gastrointestinal perforation in patients with intact primary tumours.

In contrast, our study examined the need for non-elective colorectal surgery, not limited to surgeries for perforation. We estimated an incidence of 9% in the intact primary group versus 4.6% in the resected group. Our estimates reflect the results of two previous studies. The National Surgical Adjuvant Breast and Bowel Project C-10 (NSABP C-10) trial evaluated the safety of FOLFOX combined with bevacizumab in 86 patients presenting with unresectable stage IV colon cancer and an intact primary.²⁶ Over a 12-month period, 6 (7.0%) patients required non-elective colorectal surgery. In a separate single institutional study by Bong et al.,²¹ which included 1,008 patients who underwent treatment with bevacizumab for metastatic colorectal cancer, 60 (6.0%) patients developed complications requiring surgery; 25 (9.3%) patients with intact primaries and 35 (4.7%) patients with resected primaries. Uniquely, the large number of patients included in our study allowed for multivariable adjustments without the risk of overfitting, providing greater accuracy in adjusted estimates of the association between an intact primary and need for non-elective colorectal surgery.

The use of bevacizumab prolongs survival in patients with metastatic colorectal cancer despite the increased risks of gastrointestinal complications and risks of surgery.⁵ However, the

results of our study, including over 1,840 patients with an intact primary treated with bevacizumab, are consistent with the literature and indicate the need for careful observation and monitoring of these patients. In the ACORN study, one-third of deaths from treatment-related adverse events occurred in patients with gastrointestinal perforations.¹¹ In previous work evaluating the risk of complications in patients in our cohort who underwent colorectal surgery,¹⁸ we found surgery was associated with considerable morbidity; 7.9% of patients died within 30 days of surgery, 12.5% experienced wound complications, and 20.4% required readmission after discharge. The already substantial risk of complications in patients with metastatic colorectal cancer requiring surgery after bevacizumab therapy was 2.16 times higher in the patients who underwent non-elective colorectal surgery.

Several ongoing randomized trials seek to address whether there are survival benefits from resection of the primary tumor in patients with incurable stage IV disease (NCT01606098, NCT02314182, NCT02149784, NCT02015923, ISRCTN30964555). However, with the current trend of decreasing frequency of resection of the primary,³⁰⁻³³ more patients with an intact primary will be treated with bevacizumab in the future and will be at significant risk of requiring non-elective colorectal surgery. In patients with intact primaries treated with bevacizumab, vigilance for early signs of gastrointestinal complications is essential to ensure timely recognition of and expeditious treatment for complications.

Our study evaluated the outcomes of a large number of patients with colorectal cancer treated with bevacizumab, including over 1,840 patients with an intact primary, and provides generalizable results to the community setting. Our study is population-based including all patients with advanced colorectal cancer treated with bevacizumab by oncologists throughout Ontario; the care does not reflect treatment given solely at academic centers. We used administrative data to identify non-elective colorectal surgery, and thus the outcome was captured irrespective of the location of surgery - there was no loss of patients to follow up. Additionally, our inclusion of death as a competing risk in our analysis is important given the association between the presence of an intact primary and survival found in previous studies.⁴⁰⁻⁴² However, our observational study has limitations. Patients were selected to receive bevacizumab therapy by their providers – we do not know if some metastatic colorectal cancer patients with an intact primary did not receive bevacizumab because they were perceived to be at high risk of gastrointestinal complications. We identified non-elective surgery using administrative data and

thus the indications for surgery could not be confirmed. Our observation period began at the time of treatment with bevacizumab and, therefore, we cannot comment on how frequently patients in the resected primary group had undergone resection in a non-elective setting. Additionally, highly comorbid patients experiencing severe gastrointestinal complications may not have undergone surgery, leading to underestimates of the rate of complications; however, we expect this to have been the case for only a small number of patients. Surgeons were not blinded to the presence of an intact primary and this may have affected surgical decision-making. However, it is unlikely that the patients in our cohort with metastatic disease on systemic therapy would have been subjected to emergency surgery without indication. We did not collect information on other chemotherapeutic agents – it is possible that the risk of non-elective colorectal surgery would have been as high in patients receiving non-bevacizumab containing regimens; however, given the increased risk of gastrointestinal perforation with exposure to bevacizumab demonstrated in randomized trials, this is unlikely. Finally, while our study focused on complications during and after treatment with bevacizumab, it should be noted that resection of the primary could have led to post-operative complications that delayed or prevented systemic treatment in some patients; our study cannot provide an estimate of the frequency of this event.

In conclusion, our study found that a relatively small number of patients treated with bevacizumab for metastatic colorectal cancer require non-elective colorectal surgery, however those with an intact primary are at higher risk – 9% will undergo non-elective colorectal surgery within 12 months of their last dose of bevacizumab therapy. Our findings from a large population-based study suggest that bevacizumab can be safely used in most patients with metastatic colorectal cancer, even those with an intact primary; however, strategies for early detection and prevention of gastrointestinal complications requiring surgery are needed.

Acknowledgements: This study was conducted with the support of the Ontario Institute for Cancer Research and Cancer Care Ontario through funding provided by the Government of Ontario and the Canadian Institutes of Health Research (CIHR) Foundation grant (148470) granted to Dr. Nancy Baxter. This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be

inferred. Parts of this material are based on data and information compiled and provided by Canadian Institutes of Health Information (CIHI). However, the analyses, conclusions, opinions and statements expressed herein are those of the author, and not necessarily those of CIHI. Parts of this material are based on data and information provided by Cancer Care Ontario (CCO). The opinions, results, view, and conclusions reported in this paper are those of the authors and do not necessarily reflect those of CCO. No endorsement by CCO is intended or should be inferred. The authors thank Corinne Daly from Canadian Partnership Against Cancer for her assistance with this manuscript and Hadas Fischer from ICES for help with study design.

References

1. Benson AB, Venook AP, Cederquist L, et al. Colon cancer, version 1.2017, NCCN clinical practice guidelines in oncology. *Journal of the National Comprehensive Cancer Network*. 2017;15(3):370-398.
2. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Annals of oncology : official journal of the European Society for Medical Oncology*. 2016;27(8):1386-1422.
3. 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. *Journal of Clinical Oncology*. 2007;25(12):1539.
4. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *New England journal of medicine*. 2004;350(23):2335-2342.
5. Ilic I, Jankovic S, Ilic M. Bevacizumab combined with chemotherapy improves survival for patients with metastatic colorectal cancer: evidence from meta analysis. *PLoS One*. 2016;11(8):e0161912.
6. Kabbinavar F, Irl C, Zurlo A, Hurwitz H. Bevacizumab improves the overall and progression-free survival of patients with metastatic colorectal cancer treated with 5-fluorouracil-based regimens irrespective of baseline risk. *Oncology*. 2008;75(3-4):215-223.

7. Abu-Hejleh T, Mezhir JJ, Goodheart MJ, Halfdanarson TR. Incidence and management of gastrointestinal perforation from bevacizumab in advanced cancers. *Current oncology reports*. 2012;14(4):277-284.
8. Hurwitz HI, Tebbutt NC, Kabbinavar F, et al. Efficacy and safety of bevacizumab in metastatic colorectal cancer: pooled analysis from seven randomized controlled trials. *The oncologist*. 2013;18(9):1004-1012.
9. Botrel TEA, de Oliveira Clark LG, Paladini L, Clark OAC. Efficacy and safety of bevacizumab plus chemotherapy compared to chemotherapy alone in previously untreated advanced or metastatic colorectal cancer: a systematic review and meta-analysis. *BMC cancer*. 2016;16(1):677.
10. Ranpura V, Hapani S, Wu S. Treatment-related mortality with bevacizumab in cancer patients: a meta-analysis. *Jama*. 2011;305(5):487-494.
11. Khakoo S, Chau I, Pedley I, et al. ACORN: An observational study of bevacizumab in combination with first-line chemotherapy for treatment of metastatic colorectal cancer in the UK. *Clinical Colorectal Cancer*. 2019.
12. Ganapathi AM, Westmoreland T, Tyler D, Mantyh CR. Bevacizumab-associated fistula formation in postoperative colorectal cancer patients. *Journal of the American College of Surgeons*. 2012;214(4):582-588.
13. Hapani S, Chu D, Wu S. Risk of gastrointestinal perforation in patients with cancer treated with bevacizumab: a meta-analysis. *The lancet oncology*. 2009;10(6):559-568.
14. Kabbinavar FF, Flynn PJ, Kozloff M, et al. Gastrointestinal perforation associated with bevacizumab use in metastatic colorectal cancer: results from a large treatment observational cohort study. *European Journal of Cancer*. 2012;48(8):1126-1132.
15. August DA, Serrano D, Poplin E. "Spontaneous," delayed colon and rectal anastomotic complications associated with bevacizumab therapy. *J Surg Oncol*. 2008;97(2):180-185.
16. O'Hare T, McDermott R, Hannon R. Late anastomotic breakdown with bevacizumab in colorectal cancers, a case-based review. *Ir J Med Sci*. 2018;187(2):333-336.
17. Deshaies I, Malka D, Soria JC, Massard C, Bahleda R, Elias D. Antiangiogenic agents and late anastomotic complications. *J Surg Oncol*. 2010;101(2):180-183.

18. Baxter NN, Fischer HD, Richardson DP, et al. A population-based study of complications after colorectal surgery in patients who have received bevacizumab. *Diseases of the Colon & Rectum*. 2018;61(3):306-313.
19. Scappaticci FA, Fehrenbacher L, Cartwright T, et al. Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab. *Journal of surgical oncology*. 2005;91(3):173-180.
20. Van Cutsem E, Rivera F, Berry S, et al. Safety and efficacy of first-line bevacizumab with FOLFOX, XELOX, FOLFIRI and fluoropyrimidines in metastatic colorectal cancer: the BEAT study. *Annals of Oncology*. 2009;20(11):1842-1847.
21. Bong JW, Lee JL, Kim CW, et al. Risk Factors and Adequate Management for Complications of Bevacizumab Treatment Requiring Surgical Intervention in Patients With Metastatic Colorectal Cancer. *Clinical colorectal cancer*. 2018;17(4):e639-e645.
22. Kozloff M, Yood MU, Berlin J, et al. Clinical outcomes associated with bevacizumab-containing treatment of metastatic colorectal cancer: the BRiTE observational cohort study. *The oncologist*. 2009;14(9):862-870.
23. Lee B, Wong HL, Tacey M, et al. The impact of bevacizumab in metastatic colorectal cancer with an intact primary tumor: results from a large prospective cohort study. *Asia-Pacific Journal of Clinical Oncology*. 2017;13(4):314-321.
24. Alawadi Z, Phatak UR, Hu CY, et al. Comparative effectiveness of primary tumor resection in patients with stage IV colon cancer. *Cancer*. 2017;123(7):1124-1133.
25. Cirocchi R, Trastulli S, Abraha I, et al. Non-resection versus resection for an asymptomatic primary tumour in patients with unresectable stage IV colorectal cancer. *Cochrane Database of Systematic Reviews*. 2012(8).
26. McCahill LE, Yothers G, Sharif S, et al. Primary mFOLFOX6 Plus Bevacizumab Without Resection of the Primary Tumor for Patients Presenting With Surgically Unresectable Metastatic Colon Cancer and an Intact Asymptomatic Colon Cancer: Definitive Analysis of NSABP Trial C-10. *Journal of Clinical Oncology*. 2012;30(26):3223-3228.

27. Shida D, Boku N, Tanabe T, et al. Primary Tumor Resection for Stage IV Colorectal Cancer in the Era of Targeted Chemotherapy. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract*. 2018.
28. Vogel JD, Eskicioglu C, Weiser MR, Feingold DL, Steele SR. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Treatment of Colon Cancer. *Diseases of the colon and rectum*. 2017;60(10):999-1017.
29. Tarantino I, Warschkow R, Worni M, et al. Prognostic Relevance of Palliative Primary Tumor Removal in 37,793 Metastatic Colorectal Cancer Patients: A Population-based, Propensity Score-adjusted Trend Analysis. *Annals of surgery*. 2015;262(1):112-120.
30. Birkett RT, O'Donnell MMT, Epstein AJ, Saur NM, Bleier JIS, Paulson EC. Elective colon resection without curative intent in stage IV colon cancer. *Surgical oncology*. 2019;28:110-115.
31. Raab GT, Lin A, Hillyer GC, et al. Use of Bevacizumab for Elderly Patients With Stage IV Colon Cancer: Analysis of SEER-Medicare Data. *Clin Colorectal Cancer*. 2019;18(3):e294-e299.
32. Hu C-Y, Bailey CE, You YN, et al. Time trend analysis of primary tumor resection for stage IV colorectal cancer: less surgery, improved survival. *JAMA surgery*. 2015;150(3):245-251.
33. Massarweh NN, Li LT, Sansgiry S, Berger DH, Anaya DA. Primary Tumor Resection and Multimodality Treatment for Patients with Metastatic Colon Cancer. *Annals of surgical oncology*. 2016;23(6):1815-1823.
34. Robles SC, Marrett LD, Clarke EA, Risch HA. An application of capture-recapture methods to the estimation of completeness of cancer registration. *Journal of clinical epidemiology*. 1988;41(5):495-501.
35. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. *Statistics in medicine*. 2007;26(11):2389-2430.
36. D'Agostino Jr RB. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Statistics in medicine*. 1998;17(19):2265-2281.

37. Therneau TM, Grambsch PM. *Modeling survival data: extending the Cox model*. Springer Science & Business Media; 2013.
38. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate behavioral research*. 2011;46(3):399-424.
39. Hurwitz H, Bekaii-Saab T, Bendell J, et al. Safety and effectiveness of bevacizumab treatment for metastatic colorectal cancer: final results from the Avastin® Registry–Investigation of Effectiveness and Safety (ARIES) observational cohort study. *Clinical Oncology*. 2014;26(6):323-332.
40. 't Lam-Boer J, Van der Geest LG, Verhoef C, Elferink ME, Koopman M, de Wilt JH. Palliative resection of the primary tumor is associated with improved overall survival in incurable stage IV colorectal cancer: A nationwide population-based propensity-score adjusted study in the Netherlands. *International journal of cancer*. 2016;139(9):2082-2094.
41. Ahmed S, Fields A, Pahwa P, et al. Surgical resection of primary tumor in asymptomatic or minimally symptomatic patients with stage IV colorectal cancer: a Canadian province experience. *Clinical colorectal cancer*. 2015;14(4):e41-e47.
42. Faron M, Pignon J-P, Malka D, et al. Is primary tumour resection associated with survival improvement in patients with colorectal cancer and unresectable synchronous metastases? A pooled analysis of individual data from four randomised trials. *European Journal of Cancer*. 2015;51(2):166-176.

Table Legend

Table 1. Baseline characteristics of patients undergoing bevacizumab (BV) treatment overall, and by resected versus intact primary.

Table 2. Adjusted cause-specific hazard ratios examining the association between status of primary (intact vs resected) and non-elective surgery.

Table 1. Baseline characteristics of patients undergoing bevacizumab (BV) treatment overall, and by resected versus intact primary.

	Total N = 5,624	Primary Cancer		p-value
		Resected N=3,784	Intact N=1,840	
Age at first BV cycle, Mean $\pm$ SD	62.43 $\pm$ 11.07	63.09 $\pm$ 10.87	61.08 $\pm$ 11.36	<.001
Female Sex	2,319 (41.2)	1,547 (40.9)	772 (42.0)	0.44
Primary Cancer				
Colon	4,300 (76.5)	3,008 (79.5)	1,292 (70.2)	<.001
Rectum	1,324 (23.5)	776 (20.5)	548 (29.8)	
ADG Comorbidity Score				
X 0-5	91 (1.6)	23 (0.6)	68 (3.7)	<.001
xx6-9	849 (15.1)	434 (11.5)	415 (22.6)	
xx10+	4,684 (83.3)	3,327 (87.9)	1,357 (73.7)	
Neighbourhood Income Quintile*				
xxRural	828 (14.7)	550 (14.5)	278 (15.1)	0.92
xxUrban 1	802 (14.3)	541 (14.3)	261 (14.2)	
xxUrban 2	970 (17.2)	667 (17.6)	303 (16.5)	

xxUrban 3	977 (17.4)	646 (17.1)	331 (18.0)	
xxUrban 4	1,019 (18.1)	683 (18.0)	336 (18.3)	
xxUrban 5	1,013 (18.0)	687 (18.2)	326 (17.7)	
Days since colorectal cancer diagnosis, Median (IQR)	194 (74-713)	439 (116-957)	72 (43-147)	<.001
Received Radiation before Bevacizumab	1,245 (22.1)	921 (24.3)	324 (17.6)	<.001

*Neighbourhood income quintile missing in 15 patients.

Data presented as number of patients (%) unless otherwise stated.

Table 2. Adjusted cause-specific hazard ratios examining the association between status of primary (intact vs resected) and non-elective surgery.

	HR (reference = resected primary)	95% CI	p-value
Intact primary*	2.89	2.32-3.61	<.0001
<i>Alternate models</i>			
Adjustment for baseline covariates without propensity score	2.72	2.19-3.39	<.0001
Adjustment for both baseline covariates and propensity score	2.94	2.35-3.66	<.0001

*Model adjusted for propensity of having an intact primary (based on patient age, sex, Johns Hopkins ADG score, socioeconomic status, site of primary, and receipt of radiation prior to initiation of bevacizumab), and time-varying receipt of radiation (prior to initiation of bevacizumab or at any point during follow-up)

Figure Legend

Figure 1. Persons diagnosed with metastatic colorectal cancer receiving bevacizumab (BV) treatment between January 1, 2008 through December 31, 2014.

Figure 2. Cumulative incidence function of non-elective surgery with competing risk of death in patients who received Bevacizumab therapy for metastatic colorectal cancer by status of the primary (resected versus intact).

Figure 1. Persons diagnosed with metastatic colorectal cancer receiving bevacizumab (BV) treatment between January 1, 2008 through December 31, 2014.

Figure 2. Cumulative incidence function of non-elective surgery with competing risk of death in patients who received Bevacizumab therapy for metastatic colorectal cancer by status of the primary (resected versus intact).

	Resected (n = 3,784)	Intact (n = 1,840)
Overall non-elective surgery	173 (4.6%)	165 (9.0%)
Cumulative incidence at 1 year	2.9%	6.1%
Overall death	2,184 (57.7%)	1,233 (67.0%)

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Baxter, NN;Sutradhar, R;Dossa, F;Fu, L;Rochon, P;Wei, AC;Kennedy, ED;Earle, CC

Title:

Does the presence of an intact primary increase the risk of nonelective colorectal surgery in patients treated with bevacizumab?

Date:

2020-10-06

Citation:

Baxter, N. N., Sutradhar, R., Dossa, F., Fu, L., Rochon, P., Wei, A. C., Kennedy, E. D. & Earle, C. C. (2020). Does the presence of an intact primary increase the risk of nonelective colorectal surgery in patients treated with bevacizumab?. COLORECTAL DISEASE, 22 (12), pp.1974-1983. <https://doi.org/10.1111/codi.15294>.

Persistent Link:

<http://hdl.handle.net/11343/276408>