Bevacizumab increases the risk of anastomosis site leakage in metastatic colorectal cancer

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Background: Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor and is used in combination with first-line chemotherapy in the treatment of metastatic colorectal cancer. One of the side effects of bevacizumab is gastrointestinal perforation. This study was designed to identify the effect of bevacizumab in intestinal anastomosis site healing.

Methods: From January 2010 to December 2020, patients diagnosed with stage IV colorectal cancer treated with palliative chemotherapy or chemoradiotherapy followed by radical surgery were retrospectively reviewed. Clinical signs or symptoms and computed tomography were tools used for diagnosing anastomosis site leakage. The patients were divided into two groups, the bevacizumab group (n = 136) and the non-bevacizumab group (n = 124).

Results: Among the 260 patients 14 (5.4%) patients were diagnosed with anastomosis site leakage. In the bevacizumab group, 13 (9.6%) patients were diagnosed with anastomotic leakage. In the non-bevacizumab group, 1 (0.8%) patient was diagnosed with anastomotic leakage. Anastomosis site leakage was significantly higher in the bevacizumab treatment group (P < 0.001). In the bevacizumab group, period of drug discontinuation before surgery was factor associated with anastomosis site leakage in multivariable analysis (P = 0.031).

Conclusion: Stage IV colorectal patients treated with bevacizumab before radical surgery for primary cancer should be carefully observed of anastomosis site leakage after surgery, and the period of drug discontinuation before surgery should be longer than 5 weeks to avoid anastomosis site leakage.

KEYWORDS
colorectal (colon) cancer, bevacizumab, stage IV, anastomotic leak in colorectal surgery, chemotherapy
Introduction

Bevacizumab (Avastin®) is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF) used to inhibit VEGF function and, as a result, inhibit tumor angiogenesis (1). Fluoropyrimidine-based chemotherapy combined with bevacizumab in the first and second-line treatments of metastatic colorectal cancer significantly increased oncologic outcomes in several randomized controlled trials (2, 3). However, the antiangiogenic effect of bevacizumab inhibits the capillary beds of the small bowel villi, contributing to gastrointestinal perforation by provoking the regression of normal blood vessels in the gastrointestinal tract (4). Several studies showed an increased risk of gastrointestinal perforations in patients treated with bevacizumab (5, 6). In an animal model, the administration of bevacizumab inhibited angiogenesis in the intestinal anastomosis site, resulting in a decrease in α-SMA accumulation and collagen deposition in bowel anastomosis site tissue, which might affect the healing of intestinal anastomosis (7). Because of the antiangiogenic effect of bevacizumab, the discontinuation of bevacizumab is recommended at least 6 weeks before surgery (8). Therefore, this study was conducted to evaluate the effect of bevacizumab on intestinal anastomosis site healing in stage IV colorectal cancer patients who underwent preoperative chemotherapy.

Methods

From January 2010 to December 2020, patients diagnosed with stage IV colorectal cancer treated with palliative chemotherapy or chemoradiotherapy followed by radical surgery were retrospectively reviewed. Patients with familial disease, recurrent disease, emergent operations, or who underwent abdominoperineal resections, which has no anastomosis site, or without appropriate follow-up data were excluded from the cohort. A flowchart of patient selection is illustrated in Figure 1. A total of 260 patients were enrolled. This study was reviewed and approved by the Institutional Review Board of Samsung Medical Center (No. 2021-10-041).

Chemotherapy regimens were based on the National Comprehensive Cancer Network (NCCN) guidelines. In all the patients, chemotherapy with FOLFIRI/FOLFOX/XELOX was initiated with or without cetuximab/bevacizumab. All patients underwent tests of tumor gene status for KRAS/NRAS as well as MSI/MMR status. Patients with KRAS or NRAS mutation were not treated with cetuximab or panitumumab and treated with FOLFIRI/FOLFOX/XELOX alone or in combination with bevacizumab. When the disease progressed despite of first-line FOLFOX/XELOX based chemotherapy, chemotherapy regimen was altered. In previous oxaliplatin-based therapy without irinotecan, irinotecan ± aflibercept or pembrolizumab based...
chemotherapy was continued (8). Also, patients with low to mid-
colorectal cancer were discussed in the multidisciplinary meeting
whether to undergo neoadjuvant radiotherapy before surgery.

Anastomosis site leakage was defined as a defect in the
intestinal wall integrity at the colorectal or colo-anal
anastomosis site, leading to a communication between the
intraluminal and extraluminal compartments. An abscess in
the pelvic cavity close to the anastomosis site was considered
anastomotic leakage. Clinical symptoms and signs such as fever,
tachycardia, abdominal pain or distension, leukocytosis, and
elevated C-reactive protein (CRP) levels were indicators
suspicious of anastomosis site leakage, so patients with the
symptoms or signs listed above underwent computed
tomography (CT). Peri-anastomotic loculated fluid containing
air or anastomosis wall defects in contrast CT was considered
anastomosis site leakage (9).

Statistical analyses were performed using Rex (Version 3.0.3,
RexSoft Inc., Seoul, Korea) and SPSS version 27 (SPSS Inc.,
Chicago, IL, USA). The categorical variables were analyzed using
the Chi-squared test, and the continuous variables were analyzed
using the Mann-Whitney U-test. The logistic regression model
was used to analyze the variables that could independently
influence anastomosis site leakage. Variables with a P-value of
< 0.1 in univariable analysis were entered into a multivariable
analysis. A P-value of < 0.05 in the multivariable analysis was
considered statistically significant.

Results

Among the 260 patients, a total of 136 (52.3%) patients were
treated with XELOX/FOLFOX/FOLFIRI combined with
bevacizumab, 85 (32.7%) patients were treated with FOLFOX/
FOLFIRI combined with cetuximab, 25 (9.6%) patients with
XELOX only, 8 (3.2%) patients with FOLFOX only, 2 (0.8%)
patients with FOLFIRI only, 2 (0.8%) patients with XELOX and
XELIRI, 1 (0.3%) patient with FOLFIRI with aflibercept, and 1
(0.3%) patient with pembrolizumab. Three patients received
25Gy to 44Gy of radiation. The patients received a median of
6 courses of bevacizumab (minimum 3, maximum 42), and the
median interval days between the last bevacizumab treatment
to surgery was 43 days (range 16 – 240 days).

A comparison of the baseline clinicopathologic features
between the groups is summarized in Table 1. Age, perineural
invasion, and anastomosis site leakage were significantly
different between the two groups (P = 0.012 P = 0.040, P <
0.001). In the group treated with bevacizumab, anastomosis site
leakage was higher in patients with rectal cancer, and drug
discontinuation periods shorter than 35 days (P = 0.020, P =
0.027; Table 2).

Among the all patients, 213 patients underwent radical
operation of colorectal lesion with metastasectomy. The most
common operation site for metastatic organ was liver. One
hundred seventy-one (65.8%) patients underwent liver
resection or intraoperative radio frequency ablation. Hemihepatectomy, sectionectomy, segmentectomy and wedge
resection were conducted for the liver resection. The next
common operation for metastasis was distant metastatic
lymph node dissection (15.4%). Hysterectomy or oophorectomy
were performed in 6.2% patients. Pneumonectomy, small bowel
resection, operation for bladder/ ureter were performed in 2.3% patients respectively. Splenectomy, pancreatectomy and wedge resection of stomach
were performed in each one patient.

A total of 14 (5.4%) patients were diagnosed with
anastomosis site leakage. The anastomosis site leakage events
are described in detail in Table 3. Thirteen (92.85%) patients
were treated with bevacizumab and 1 (7.15%) patient was treated
with cetuximab. Among 14 patients, 1 (7.2%) was diagnosed
before 7 postoperative days (PODs), 10 (71.4%) patients between
1 – 2 weeks, 3 (21.4%) patients between 3 – 4 weeks. 10 (71.4%)
patients were diagnosed at hospitalization and 4 (28.6%) were
diagnosed after discharge. 9 (64.3%) patients had body
temperatures higher than 38 °C and 10 (71.4%) patients had
elevated white blood cell (WBC) counts with elevated absolute
neutrophil counts, and all patients had elevated CRP levels.
Two (14.3%) patients had stable vital signs with elevated CRP levels.
Among 9 patients with fever, 2 patients had septic shock and 1
patient had sepsis before emergent surgery.

Eight (57.1%) patients underwent emergent operations.
Seven underwent intra-abdominal irrigation with loop
ileostomy and 1 underwent irrigation and drainage only
because this patient already had an ileostomy from the initial
operation. Three (18.75%) patients were treated with antibiotics
with percutaneous catheter drainage insertion for complicated
fluid collection. Three (18.75%) patients were treated with
antibiotics only.

Among 14 patients, 3 (21.4%) patients had an ileostomy
from the primary operation. One patient underwent irrigation
and drainage because she was diagnosed with sepsis with
complicated fluid collection with anastomosis site dehiscence
in the CT examination. One patient was treated with antibiotics
with percutaneous catheter drainage insertion. He had a high
fever of over 38 °C with tachycardia and bacteremia. The CT
showed air containing fluid collection abutting the anastomosis
site with localized peritonitis. One patient was treated with antibiotics
only because his vital signs were stable and CT
showed air containing fluid collection suspicious of connection
with anastomosis site with localized peritonitis. All patients
with a stoma underwent ileostomy take down after the end of
chemotherapy treatment with the confirmation of anastomosis
site healing by colon fluoroscopy using gastrografin. In patients
who didn’t need ileostomy for anastomosis site leakage, median
days of fistula to close was 18days (range, 12-62). In patient
repaired with laparotomy with ileostomy, median months of
fistula to close was 5.5 months (range, 3-24).
In multivariable analysis, chemotherapy agent was independent factor associated with anastomosis site leakage (P = 0.008, Table 4). In the bevacizumab group, the discontinuation period before surgery was independent factor associated with anastomosis site leakage in multivariable analysis (P = 0.031, Table 5).

**Discussion**

Monoclonal antibodies are chemotherapeutic agents targeting specific receptors on cancer cells (10). Bevacizumab, a monoclonal antibody, acts as an anti-angiogenic agent inhibiting VEGF-A (2). The addition of bevacizumab to fluorouracil-based combination therapy resulted in significant improvement in survival among patients with stage IV colorectal cancer (11, 12). However, because of the anti-angiogenic effects, many studies have reported the complications of surgical wound healing or gastrointestinal perforation in patients treated with bevacizumab (13–16). In previous studies, bevacizumab-associated GI perforation was

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**TABLE 1 Baseline clinicopathologic features of patients in the bevacizumab and non-bevacizumab groups.**

|                        | Non-bevacizumab (n=124) | Bevacizumab (n=136) | P-value |
|------------------------|--------------------------|---------------------|---------|
| Age, Median (range)    | 54 (26–79)               | 57 (23–82)          | 0.005   |
| Sex                    |                          |                     | 0.250   |
| Male                   | 78 (62.9%)               | 76 (55.9%)          |         |
| Female                 | 46 (37.1%)               | 60 (44.1%)          |         |
| BMI (kg/m²), Median (range) | 23.9 (17.8–30.5) | 24.0 (15.2–32.8)       | 0.889   |
| Underlying DM          |                          |                     | 0.309   |
| No                     | 104 (83.9%)              | 120 (88.2%)         |         |
| Yes                    | 20 (16.1%)               | 16 (11.8%)          |         |
| ASA score              |                          |                     | 0.549   |
| 1-2                    | 114 (91.9%)              | 111 (89.0%)         |         |
| 3                      | 10 (8.1%)                | 15 (11.0%)          |         |
| Preoperative CEA       |                          |                     | 0.063   |
| <5                     | 89 (71.8%)               | 83 (61.0%)          |         |
| ≥5                     | 35 (28.2%)               | 53 (39.0%)          |         |
| Location               |                          |                     | 0.174   |
| Colon                  | 57 (46.0%)               | 74 (54.4%)          |         |
| Rectum                 | 67 (54.0%)               | 62 (45.6%)          |         |
| Route of access        |                          |                     | 0.109   |
| Open                   | 53 (42.7%)               | 44 (32.4%)          |         |
| MIS                    | 71 (57.3%)               | 92 (67.6%)          |         |
| Diverting stoma        |                          |                     | 0.065   |
| No                     | 98 (79.0%)               | 120 (88.2%)         |         |
| Yes                    | 26 (21.0%)               | 16 (11.8%)          |         |
| Cancer obstruction     |                          |                     | 0.736   |
| No                     | 97 (78.2%)               | 104 (76.5%)         |         |
| Yes                    | 27 (21.8%)               | 32 (23.5%)          |         |
| Cancer perforation     |                          |                     | 0.251   |
| No                     | 122 (98.4%)              | 134 (98.5%)         |         |
| Yes                    | 2 (1.6%)                 | 2 (1.5%)            |         |
| EBL (ml), Median (range)| 243.5 (50-3000)         | 200 (50-2000)       | 0.064   |
| Transfusion            |                          |                     | 0.231   |
| No                     | 112 (90.3%)              | 128 (94.1%)         |         |
| Yes                    | 12 (9.7%)                | 8 (5.9%)            |         |
| Operation time (min)   | 283 (89-713)             | 281 (65-604)        | 0.329   |
| Ulceration             |                          |                     | 0.196   |
| No                     | 33 (26.6%)               | 27 (19.9%)          |         |
| Yes                    | 91 (73.4%)               | 109 (80.1%)         |         |
| Tumor size (cm)        | 4.0 (0-10.0)             | 3.9 (0-13)          | 0.527   |
| Differentiation        |                          |                     | 0.688   |
| Well to moderate       | 114 (91.9%)              | 123 (90.4%)         |         |
| Poor, SRC, MAC         | 10 (8.1%)                | 13 (9.6%)           |         |
| T stage                |                          |                     | 0.509   |
| T0-T2                  | 21 (16.9%)               | 18 (13.2%)          |         |
| T3-T4                  | 103 (83.1%)              | 118 (86.8%)         |         |
| N stage                |                          |                     | 0.125   |

(Continued)
seen in 1.5% – 1.6% of the patients with metastatic colorectal cancer (4, 11). Also bevacizumab is considered a preoperative risk factor for colorectal anastomotic leakage (17). And some studies reported spontaneous delayed anastomotic complications associated with bevacizumab (18, 19).

In our study, postoperative anastomosis site leakage was observed in 5.4% of the patients with stage IV colorectal cancer treated with preoperative chemotherapy/chemoradiotherapy. Of the anastomosis site leakage patients, 93.75% were treated with bevacizumab combined with FOLFOX/FOLFIRI/XELOX. Patients treated with bevacizumab showed significantly higher anastomosis site leakage compared to the non-bevacizumab group. Bevacizumab was also a factor associated with anastomosis site leakage in stage IV colorectal patients. Kościelny et al. reported that bevacizumab was associated with significantly higher anastomosis site leakage in the non-ileostomy group who underwent debulking surgery for ovarian cancer (20). Also, Uehara et al. reported 27.8% of anastomosis site leakage in

TABLE 2 Baseline clinicopathologic features of patients with anastomotic leakage and non-leakage treated with bevacizumab.

|                          | Without leakage (n=123) | With leakage (n=13) | P-value |
|--------------------------|-------------------------|---------------------|---------|
| Age                      | 59 (24-82)              | 53 (23-69)          | 0.089   |
| Sex                      |                         |                     | 0.876   |
| Male                     | 69 (56.1%)              | 7 (53.8%)           |         |
| Female                   | 54 (43.9%)              | 6 (46.2%)           |         |
| BMI                      | 23.8 (15.2-32.8)        | 24.3 (20.0-29.1)    | 0.679   |
| Underlying disease       |                         |                     |         |
| No                       | 60 (48.8%)              | 7 (53.8%)           | 0.956   |
| Yes                      | 63 (51.2%)              | 6 (46.2%)           |         |
| Underlying DM            |                         |                     | 0.651   |
| No                       | 109 (86.2%)             | 11 (84.6%)          |         |
| Yes                      | 14 (13.8%)              | 2 (15.4%)           |         |
| ASA score                |                         |                     | 0.686   |
| 1-2                      | 109 (88.6%)             | 12 (92.3%)          |         |
| 3                        | 14 (11.4%)              | 2 (15.4%)           |         |
| Preoperative CEA         |                         |                     | 0.795   |
| <5                       | 76 (61.8%)              | 7 (53.8%)           |         |
| ≥5                       | 47 (38.2%)              | 6 (46.2%)           |         |
| Location                 |                         |                     | 0.020   |
| Colon                    | 70 (56.9%)              | 3 (30.8%)           |         |
| Rectum                   | 53 (43.1%)              | 10 (46.2%)          |         |
| Route of access          |                         |                     | 0.117   |
| Open                     | 37 (30.1%)              | 7 (53.8%)           |         |
| MIS                      | 86 (69.9%)              | 6 (46.2%)           |         |
| Diverting stoma          |                         |                     | 0.651   |
| No                       | 109 (88.6%)             | 11 (84.6%)          |         |
| Yes                      | 14 (11.4%)              | 2 (15.4%)           |         |
| Cancer obstruction       |                         |                     | 0.732   |
| No                       | 93 (75.6%)              | 11 (84.6%)          |         |
| Yes                      | 30 (24.4%)              | 2 (15.4%)           |         |
| Cancer perforation       |                         |                     | 0.643   |
| No                       | 121 (98.4%)             | 13 (100%)           |         |
| Yes                      | 2 (1.6%)                | 0 (0%)              |         |
| EBL (ml)                 | 200 (5-2000)            | 150 (30-700)        | 0.631   |
| Transfusion              |                         |                     | 0.562   |
| No                       | 116 (94.3%)             | 12 (92.3%)          |         |
| Yes                      | 7 (5.7%)                | 1 (7.7%)            |         |
| Operation time (min)     | 282 (65-604)            | 273 (81-560)        | 0.441   |
| Ulceration               |                         |                     | 0.722   |
| No                       | 24 (19.5%)              | 3 (23.1%)           |         |
| Yes                      | 99 (80.5%)              | 10 (76.9%)          |         |
| Tumor size (cm)          | 4 (0-13)                | 3.5 (0-8.8)         | 0.900   |
| Differentiation          |                         |                     | 0.360   |
| Well to moderate         | 112 (91.1%)             | 11 (84.6%)          |         |
| Poor, SRC, MAC           | 11 (8.9%)               | 2 (15.4%)           |         |
| T stage                  |                         |                     | 0.683   |
| T0-T2                    | 16 (13.0%)              | 2 (15.4%)           |         |
| T3-T4                    | 107 (87.0%)             | 11 (84.6%)          |         |

(Continued)
rectal cancer patients who underwent neoadjuvant XELOX + Bevacizumab followed by total mesorectal excision (21).

Anastomotic leakage after rectal cancer surgery commonly occurs in the early postoperative period within 7 days (22, 23). Previous studies revealed that treatment with bevacizumab could be associated with delayed anastomosis site perforation, even 15 months after surgery (18, 19). In our study, the median time to leakage was 9 days (range, 6 – 27 days), which was longer than

TABLE 3 Detailed information and treatment of patients diagnosed with anastomosis site leakage.

| No. | Sex | Age | Chemotherapy agent | No. of target agent doses | Drug discontinuation day/Diagnosed date | Vital signs and laboratory findings | Treatment |
|-----|-----|-----|---------------------|--------------------------|----------------------------------------|-----------------------------------|-----------|
| 1 M 57 | FOLFIRI/Avastin | 7 | 34/POD#7 | BT 39.2, WBC 10k, CRP 5.26 | Antibiotics, PCD insertion | Loop ileostomy |
| 2 F 34 | XELOX/Avastin | 9 | 28/POD#7 | Tachycardia, WBC 30k, CRP 23 | | Antibiotics, PCD insertion |
| 3 M 63 | FOLFIRI/Avastin | 5 | 21/POD#10 | BT 38.3, WBC 22k, CRP 10 | | Antibiotics, PCD insertion |
| 4 M 68 | FOLFIRI/Avastin | 4 | 47/POD#11 | BT 38.3, WBC 20k, CRP 6.8 | | Loop ileostomy |
| 5 M 50 | FOLFIRI/Cetuximab | 11 | 30/POD#8 | Tachycardia, WBC 18k, CRP 8 | | Antibiotics |
| 6 F 53 | FOLFIRI/Avastin | 8 | 44/POD#7 | Septic shock, WBC 17k, CRP 11 | | Loop ileostomy |
| 7 F 56 | FOLFOX/Avastin | 4 | 43/POD#23 | BT 38.4, WBC 20k, CRP 37 | | Antibiotics |
| 8 F 45 | FOLFIRI/Avastin | 15 | 46/POD#9 | BT 39.1, tachycardia, WBC 19k, CRP 9 | | Irrigation and drain replacement |
| 9 M 43 | FOLFIRI/Avastin | 3 | 28/POD#27 | BT 38.1, normal WBC, CRP 1.9 | | Loop ileostomy |
| 10 M 69 | FOLFOX/Avastin | 3 | 56/POD#6 | Tachycardia, Tachypnea, WBC 8k, CRP 6.9 | | Loop ileostomy |
| 11 M 69 | FOLFIRI/Avastin | 17 | 34/POD#9 | Septic shock, WBC 17k, CRP 2.28 | | Loop ileostomy |
| 12 M 36 | FOLFOX/Avastin | 9 | 50/POD#23 | V/S stable, normal WBC, CRP 2.5 | | Antibiotics |
| 13 F 45 | FOLFOX/Avastin | 2 | 47/POD#13 | V/S stable, normal WBC, CRP 6 | | Antibiotics |
| 14 F 23 | FOLFIRI/Avastin | 42 | 28/POD#7 | Sepsis, WBC 13k, CRP 13 | | Loop ileostomy |

BT, Body temperature; WBC, White blood cell; CRP, C-reactive protein; PCD, Percutaneous catheter drainage; V/S, Vital sign.

TABLE 4 Univariable and multivariable analyses of factors associated with anastomosis site leakage in stage IV colorectal cancer patients.

| Factors | P-value | Odds ratio | 95% CI | P-value |
|---------|---------|------------|--------|---------|
| Age | 0.085 | 0.958 | 0.915-1.004 | 0.071 |
| Sex | 0.852 | 1 | 0.93-1.03 | 0.89 |
| BMI | 0.882 | 0.97 | 0.94-1.01 | 0.16 |
| Underlying DM | 0.995 | 1 | 0.99-1.00 | 0.99 |
| ASA score | 0.791 | 1 | 0.96-1.05 | 0.43 |
| Location | 0.098 | 2.777 | 0.811-9.513 | 0.104 |
| Chemotherapy agent | 0.017 | 16.720 | 2.111-132.401 | 0.008 |
| Route of access | 0.116 | 1 | 0.99-1.02 | 0.39 |
| Diverting stoma | 0.561 | 1 | 0.97-1.05 | 0.43 |
| Cancer obstruction | 0.468 | 1 | 0.96-1.06 | 0.40 |
| Cancer perforation | 0.991 | 1 | 0.98-1.00 | 0.99 |
| EBL | 0.933 | 1 | 0.92-1.05 | 0.49 |
| Transfusion | 0.954 | 1 | 0.99-1.02 | 0.37 |
| T stage | 0.939 | 1 | 0.91-1.00 | 0.10 |
| N stage | 0.947 | 1 | 0.93-1.00 | 0.36 |
| Harvested LN | 0.855 | 1 | 0.92-1.00 | 0.19 |

BML, Body mass index; EBL, Estimated blood loss; LN, Lymph node.
anastomotic leakage after surgery in patients without bevacizumab treatment. Therefore, even if time has passed since the operation, if the patient complains of anal pain or bleeding, anastomotic leakage should be suspected, and further examinations should be performed.

Bevacizumab has a long terminal half-life (20 days) and the bevacizumab prescribing information recommends discontinuing bevacizumab at least 4 weeks before surgery (24). The NCCN guidelines suggest withholding bevacizumab at least 6 weeks prior to surgery (8). Yoshioka et al. reported that the interval between bevacizumab and surgery was not a risk factor for anastomotic leakage, but study was based on a median interval of 9 weeks so effect of bevacizumab on anastomosis site healing would be small (25). In this study, anastomosis site leakage was significantly higher in patients with discontinuation dates shorter than 5 weeks and there was no significant difference between the two groups when compared based on a 4 or 6-week discontinuation interval. Therefore, the discontinuation of bevacizumab is recommended at least 5 weeks prior to major surgery.

Despite the limitation that this study was a retrospective study from a single-center, to our knowledge, this was the first study to evaluate the effect of bevacizumab on anastomosis site healing in stage IV colorectal patients. Further prospective studies from multi-centers should be conducted to confirm our study results.

In conclusion, bevacizumab affected anastomosis site healing after colorectal cancer, and at least 5 weeks from bevacizumab discontinuation to surgery was associated with lower anastomosis site leakage compared to discontinuation dates shorter than 5 weeks. Thus, stage IV colorectal patients treated with bevacizumab before radical surgery for primary cancer should be carefully observed after the operation, and the period of drug discontinuation before surgery should be longer than 5 weeks to avoid anastomosis site leakage.

**Data availability statement**

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

**Ethics statement**

The studies involving human participants were reviewed and approved by the Institutional Review Board of Samsung Medical Center. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

**Author contributions**

Guarantor of integrity of the entire study: WL, YC. Study concepts and design: YC, SY. Literature research: JS, YP. Data

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**TABLE 5** Univariable and multivariable analyses of factors associated with anastomosis site leakage in the bevacizumab group.

| Factor                        | Univariable analysis | Multivariable analysis |
|-------------------------------|----------------------|------------------------|
|                               | P-value              | Odds ratio             | 95% CI      | P-value |
| Age                           | 0.038                | 0.963                  | 0.916-1.013 | 0.141   |
| Sex                           | 0.877                |                        |             |         |
| BMI                           | 0.799                |                        |             |         |
| Underlying DM                 | 0.671                |                        |             |         |
| ASA score                     | 0.688                |                        |             |         |
| Location                      | 0.083                | 3.646                  | 0.921-14.430| 0.065   |
| Route of access               | 0.091                | 0.391                  | 0.111-1.385 | 0.065   |
| Diverting stoma               | 0.672                |                        |             |         |
| Cancer obstruction            | 0.472                |                        |             |         |
| Cancer perforation            | 0.993                |                        |             |         |
| EBL                           | 0.911                |                        |             |         |
| Transfusion                   | 0.772                |                        |             |         |
| T stage                       | 0.810                |                        |             |         |
| N stage                       | 0.807                |                        |             |         |
| Harvested LN                  | 0.501                |                        |             |         |
| Drug holiday                  | 0.023                | 4.141                  | 1.136-15.097| 0.031   |
| Number of doses               | 0.290                |                        |             |         |

BMI, Body mass index; EBL, Estimated blood loss; LN, Lymph node.
analysis: SK, JS. Statistical analysis: SK, JH. Manuscript preparation: SK, YC, HK. Critical revision of manuscript: SK, JH, WL, SY, HK, YC, YP, JS. All authors contributed to the article and approved the submitted version.

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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