

Original Article

Effects of antithrombotic therapy on the diagnosis and long-term postoperative outcomes of patients with colorectal cancer

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Abstract

Purpose: This study aimed to examine the effects of antithrombotic therapy (ATT) on the early detection and long-term postoperative outcomes of colorectal cancer (CRC).

Methods: This retrospective cohort study included 311 patients who underwent surgery for CRC between January 2004 and December 2017 at our institution. Cancer staging, overall survival (OS), and disease-specific survival (DSS) at the final postoperative diagnosis of patients with and without preoperative ATT (ATT group [$n = 66$] and control group [$n = 245$], respectively) were analyzed. Patients were followed up 3 years after their last registration.

Result: The ATT group had a higher mean age than the control group (77.8 ± 8.3 vs. 72.8 ± 11.5 years). Disease stage distribution showed no difference. The ATT group had a significantly higher frequency of CRC diagnosed by bleeding-related events ($P = 0.034$) and tended to have a right-sided colon primary, pTis/pT1, and smaller tumor size. Additionally, postoperative OS did not differ between the groups ($P = 0.81$), but the ATT group tended to have better DSS ($P = 0.12$).

Conclusion: Although gastrointestinal tract bleeding in patients undergoing ATT may contribute to the drug's adverse events, it facilitated the early detection of CRC. ATT may lead to early CRC detection and improved long-term postoperative outcomes.

(Keywords: antithrombotic therapy, colorectal cancer, early detection, long-term prognosis)

Introduction

Low-dose aspirin administration has been widely reported to reduce colorectal cancer (CRC) incidence and mortality [1–6]. In recent years, anticoagulation therapy (ACT) has also been reported to be useful in detecting CRC [7–12].

With population aging and the widespread use of direct oral anticoagulants, more surgical patients can have the opportunity to receive ACT as well as antiplatelet therapy (APT). Although patients receiving antithrombotic therapy (ATT) might experience hemorrhagic complications [1, 2, 7, 8], only few studies have examined the effects of these drugs on the early detection of CRC and long-term outcomes after surgery. In this study, we aimed to investigate the effects of ATT on the early detection of CRC and patients' long-term outcomes after surgery from the surgeons' perspective.

Methods

The institutional review board of Nagano Prefectural Kiso Hospital approved this study, which maintained patient privacy and confidentiality and conformed to the ethical standards of the 1964 Declaration of Helsinki and its later amendments (29-3-3).

This retrospective cohort study included patients who underwent surgery for CRC between January 2004 and December 2017 at Nagano Prefectural Kiso Hospital. Among them, 66 (21.2%) received ATT, and 44 (14.1%) were clinicopathologically diagnosed with stage IV CRC. The CRC stage was evaluated by computed tomography of the thorax, abdomen, and pelvis. Clinicopathological staging was assessed according to the seventh edition of the International Union against Cancer TNM classification.

Pathologists examined all pathological specimens collected via endoscopy and surgery. Pathological examinations routinely included tumor detection and the assessment of the invasion depth, the number of metastatic lymph nodes, and surgical margins.

From the medical records, data on patient characteristics, CRC detection opportunity, ATT type, clinicopathological findings, and outcomes were obtained.

We divided the patients into those who received preoperative ATT at CRC diagnosis (ATT group) and those who did not receive ATT preoperatively (control group). The ATT group was further divided into two subgroups: the APT and ACT groups.

The endpoints of this study were analyzed using the overall survival (OS) and disease-specific survival (DSS) of patients with ATT. OS and DSS were calculated from the date of operation for CRC to the date of death and final checkup. Patients' follow-up data were obtained from the medical records.

Statistical analysis

All statistical data were analyzed using the EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [13]. The results are expressed as means \pm standard deviation and percentages. The CRC detection, comorbidity, and clinicopathological factors were compared between the ATT and control groups by utilizing the Mann-Whitney *U* test for the continuous variables, and chi-square test or Fisher's exact test for the categorical variables. The patients were followed up periodically until the final checkup or death. Survival rates were calculated using the Kaplan-Meier method. A probability (*P*) value of less than 0.05 was considered statistically significant.

Results

We included 311 patients, with 146 males and 165 females, and the median age was 73.9 ± 11.1 years. Among them, 66 (21.2%) received ATT at CRC diagnosis (ATT group), and 245 (78.8%) did not (control group). Table 1 lists the cardiovascular comorbidities in both groups, and Table 2 summarizes the main indications leading to CRC detection and the differences by colon location. Oral medications included aspirin, warfarin, direct oral anticoagulants (rivaroxaban, apixaban, dabigatran, and edoxaban), ticlopidine, cilostazol, clopidogrel, dipyridamole, and ozagrel, which were administered to 32 (48%), 8 (12%), 11 (17%), 7 (11%), 7 (11%), 4 (6%), 3 (5%), and 1 (2%) patients, respectively. Seven patients (11%) received a combination therapy. CRC was detected in one (2%) patient treated with ozagrel during acute stroke treatment because of a bloody stool. In the ATT group, there were significantly more

Table 1. Comorbidities of the study participants

Disease	With ATT (n=66)	Without ATT (n=245)	P-value
IHD	23 (35%)	4 (2%)	<0.001
CVD	26 (39%)	5 (2%)	<0.001
Af	16 (24%)	3 (1%)	<0.001
DVT · PE	4 (6%)	0	<0.01

ATT, antithrombotic therapy; IHD, ischemic heart disease including myocardial infarction and angina; CVD, cerebrovascular diseases; Af, atrial fibrillation; DVT, deep vein thrombosis; PE, pulmonary embolism.

Table 2. Diagnostic opportunity and location of colorectal cancer

Opportunity for discovery	With ATT (n=66)	Without ATT (n=245)	P-value
Bleeding	33 (50%)	87 (35.5%)	0.034*
FOB, Others	33 (50%)	158 (64.5%)	
FOB, Others			0.838
FOB	11 (33.3%)	49 (31%)	
Others	22 (66.7%)	109 (69%)	
Right-sided colon			0.096
Bleeding	16 (48.5%)	29 (31.9%)	
FOB, Others	17 (51.5%)	62 (68.1%)	
Left-sided colon			0.171
Bleeding	17 (51.5%)	58 (37.7%)	
FOB, Others	16 (48.5%)	96 (62.3%)	

Bleeding includes anemia, and melena or hematochezia.

FOB, fecal occult blood.

ATT, antithrombotic therapy.

diagnoses due to bleeding-related events (50% vs. 35.5%, $P = 0.034$). This was more likely in the right-sided colon, although the difference was not significant.

Table 3 summarizes the clinicopathological findings of the ATT and control groups. The mean age was significantly higher in the ATT group than in the control group (77.8 ± 8.3 years vs. 72.8 ± 11.5 years, $P = 0.0017$). The ATT group also had a significantly higher prevalence of diabetes mellitus (DM) than the control group (30.3% vs. 12.2%, $P = 0.001$). On the clinicopathological findings, the TNM factors and the rate of curative resection were not significantly different between the two groups, although tumor location on the right-side colon and superficial cancer were often observed in the ATT group.

In the ATT group, 49 patients (15.8%) received APT, and 18 (5.8%) received ACT. One (0.3%) patient was given both APT and ACT. Table 4 shows the cause of death in each group. In both groups, there was a significant difference in cause of death between death from CRC and death from other diseases. In other disease deaths, cardiovascular disease was the most common in the ATT group, while

Table 3. Patient characteristic

Variable	With ATT (n=66)	Without ATT (n=245)	P-value
Age (year-old mean±SD)	77.8 ± 8.3	72.8 ± 11.5	0.0017*
Sex			0.49
male	28 (42.4%)	118 (48.2%)	
female	38 (57.5%)	127 (51.8%)	
Alcohol consumption (every day)			0.057
with	7 (10.5%)	54 (22%)	
without	59 (89.4%)	191 (78%)	
Current smoking			0.278
with	5 (7.6%)	33 (13.5%)	
without	61 (92.4%)	212 (86.5%)	
Metachronous OPM previously			1
with	6 (9.1%)	22 (9%)	
without	60 (90.9%)	223 (91%)	
BMI (kg/m ³)	22.7 ± 4.0	22.0 ± 4.0	0.177
Diabetes mellitus			0.001*
with	20 (30.3%)	30 (12.2%)	
without	46 (69.7%)	215 (87.8%)	
Tumor location			0.066
right	33 (50%)	91 (37.1%)	
left	33 (50%)	154 (62.9%)	
Tumor size (mm: mean±SD)	43 ± 27.1	46.9 ± 24.8	0.15
Histologic type			0.291
differentiated (tub/pap)	58 (87.9%)	221 (90.2%)	
undifferentiated (por/sig/muc)	8 (12.1%)	19 (7.8%)	
others or no data	0	5 (2.0%)	
Depth of invasion			0.08
pTis or pT1	15 (22.7%)	32 (13.1%)	
pT2 or more	51 (77.3%)	213 (86.9%)	
Lymph node metastasis			0.677
pN0	39 (59.1%)	137 (55.9%)	
pN1 or more	27 (40.9%)	108 (44.1%)	
TNM Stage			0.588
I	18 (27.3%)	50 (20.4%)	
II	20 (30.3%)	79 (32.2%)	
III	21 (31.8%)	79 (32.2%)	
IV	7 (10.6%)	37 (15.1%)	
Curative resection			0.704
Yes	56 (84.8%)	200 (81.6%)	
No	56 (15.2%)	45 (18.4%)	
Clavien-Dindo classification ≥ 3			0.537
With	10 (15.2%)	30 (12.5%)	
without	56 (84.8%)	215 (87.8%)	
Chemotherapy after surgery			0.192
with	21 (31.8%)	102 (41.6%)	
without	45 (68.2%)	143 (58.4%)	

OPM, other primary malignancies; BMI, body mass index

Table 4. Causes of death in each group

Cause of death	With ATT (n=66)	Without ATT (n=245)	P-value
Colorectal cancer	13 (19.7%)	77 (31.4%)	0.01*
Other diseases	21 (31.8%)	44 (18%)	
Other diseases			0.768
Pneumonia	3 (4.5%)	10 (13.0%)	
Cardiovascular disease	5 (7.6%)	5 (2.0%)	
Cerebrovascular disease	2 (3.0%)	4 (1.6%)	
Senility	3 (4.5%)	4 (1.6%)	
Other cancers	4 (6.0%)	10 (4.1%)	
Others	4 (6.0%)	11 (4.5%)	

ATT, antithrombotic therapy.

pneumonia was the most common in the control group. OS was not significant in the ATT group ($P = 0.81$, Fig. 1a) as well as its subgroups (APT: $P = 0.921$, Fig. 1b; ACT: $P = 0.637$, Fig. 1c). However, they showed a slight trend toward improvement in DSS, although the difference was not significant (ATT: $P = 0.115$, Fig. 2a; APT: $P = 0.167$, Fig. 2b; ACT: $P = 0.331$, Fig. 2c).

Discussion

Gastrointestinal tract (GI) bleeding is generally regarded as an adverse event in patients receiving ATT [1, 2, 7, 8]. Part of our analysis was to investigate whether bleeding during ATT is useful for the early detection of CRC and improvement of long-term outcomes in surgical patients.

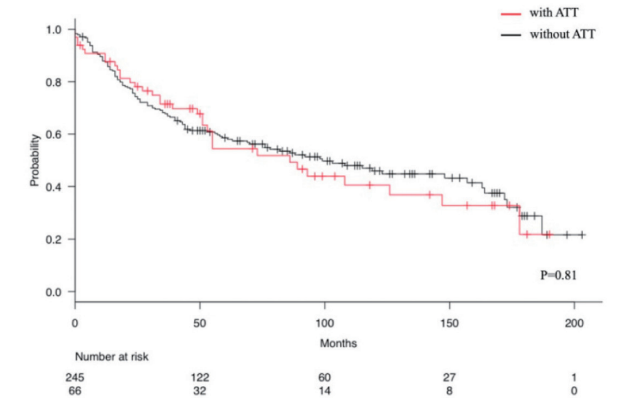
Some studies investigating the effects of ATT using aspirin and/or anticoagulants on immunochemical fecal occult blood test (iFOBT) showed reduced positive predictive value, while other studies reported no effect [14–21]. However, several studies reported effects such as increased sensitivity for iFOBT [16, 21], and the tendency is higher for advanced neoplasms [16]. Many cohort studies examining the impact of ATT on iFOBT may have not included patients diagnosed with CRC immediately after ATT initiation. One randomized controlled trial examining the effect of aspirin administration on iFOBT reported that aspirin administered 2 days before the iFOBT in patients not previously receiving aspirin or ATT had no effect on the sensitivity of detecting malignant neoplasm compared with placebo [20]. The ATT group in this study had more diagnostic events due to FOB (33.3% vs. 31%, $P = 0.838$), but the differences were not significant. The cause was thought to be increased CRC detection due to other hemorrhage-related events.

While the evidence of reduced mortality from the early detection of CRC by FOBT and other screening methods has accumulated [22–24], the long-term outcomes of CRC detected early by ATT remain insufficiently reported. In patients undergoing ACT, lower GI bleeding often occurs

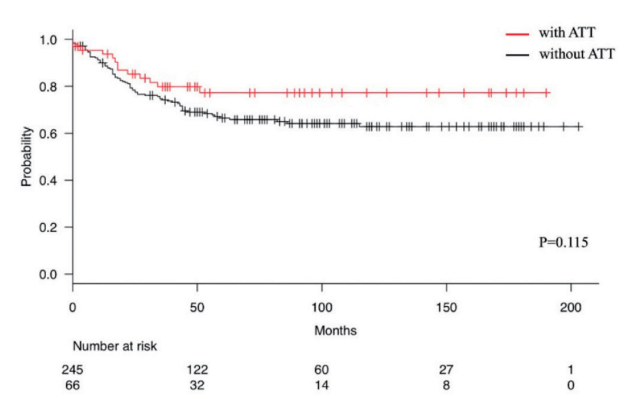
within the first month of treatment, and they are often diagnosed with CRC within 6 months of the bleeding [8, 9, 12]. GI bleeding during ACT reportedly has a strong and relatively specific association with newly diagnosed cancers (hazard ratio: 13.4–24.2) [7–9], with the strength of this association increasing with the severity of the bleeding [8]. We can extrapolate from the results of these previous studies that patients with CRC detected soon after ATT

initiation, especially within 6 months, can be diagnosed at the early cancer stage. The present study may include such cases, but we could not analyze the time from the start of ATT.

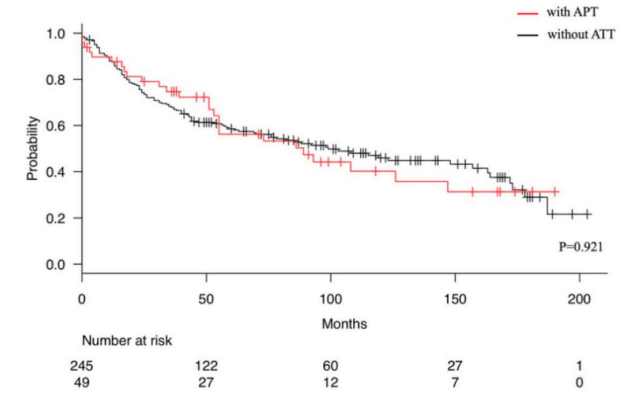
According to many studies, aspirin reduces the incidence and mortality of CRC [1–6]. The pathway for CRC prevention is still poorly known, although the COX-2-mediated pathway [25–27] and other pathways [27–29]



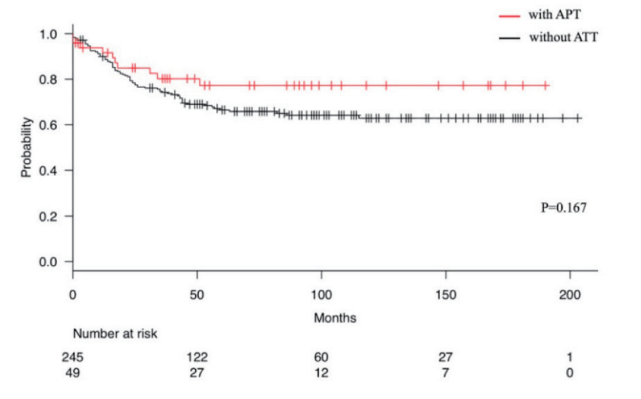
a With the antithrombotic therapy group vs. the control group



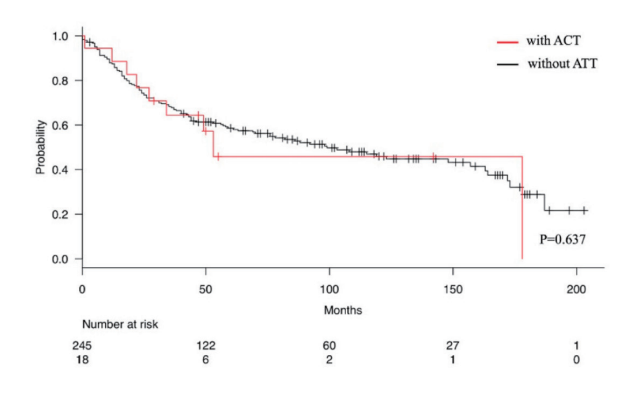
a With the antithrombotic therapy group vs. the control group



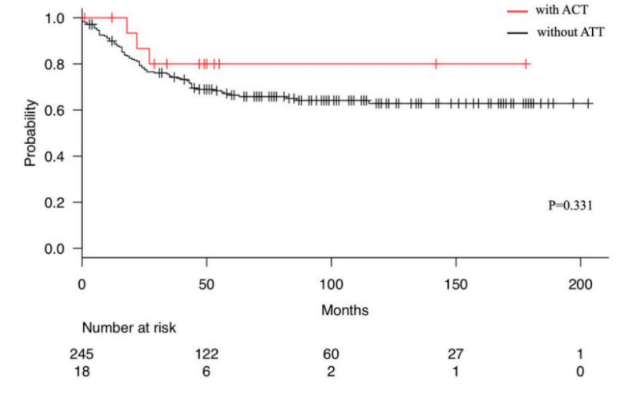
b With the antiplatelet therapy group vs. the control group



b With the antiplatelet therapy group vs. the control group



c With the anticoagulant therapy group vs. the control group



c With the anticoagulant therapy group vs. the control group

Fig. 1 Kaplan–Meier curves showing the overall survival of the enrolled patients. The antithrombotic, antiplatelet, and anticoagulant therapy groups are compared with the control group

Fig. 2 Kaplan–Meier curves showing the disease-specific survival of the enrolled patients. The antithrombotic, antiplatelet, and anticoagulant therapy groups are compared with the control group

have already been reported. In addition, aspirin reduces CRC mortality more than CRC morbidity; however, data on early diagnosis remain unavailable, probably because of the difference in tumor progression [1]. Although no significant differences were found in this study, our results suggest that CRC can be detected at the early stage through the tumor size and depth of invasion in patients undergoing ATT.

The reduction of CRC and its mortality has been reported to be greater in the proximal colon than in the distal colorectum, and both risks are reduced when aspirin was administered for more than 5 years [1]. In the present study, a higher proportion of patients in the ATT group had a primary tumor located in the right-sided colon than the control group. Additionally, there was a trend toward more detection by hemorrhage-related events. The frequency of new cancer diagnoses in patients receiving ATT for atherosclerosis is not significantly different between treatment regimens such as rivaroxaban alone (3.9%), rivaroxaban plus aspirin (4.0%), and aspirin alone (3.9%), when GI bleeding is observed during ATT, a 20-fold increase in the likelihood of CRC has been reported [7].

In this study, although OS or DSS improvement was not statistically significant in patients undergoing preoperative ATT with detected CRC, we found a trend toward DSS improvement despite older age and higher comorbidity of DM. One factor to be considered is that the tumor was diagnosed at the early stage because of the occurrence of bleeding associated with ATT. We also noted that the ATT group tended to more cases of right-sided colon cancer. Therefore, cases of early CRC detection by bleeding may increase, especially right-sided colon cancer, which generally has poor prognosis caused by lack of symptoms. Although negative, these data suggest early detection of CRC through bleeding in patients receiving ATT and the associated improvement in long-term prognosis.

A previous study reported significant OS improvement in patients with stage 0–III CRC receiving ATT [30]; however, we did not find a similar trend in this study. Perhaps, our patients with ATT were older than those in the previous study (mean: 77.8 years vs. 73.8 years). Showing a significant difference in OS was difficult because our patients with ATT were significantly older than the control group and they also had many comorbidities.

Considering that this study is a retrospective cohort study conducted in a single hospital, the possibility of various biases cannot be excluded, and the results were negative data because of the lack of volume. However, according to our study results, ATT may improve the long-term prognosis of patients with CRC, which was detected early by GI bleeding in this study.

Conclusion

Although GI bleeding in patients undergoing ATT may

contribute to the drug's adverse events, it facilitated the early detection of CRC. Further evaluation should be conducted in future multicenter studies or studies using a large database, focusing on patients diagnosed within 6 months of ATT initiation and those with primary right-sided colon cancer.

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Conflict of interest statement

All authors have no conflict of interest.

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抗血栓療法が大腸癌の診断，術後の長期治療成績に及ぼす影響の検討

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要 約

目的：抗血栓療法が大腸癌早期発見と術後の長期転帰に及ぼす影響の検討をした。

方法：大腸癌に対して手術を行った311症例において，抗血栓薬内服の有無（有群66例，無群245例）で術後最終診断における病期，生存期間（OS），疾患特異的生存期間（DSS）を解析した。

結果：抗血栓薬内服群の平均年齢は対照群より有意に高かったが（ 77.8 ± 8.3 歳 vs 72.8 ± 11.5 歳），病期の分布に差は認めなかった。内服群では，大腸癌の発見契機における出血要因が有意に多く（ $P = 0.034$ ），有意差はないが，右側結腸原発，深達度のpTis/pT1が多く，腫瘍径が小さい傾向を認めた。さらに，術後OSは両群間に差は認められなかったが（ $P = 0.81$ ），DSSはATT群で良好な傾向がみられた（ $P = 0.12$ ）。

結論：消化管出血は抗血栓療法の有害事象ではあるが，大腸癌の早期発見と大腸癌における術後長期予後の改善を促す可能性があると考えられた。

（キーワード：抗血栓療法，大腸癌，早期発見，長期予後）