

Original Article

# Association Between Neoadjuvant Anti-VEGF Use and Surgical Complications in Metastatic Colon Cancer

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## Key Words

Metastatic colon cancer;  
Anti-VEGF therapy;  
Colorectal surgery;  
Postoperative complications;  
Wound healing

**Background.** Anti-VEGF agents have demonstrated oncologic benefits in metastatic colorectal cancer (mCRC), yet their anti-angiogenic properties may impair postoperative wound healing and increase surgical risks.

**Objective.** To assess whether preoperative anti-VEGF therapy is associated with postoperative complications in patients with metastatic colon cancer treated with chemotherapy before surgery.

**Design.** Retrospective cohort study.

**Settings.** Single-center study at Taipei Veterans General Hospital.

**Patients.** Sixty-eight patients with metastatic colon cancer receiving preoperative chemotherapy, including 37 with anti-VEGF therapy and 31 without, between 2010 and 2021.

**Main Outcome Measures.** Postoperative complication rate, severity (Clavien-Dindo classification), and complication details.

**Results.** Patients treated with anti-VEGF had significantly higher postoperative complication rates (59.5% vs. 22.6%,  $p = 0.01$ ). Infections (43.2% vs. 12.9%,  $p = 0.01$ ), cardiopulmonary complications (13.5% vs. 0%,  $p = 0.03$ ), and surgical site infections (29.7% vs. 9.7%,  $p = 0.04$ ) were more prevalent in the anti-VEGF group.

**Limitations.** Retrospective design and small sample size may introduce bias.

**Conclusions.** Preoperative use of anti-VEGF agents is associated with increased postoperative morbidity, particularly severe infections and cardiopulmonary complications. Careful timing and perioperative planning are warranted to reduce surgical risks.

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Colon cancer, especially cases with metastatic disease, is one of the leading causes of cancer-related mortality worldwide.<sup>1</sup> In Taiwan, colon cancer ranked as the third leading cause of cancer-related death in 2023. Cases are categorized as resectable, unresectable, and potentially resectable based on the primary tumor and metastatic lesions. For cases of resectable disease, the National Comprehensive Cancer

Network (NCCN) guidelines and previous studies have demonstrated better prognosis after primary tumor resection plus metastasectomy for liver<sup>2</sup> and lung<sup>3,4</sup> metastases. For cases of unresectable metastatic disease, treatment typically involves chemotherapy plus targeted agents and/or radiotherapy, with the goal of shrinking the tumor and extending survival.<sup>5</sup> The choice between chemotherapy and targeted therapy regimens is based

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on the location of the tumor, its genetic mutation profile, and underlying resistance mechanisms.<sup>6</sup> Notably, in some patients with potentially resectable metastatic colon cancer, systemic chemotherapy plus targeted therapy can convert the disease from being initially unresectable to resectable.<sup>7</sup>

Anti-VEGF, like bevacizumab, is a humanized monoclonal IgG1 antibody that targets vascular endothelial growth factor A (VEGF-A) which has been approved by the United States Food and Drug Administration for the treatment of metastatic colon cancer.<sup>8</sup> Based on the NCCN guidelines, the standard treatment options for metastatic colon cancer include double or triple chemotherapy regimens in combination with anti-VEGF agents. Previous studies have demonstrated significantly improved outcomes after adding anti-VEGF agents in the treatment of patients with metastatic colorectal cancer, specifically in terms of overall survival (OS), progression-free survival (PFS), and response rate.<sup>9-11</sup>

Despite their established clinical benefits, the therapeutic inhibition of angiogenesis by anti-VEGF agents has raised concerns regarding potential adverse effects in the perioperative setting, prompting investigations regarding its impact on the wound-healing process. Wound-healing is a complex and dynamic process involving four phases: hemostasis, inflammation, proliferation, and remodeling.<sup>12</sup> VEGF inhibition disrupts key processes involved in tissue repair such as endothelial proliferation, neovascularization, and fibroblast activation, all of which are essential for effective wound-healing. Consequently, anti-VEGF therapy may impair surgical wound-healing, and this has been suggested by multiple clinical studies.<sup>13,14</sup> Anti-VEGF agents suppress tumor neovascularization through a mechanism that closely mirrors the physiological processes required for tissue repair,<sup>15</sup> thus creating a growing concern that their perioperative use can delay or compromise wound-healing. Nevertheless, due to their established efficacy in metastatic colon cancer, the use of anti-VEGF agents in the preoperative setting may be warranted in certain patients, such as those whose disease was downstaged as resectable after systemic therapy and those with symptomatic primary tumors.

Although some studies have reported postopera-

tive complications associated with anti-VEGF therapy in metastatic colorectal cancer, most have primarily focused on treatment efficacy rather than surgical outcomes. Data specifically examining postoperative complications in metastatic colon cancer patients who received preoperative chemotherapy — with or without anti-VEGF therapy — remain limited. To further clarify these potential risks in detail, we retrospectively compared postoperative complications between patients who received preoperative anti-VEGF therapy and those who did not.

## Materials and Methods

### Study design and patient population

This retrospective cohort study was carried out at a single tertiary medical center (Taipei Veterans General Hospital), including patients with metastatic colon cancer between January 2010 and December 2021.

Clinical data was obtained through a comprehensive review of medical records and the electronic database of the hospital. The following demographic and clinical variables were collected as baseline patient characteristics: sex, age, body mass index (BMI), serum albumin level, Eastern Cooperative Oncology Group (ECOG) performance status, American Society of Anesthesiologists (ASA) classification, carcinoembryonic antigen (CEA) level, carbohydrate antigen 19-9 (CA19-9) level, and pretreatment clinical status. The primary tumor location and metastatic burden were collected as tumor-related variables. The following operative parameters were collected: whether metastasectomy was performed, surgical approach, urgency of the procedure (elective vs. emergency), duration of hospital stay, operative time, and intraoperative blood loss. The details of systemic therapy were also recorded, including the type of preoperative chemotherapy regimen, total number of chemotherapy cycles, and number of targeted therapy cycles administered.

### Inclusion and exclusion

All patients with metastatic colon cancer who re-

ceived treatment at Taipei Veterans General Hospital between January 2010 and December 2021 were retrospectively reviewed and considered for inclusion. The exclusion criteria were as follows: primary tumor located less than 15 cm from the anal verge on imaging, a nonadenocarcinoma histology, concurrent double primary malignancies diagnosed during the treatment period, incomplete clinical data, and incomplete follow-up data after treatment.

### Patient grouping and variable comparison

Patients were grouped between those who received preoperative chemotherapy with anti-VEGF agents and those who did not. The baseline patient characteristics, tumor-related factors, operative parameters, and systemic therapy information were compared between the two groups.

### Complication outcome and details

Postoperative complications were documented and graded according to the Clavien–Dindo classification<sup>16</sup> to assess the severity of surgical morbidity. Other details were also recorded, including anastomotic leakage, postoperative ileus, hemorrhage, cardiopulmonary events, infections (e.g., pneumonia, intra-abdominal infections, and urinary tract infections), and surgical site infections. The overall incidence, severity, and distribution of specific complications were compared between both groups.

### Statistical analysis

Continuous variables were described using means and standard deviations, while categorical variables were described as frequencies with percentages. Due to the presence of notable outliers, the CEA and CA 19-9 levels were reported as medians with interquartile ranges to better represent their distributions and reduce the influence of extreme values on the analysis.

Comparative analyses between the two groups were performed using the Wilcoxon rank-sum test for non-normally distributed continuous variables (median analysis), the independent t-test for normally distributed

continuous variables (mean analysis), and the Chi-squared test for categorical variables. All analyses were conducted using the SPSS software (version 25.0, IBM Corp., Armonk, NY), with  $p < 0.05$  considered statistically significant.

## Results

The study initially enrolled 847 patients diagnosed with metastatic colon cancer between January 2010 and December 2021. Postoperative follow-up was conducted for up to one year or until death, if it occurred during that period. Patients with double primary malignancies ( $n = 12$ ) and those with a nonadenocarcinoma histology ( $n = 8$ ) were excluded. Only patients who received chemotherapy prior to surgery were included. Patients with incomplete data or lost to follow-up were excluded. After applying all the eligibility criteria, the final analysis included 68 patients, including 37 who received preoperative chemotherapy with anti-VEGF agents and 31 who did not. Fig. 1 illustrates the process of patient selection and group allocation.

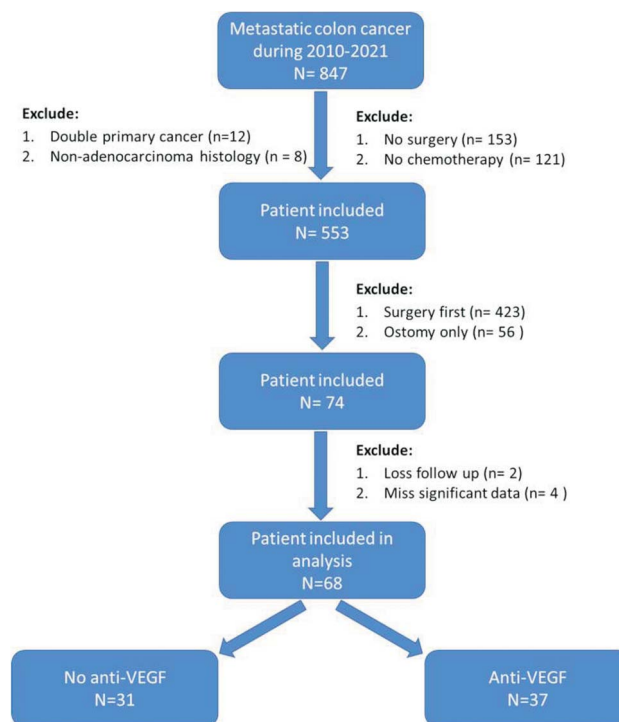


Fig. 1. Patient selection and group allocation.

**Patient characteristics**

The baseline clinical characteristics are summarized in Table 1. Male patients accounted for 48.39% in the no anti-VEGF group and 43.24% in the anti-VEGF group. The mean age was 55.35 ± 11.12 years in the no anti-VEGF group and 57.95 ± 10.68 years in the anti-VEGF group. The average body mass index was 22.99 ± 4.39 and 24.06 ± 4.61, respectively. Mean serum albumin levels were 3.76 ± 0.34 g/dL in the no anti-VEGF group and 3.72 ± 0.46 g/dL in the anti-VEGF group. ECOG performance status of 0 and 1, respectively, was seen in 25 and 6 patients in the group without anti-VEGF and in 32 and 5 patients in the anti-VEGF group. In the anti-VEGF group, 17, 17, and 2 patients were classified as ASA I, II, and III, respectively, while 1 patient was classified as ASA IV. In the group without anti-VEGF, 12 and 18 patients were classified as ASA I and II, respectively, while 1 patient was classified as ASA III. The groups with and without anti-VEGF, respectively, had median CEA levels of 92.80 ng/mL (range: 18.55-492.15) and 157.84 ng/mL (range: 17.44-674.5), as well as median CA 19-9 levels of 212.7 U/mL (range: 26.8-863.7) and 101.87 U/mL (range: 12.46-1137.5).

In the groups with and without anti-VEGF, re-

spectively, the clinical conditions present prior to treatment included bowel obstruction (n = 7 [18.92%], n = 2 [6.45%]), perforation (n = 1 [2.70%], n = 1 [3.23%]), and ostomy creation prior to surgery (n = 7 [18.92%], n = 3 [9.68%]).

**Tumor and systemic therapy characteristics**

The details regarding tumor characteristics and systemic therapy are presented in Table 2. In the anti-

**Table 2.** Patient tumor and treatment characteristics

(a) Tumor location and metastasis status

	No anti-VEGF	Anti-VEGF	p-value
Primary tumor location			0.23
Right side	9	16	
Left side	22	21	
Metastasis status			0.59
Oligometastasis	22	24	
Multiple metastasis	9	13	

(b) Patient pre-operative treatment characteristics

	No anti-VEGF	Anti-VEGF	p-value
Chemotherapy regimen			0
FOLFOX	25	5	
FOLFIRI	6	32	
Chemotherapy courses number	7.26 ± 4.73	9.19 ± 3.54	0.06
Target therapy courses		6.19 ± 2.83	

**Table 1.** Patient baseline characteristics

	No anti-VEGF	Anti-VEGF	p-value
Male	15/31 (48.39%)	16/37 (43.24%)	0.67
Age	55.35 ± 11.12	57.95 ± 10.68	0.33
BMI	22.99 ± 4.39	24.06 ± 4.61	0.34
Albumin	3.76 ± 0.34	3.72 ± 0.46	0.70
ECOG			0.52
0	25	32	
1	6	5	
ASA			0.64
1	12	17	
2	18	17	
3	1	2	
4	0	1	
CEA	157.84 (17.44-674.5)	92.80 (18.55-492.15)	0.87
CA-199	101.87 (12.46-1137.5)	212.7 (26.8-863.7)	0.47
Pre-treatment			
Obstruction	2/31 (6.45%)	7/37 (18.92%)	0.13
Perforation	1/31 (3.23%)	1/37 (2.70%)	0.90
Ostomy	3/31 (9.68%)	7/37 (18.92%)	0.28

VEGF group, 16 and 21 patients had right- and left-sided tumors, respectively. Meanwhile, in the group without anti-VEGF, 9 and 22 had right- and left-sided primary tumors, respectively. In the groups with and without anti-VEGF, respectively, 24 and 22 patients had oligometastatic disease, while 13 and 9 patients had multiple metastases. Regarding chemotherapy regimens, FOLFOX and FOLFIRI were administered in 5 and 32 patients in the group with anti-VEGF, and in 25 and 6 patients in the group without anti-VEGF. The distribution of chemotherapy regimens was significantly different between both groups ( $p < 0.001$ ). The mean number of chemotherapy courses was  $7.26 \pm 4.73$  in the no anti-VEGF group and  $9.19 \pm 3.54$  in the anti-VEGF group, with a  $p$ -value of 0.06. The mean number of targeted therapy courses in the anti-VEGF group was  $6.19 \pm 2.83$ .

### Operative characteristics

The operative characteristics are summarized in Table 3. Open surgery was performed in 23 patients in both groups, while laparoscopic procedures were done in 14 and 8 patients in the groups with and without anti-VEGF, respectively. Simultaneous metastasectomy was performed in 19 out of 37 patients (51.35%) and in 15 out of 31 patients (48.39%) in the groups with and without anti-VEGF, respectively. Emergent operations were done in 2 patients in each group.

The mean length of hospital stay was  $13.81 \pm 5.43$  days in the no anti-VEGF group and  $18.81 \pm 10.05$  days in the anti-VEGF group, showing a statistically significant difference ( $p = 0.02$ ). The groups with and without anti-VEGF were similar in terms of mean op-

erative time ( $343.11 \pm 161.60$  vs.  $344.42 \pm 147.94$  min,  $p = 0.97$ ) and estimated blood loss ( $426.76 \pm 805.89$  vs.  $481.33 \pm 859.55$  mL,  $p = 0.79$ ).

### Operative complications and details

The postoperative complications and their severity are summarized in Table 4(a), while the details regarding specific complications are shown in Table 4(b). There were significantly more postoperative complications seen in the anti-VEGF group versus those without anti-VEGF (22/37 [59.46%] vs. 7/31 [22.58%],  $p = 0.01$ ). In the anti-VEGF group, there were 4, 8, 6, and 3 events classified as Clavien-Dindo grade 1, 2, 3a, and 3b, plus 1 event classified as grade 5. In contrast, the group without anti-VEGF had 1, 4, and 2 events classified as grade 1, 2, and 3a. The distribution of severity grades approached statistical significance ( $p = 0.05$ ). There was 1 case of mortality within 90 days in the anti-VEGF group, with no mortality in either group within 30 days.

Regarding specific postoperative complications, the group with anti-VEGF, versus those without anti-VEGF, tended to have a higher occurrence of anastomotic leak (3 [8.11%] vs. 0 [0%],  $p = 0.11$ ), ileus (4 [10.81%] vs. 1 [3.23%],  $n = 0.23$ ), and postoperative hemorrhage (1 [2.7%] vs. 0 [0%],  $p = 0.36$ ), but these were not statistically significant. However, the anti-VEGF group had significantly higher rates of cardiopulmonary complications (5 [13.51%] vs. 0 [0%],  $p = 0.03$ ), infections (16 [43.24%] vs. 4 [12.9%],  $p = 0.01$ ), and surgical site infections (11 [29.73%] vs. 3 [9.68%],  $p = 0.04$ ) versus those without anti-VEGF.

**Table 3.** Patient operative characteristics

	No anti-VEGF	Anti-VEGF	$p$ -value
Operative method			0.29
Open	23	23	
Laparoscope	8	14	
Simultaneous metastasectomy	15/31 (48.39%)	19/37 (51.35%)	0.8
Emergent operation	2/31 (6.45%)	2/37 (5.41%)	0.86
Hospital stay (days)	$13.81 \pm 5.43$	$18.81 \pm 10.05$	0.02
Operative time (mins)	$344.42 \pm 147.94$	$343.11 \pm 161.60$	0.97
Blood loss (ml)	$481.33 \pm 859.55$	$426.76 \pm 805.89$	0.79

**Table 4.** Patient operative outcomes

## (a) Operative complication rate and severity

	No anti-VEGF	Anti-VEGF	<i>p</i> -value
Operative complication	7/31 (22.58%)	22/37 (59.46%)	0.01
Clavien-Dindo classification (grade)			0.05
1	1	4	
2	4	8	
3a	2	6	
3b		3	
5		1	
Mortality in 30 days	0	0	
Mortality in 90 days	0	1/37 (2.7%)	

## (b) Operative complication details

	No anti-VEGF	Anti-VEGF	<i>p</i> -value
Anastomosis leak	0/31 (0%)	3/37 (8.11%)	0.11
Ileus	1/31 (3.23%)	4/37 (10.81%)	0.23
Post operative hemorrhage	0/31 (0%)	1/37 (2.7%)	0.36
Cardiopulmonary complications	0/31 (0%)	5/37 (13.51%)	0.03
Infection	4/31 (12.9%)	16/37 (43.24%)	0.01
Surgical site infection	3/31 (3.68%)	11/37 (29.73%)	0.04

## Discussion

This retrospective cohort study evaluated the impact of anti-VEGF therapy on the perioperative outcomes of patients with metastatic colon cancer undergoing surgical resection. There were several notable differences between the two groups. Although the baseline characteristics were largely comparable, a significantly higher proportion of patients in the anti-VEGF group received FOLFIRI as the chemotherapy backbone, whereas FOLFOX was more commonly used in the group without anti-VEGF. This imbalance may reflect clinical decision-making based on tumor biology or patient condition, which can be a potential confounding factor. To address this, propensity score matching was performed using the chemotherapy regimen as the matching variable, which yielded an even distribution of FOLFOX and FOLFIRI between the two groups. In the matched cohort, the association between anti-VEGF use and the higher incidence of surgical complications remained significant (odds ratio = 9.39,  $p < 0.001$ ), indicating that the observed effect was independent of the chemotherapy regimen and likely attributable to anti-VEGF itself.

Regarding operative outcomes, hospital stay was

significantly longer in the anti-VEGF group. Although the operative time and estimated blood loss were similar between the two groups, the increased length of hospitalization could reflect the higher rate of postoperative complications in the anti-VEGF group. The most striking difference was the significantly higher incidence of postoperative complications in the anti-VEGF group, wherein nearly 60% of patients had at least 1 complication, in contrast to only 22.6% in the group without anti-VEGF. Furthermore, complications classified as Clavien–Dindo grade 3 and higher were more frequently observed in the anti-VEGF group, including one mortality within 90 days. In line with this, previous studies have suggested that anti-angiogenic therapy may impair wound-healing and increase the risk of surgical complications.<sup>13,14</sup>

Regarding individual complications, the anti-VEGF group had significantly higher rates of infection, surgical site infections, and cardiopulmonary complications. These complications can contribute to prolonged recovery and increased perioperative morbidity. These findings emphasize the importance of careful perioperative planning when incorporating targeted therapy into the treatment of metastatic colon cancer.

Our findings are consistent with existing reports

that describe an increased risk of postoperative complications associated with anti-VEGF therapy in patients with metastatic colon cancer. Nevertheless, the therapeutic efficacy of anti-VEGF is well-established in metastatic colorectal cancer, and its use is recommended by the NCCN guidelines. Accordingly, numerous studies have demonstrated the oncologic benefits of anti-VEGF-based chemotherapy in metastatic colorectal cancer. For instance, Masi et al.<sup>17</sup> reported that first-line treatment with FOLFIRI plus anti-VEGF therapy yielded favorable response rates and survival outcomes in patients with metastatic colorectal cancer. Similarly, Folprecht et al.<sup>18</sup> emphasized the importance of effective tumor downsizing through systemic therapy for achieving surgical resectability, and incorporating anti-VEGF therapy improved the response rates by approximately 10%. The BEAT study by Van Cutsem et al.,<sup>19</sup> which included over 1,900 patients, further confirmed the efficacy of anti-VEGF agents across various first-line chemotherapy regimens, including FOLFOX and FOLFIRI. Additionally, wound-healing complications occurred in approximately 5% of patients undergoing surgery during treatment, especially when done within 60 days of anti-VEGF exposure. The link between anti-VEGF and impaired wound-healing has been well-documented. Scappaticci et al.<sup>13</sup> observed a significantly higher incidence of wound-healing complications in patients undergoing major surgery during active anti-VEGF therapy versus those receiving chemotherapy alone (13% vs. 3.4%). However, patients who underwent surgery prior to anti-VEGF therapy had substantially lower rates of complications, thereby highlighting the potential perioperative risks associated with anti-VEGF therapy. In support of this, a meta-analysis by Zhang et al.<sup>14</sup> demonstrated a 2.3-fold increased risk of wound-healing complications associated with anti-VEGF use, particularly in patients with colorectal cancer. A retrospective analysis by Yoshimoto et al.<sup>20</sup> further examined both emergency and elective surgical outcomes in patients receiving anti-VEGF, revealing that 7 patients underwent emergency surgery because of anti-VEGF-associated gastrointestinal perforation, among which 2 died from postoperative sepsis or bleeding. In contrast, there were no severe peri-

operative complications among patients who underwent elective surgery after an appropriate anti-VEGF washout period (median: 24 days). These findings describe the increased risks associated with emergency interventions during active anti-VEGF treatment, thus supporting feasibility of elective surgery after an adequate washout period.

In line with previous reports, our study also observed a higher incidence and severity of postoperative complications in patients receiving anti-VEGF therapy, particularly infections and cardiopulmonary events. These findings highlight the importance of meticulous perioperative planning, including adequate drug-free intervals, individualized risk assessment, and close postoperative monitoring to mitigate surgical risks. Despite the substantial oncologic benefits of anti-VEGF in systemic disease control, its use may increase perioperative morbidity. Therefore, the timing of surgery relative to anti-VEGF administration should be carefully considered, and this should be accompanied by vigilant monitoring for complications.

Several limitations of this study should be acknowledged. First, the retrospective, single-center study design may introduce selection bias and limit the generalizability of the findings. Second, the relatively small sample size weakens the statistical power and can obscure meaningful associations. Most notably, data regarding the interval between the last dose of anti-VEGF and surgery was inconsistently available. Since this interval is a well-established determinant of postoperative safety, its absence limits our ability to infer causality. Future studies should employ a prospective multicenter design with detailed perioperative timelines in order to determine the optimal interval between anti-VEGF discontinuation and surgery. Further research is also warranted to identify specific patient subgroups with an increased risk for related complications, as well as to explore the predictive markers of wound-healing. This information can enable safer, more personalized treatment strategies.

## Conclusions

This retrospective single-center analysis demon-

strated that preoperative anti-VEGF use in patients with metastatic colon cancer is associated with an elevated risk of postoperative complications, particularly those with greater severity. Patients who received anti-VEGF therapy prior to surgery had a higher incidence of cardiopulmonary complications, surgical site infections, and other infectious events. These findings highlight the importance of heightened clinical vigilance in the perioperative care of patients on anti-VEGF therapy, specifically regarding the potential development of serious postoperative complications.

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原 著

## 轉移性大腸癌術前抗血管內皮生長因子治療與手術併發症之相關性研究

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**背景** 抗血管內皮生長因子 (anti-VEGF) 藥物已證實對轉移性大腸直腸癌具有腫瘤控制上的療效，但其抑制血管新生的機轉可能對術後傷口癒合產生負面影響，進而提高手術相關風險。

**研究目的** 本研究旨在評估轉移性結腸癌病人於手術前接受化學治療期間，是否使用 anti-VEGF 藥物與其術後併發症風險之相關性。

**研究設計** 回溯性世代研究。

**研究場域** 台北榮民總醫院單一中心研究。

**研究對象** 2010 至 2021 年間，68 位接受術前化學藥物治療之轉移性結腸癌病人，其中 37 位接受 anti-VEGF 治療，31 位未接受。

**主要觀察指標** 手術後併發症發生率、嚴重程度 (依 Clavien-Dindo 分級)、及併發症細項。

**研究結果** 接受 anti-VEGF 治療病人之術後併發症發生率明顯較高 (59.5% 對比 22.6%， $p = 0.01$ )。其中感染 (43.2% 對比 12.9%， $p = 0.01$ )、心肺併發症 (13.5% 對比 0%， $p = 0.03$ )、與手術傷口感染 (29.7% 對比 9.7%， $p = 0.04$ ) 在 anti-VEGF 組中亦顯著增加。

**研究限制** 回溯性設計與樣本數較小可能導致偏倚。

**結論** 術前使用 anti-VEGF 藥物與術後併發症風險增加相關，特別是嚴重感染與心肺併發症。建議臨床上於抗血管新生治療與手術安排之間進行審慎的時機規劃與術前準備，以降低相關風險。

**關鍵詞** 轉移性大腸癌、術前輔助治療、抗血管內皮生長因子、術後併發症。