Does Antiplatelet Therapy Affect Short-Term and Long-Term Outcomes of Patients Undergoing Surgery for Colorectal Cancer? - Surgical Radicality Versus Perioperative Antiplatelet-Related Morbidity Risks

Norihiro Shimoike, Takahisa Fujikawa, Yasunori Yoshimoto, Akira Tanaka

BACKGROUND: The effect of antiplatelet therapy (APT) on short-term and long-term outcomes in patients receiving surgery for colorectal cancer is still unknown.

METHODS: A total of 491 patients undergoing surgery for colorectal cancer between 2005 and 2011 were reviewed. The perioperative management protocol (“Kokura Protocol”) included preoperative continuation of aspirin monotherapy and early postoperative reinstitution in patients at high thromboembolic risks. Both short-term and long-term outcomes of patients with APT (n = 148), including perioperative morbidity, disease free survival (DFS) and overall survival (OS), were compared to those of patients without APT (n = 343).

RESULTS: Among 148 patients with APT, none suffered from excessive hemorrhage intraoperatively. There were only 4 postoperative bleeding complications (0.8%) and 1 thromboembolic event (0.2%), and operative mortality was zero. In the APT and non-APT groups, 5-year DFS rates were 75.5% and 77.7% (P = 0.207), respectively; 5-year OS rates were 68.8% and 78.9% (P = 0.004), respectively. OS rates were lower in APT group compared with non-APT group, but multivariate analysis showed that APT was not a significant factor for either DFS or OS.

CONCLUSIONS: The resection of colorectal cancer in patients with APT was performed safely, and satisfactory long-term outcome was obtained without any decrease of surgical radicality. The Kokura Protocol is valid and feasible to secure both short-term and long-term outcomes of such patient population.

Key Words: Colorectal cancer; Colorectal surgery; Antiplatelet therapy; Bleeding complication; Thromboembolic complication; Disease-free survival; Overall survival; Risk factor

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laparoscopic abdominal surgery can be performed safely and satisfactorily in patients with APT\textsuperscript{8,9}. However, the effect of APT on both short-term and long-term outcomes in patients receiving surgeries for malignancy still remains largely unknown.

The aim of this study is to review patients undergoing resection of colorectal cancer and to assess both short-term and long-term outcomes of surgery for colorectal cancer in patients who have been receiving APT.

**METHODS**

A total of 491 patients who had received radical resection of colorectal cancer in our institution between January 2005 and December 2011 were reviewed in this study. Patients diagnosed with Stage IV, or patients with insufficient information in the medical record were excluded from the study. Surgical procedures in this cohort included laparoscopic surgery \( (n = 191) \) and open surgery \( (n = 300) \). Lesion locations were colon \( (n = 318) \) and rectum \( (n = 173) \). Operations were performed according to Japanese guidelines and classification of colorectal cancer\textsuperscript{10,11}. D2 lymphadenectomy was performed for Stage 0 and I cancer and D3 lymphadenectomy for Stage II and III cancer. If patients had poor general conditions or operations were in an emergent situation (e.g. bowel obstruction, cancer perforation, etc.), D1 lymphadenectomy was chosen. Laparoscopic surgery was generally performed for colon cancer without serosal invasion and rectal cancer in clinical Stage 0 and I. APT was not usually taken into account when we decided to choose the operative procedure, but open surgery was chosen when long time operation was not tolerable due to severe heart disease or decreased pulmonary function. All procedures were performed by or under the guidance of one of the attending surgeons at our institution.

We have established our own perioperative protocol ("Kokura Protocol") about antithrombotic agents and risk stratification using several guidelines concerning antithrombotics as references\textsuperscript{8,9}. The perioperative management of antithrombotic agents is shown in Figure 1. In patients at low thromboembolic risk, APT was interrupted 1 week before surgery and reinstated 1 or 2 days after surgery (protocol A). For patients at high thromboembolic risk, aspirin monotherapy was maintained preoperatively (protocol B). Emergent operations were performed without reversal of the antithrombotic effect. If patients received chronic oral antiocoagulation (mainly warfarin) therapy, patients were managed by interruption of oral antiocoagulation 5 to 7 days before surgery, bridging antiocoagulation with unfractionated heparin, and early postoperative re-institution. High thromboembolic risk patients were defined as follows: (1) patients with drug-non-eluting coronary bare metal stent (BMS) implantation within two months; (2) patients with drug-eluting coronary stent (DES) implantation (regardless of the interval between DES implantation and surgical procedures); (3) patients who received cerebrovascular reconstruction within two months; (4) patients who had recent-onset cerebral infarction or transient ischemic attack; and (5) patients having cardiovascular or cerebrovascular diseases who were assessed as "high risk" for other reasons by cardiac/cerebral specialists.

Demographics, diagnosis, surgical treatments and postoperative outcomes were collected from the electronic surgery database as well as hospital and clinic charts. The status of patients’ symptoms and functions about daily living abilities was described using the ECOG Scale of Performance Status (PS)\textsuperscript{12}. Postoperative complications were assessed and categorized according to Clavien-Dindo classification (CDC)\textsuperscript{13} and CDC class II and more was considered significant. Postoperative bleeding complications included intraluminal bleeding, intra-abdominal bleeding, and abdominal wall hematoma. Intraluminal bleeding was defined as gastrointestinal bleeding with a significant decline in hemoglobin and requiring red blood cell (RBC) transfusion and/or therapeutic intervention. Intra-abdominal bleeding was diagnosed by abdominal distention or bloody abdominal drainage accompanied by imaging studies and a drop in hemoglobin. Bleeding complications with CDC class II were defined as minor bleeding complications, whereas those with CDC class III or more were defined as major bleeding complications. Thromboembolic complications included cerebral infarction, myocardial infarction (either due to stent thrombosis or not), pulmonary thromboembolism, and mesenteric infarction, which was diagnosed clinically and confirmed by imaging studies. The status of cancer was described according to TNM classification of malignant tumors. Operative mortality included death within 30 days after surgery.

The primary outcome included both disease free survival (DFS) and overall survival (OS). DFS was defined as the time from surgery to relapse or death without recurrence, whichever occurred first. The duration of follow-up was defined as the number of months from surgery until the last follow-up visit or data cutoff. OS was measured from surgery until death from any cause. Perioperative and outcome variables were compared between patients with APT (APT group, \( n = 148 \)) and without APT (non-APT group, \( n = 343 \)), and univariate and multivariate analysis were used to clarify the risk factors for DFS and OS.

The categorized data in each group was compared by chi-square or Fisher’s exact probability test. Continuous variables in the characteristics were expressed as a median with range and compared by one-way ANOVA or Kruskal-Wallis test. Non-parametric variables were also compared using Kruskal-Wallis test with Scheffe’s F test. Comparisons of DFS and OS between groups were performed using a two-sided stratified log-rank test. Hazard ratio (HR) with 95% confidence interval (CI) was calculated using COX proportional hazard models. Multivariante COX models began with all suspected prognostic variables obtained by univariate analysis. Survival curves were presented according to Kaplan-Meier methods. Statistical significance was set at \( p < 0.05 \). Data were analyzed using the SPSS package software.

This study was approved by our institutional review board.
RESULTS

Regular APT use was seen in 148 patients (30.1%) in this cohort. Table 1 shows profile of APT patients undergoing surgery for colorectal cancer. Concerning the type and agents of APT, single APT was dominant with the rate of 73.0% and aspirin was the most preferred agent. Angina pectoris (68.9%) and cerebral infarction (29.0%) explain the most of indications for APT. Among APT group, 18 patients (12.2%) required preoperative continuation of APT.

The patient characteristics for this cohort are listed in table 2 and table 3. A race of patients in the cohort was exclusively Asian and no other races were observed. Male gender (P < 0.001), patients with poor American Society of Anesthesiologists (ASA) score (ASA 3 or 4) (P < 0.001), diabetes mellitus (P < 0.001), history of cerebral infarction or transient ischemic attack (P < 0.001), maintenance of hemodialysis or peritoneal dialysis (P < 0.001), history of heart failure (P < 0.001), history of percutaneous coronary intervention (PCI) (P < 0.001), use of anticoagulation (P < 0.001), and intraoperative RBC transfusion (P = 0.006) were more prevalent in the APT group, on the other hand non-APT group included more patients with laparoscopic surgery (P = 0.021) or periperooperative chemotherapy (P = 0.026). There was no difference between the groups in the site of surgery (colon or rectum), the grade of lymphadenectomy (D1, D2 or D3) or cancer stage (0, I, II or III). There were only four postoperative bleeding complications (0.8%) and one thromboembolic event (0.2%) in a whole cohort.

Figure 2 shows the DFS and OS in the APT and non-APT groups. In the APT and non-APT groups, 5-year DFS rates were 75.5% and 77.7% (P = 0.458), respectively; median follow-up time was 31 months and 37 months, respectively. Five-year OS rates were 68.8% with 36 months of median follow-up in the APT group, as compared with 78.9% with 42 months of median follow-up in the non-APT group (P = 0.004).

Figure 3 shows the DFS and OS among patients in each cancer stage. Five-year DFS rates in the APT and non-APT groups were 89.2% and 95.7% among patients with Stage I disease, 80.3% and 77.2% among Stage II patients, and 61.9% and 63.6% among stage III patients. No significant difference was seen in each stage. Five-year OS in the APT and non-APT groups were 100% and 87.5% among patients with Stage 0 disease, 82.4% and 94.4% among patients with Stage I disease, 58.4% and 88.9% among patients with Stage II disease, and 69.4% and 63.2% among Stage III disease. The cause of death in each stage was shown in table 4. In the APT group death from other disease was more likely than in the non-APT group.

Univariate and multivariate analyses for DFS and OS were shown in table 5 and 6. In DFS, gender, cancer stage, intraoperative RBC transfusion, and perioperative chemotherapy were associated on univariate analysis, and using multivariate analysis, female gender (P = 0.003; HR = 2.099), cancer stage III (P = 0.005; HR = 2.141), and perioperative chemotherapy (P = 0.005; HR = 2.142) were significant prognostic factors. In OS, while PS, ASA score, maintenance of hemodialysis or peritoneal dialysis, history of heart failure, history of PCI, APT, cancer stage, intraoperative RBC transfusion, and perioperative chemotherapy were significant on univariate analysis, poor PS (grade 3 or 4) (P = 0.001; HR = 4.006), history of heart failure (P = 0.006; HR = 2.382), history of PCI (P = 0.02; HR = 2.562), cancer stage III (P = 0.01; HR = 2.088), and intraoperative RBC transfusion (P = 0.005; HR = 2.477) were independently associated with reduced OS. APT was not a significant factor for either DFS (P = 0.207; HR = 1.377) or OS (P = 0.213; HR = 0.605).

DISCUSSION

This retrospective cohort study showed that APT does not significantly affect either short-term or long-term outcomes of patients undergoing radical resection of colorectal cancer. There were only 4 postoperative bleeding complications (0.8%) and 1 thromboembolic event (0.2%), and operative mortality was zero in the whole cohort. Although 5-year OS rates in APT group appeared to be lower than those of non-APT group, statistical analysis suggested that the reduced OS rates largely resulted from severe underlying disease including heart failure or cardiovascular disease, and were not related to APT.

Table 1 Profile of antiplatelet therapy patients undergoing colorectal surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>APT group, total</td>
<td>148 (100)</td>
<td></td>
</tr>
<tr>
<td>Type and agents used in APT</td>
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<td></td>
</tr>
<tr>
<td>Single APT</td>
<td>108 (73.0)</td>
<td></td>
</tr>
<tr>
<td>Multidrug APTs</td>
<td>40 (27.0)</td>
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</tr>
<tr>
<td>Indication of APT</td>
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</tr>
<tr>
<td>Angina pectoris</td>
<td>102 (68.9)</td>
<td></td>
</tr>
<tr>
<td>s/p PCI with BMS</td>
<td>60 (40.5)</td>
<td></td>
</tr>
<tr>
<td>s/p PCI with DES</td>
<td>12 (8.1)</td>
<td></td>
</tr>
<tr>
<td>s/p CABG</td>
<td>18 (12.2)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>12 (8.1)</td>
<td></td>
</tr>
<tr>
<td>History of cerebral infarction</td>
<td>43 (29.3)</td>
<td></td>
</tr>
<tr>
<td>ICA stenosis</td>
<td>10 (6.8)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>12 (8.1)</td>
<td></td>
</tr>
<tr>
<td>Preoperative continuation of APT</td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>18 (12.2)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>130 (87.8)</td>
<td></td>
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</table>

Table 2 Background characteristics of patients in the cohort.

<table>
<thead>
<tr>
<th>Variables</th>
<th>APT (n = 148)</th>
<th>non-APT (n = 343)</th>
<th>Total (n = 491)</th>
<th>p value</th>
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<tbody>
<tr>
<td>Age median(range)</td>
<td>75 (55-96)</td>
<td>69 (41-94)</td>
<td>71 (41-96)</td>
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<tr>
<td>Gender, n(%)</td>
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</tr>
<tr>
<td>Female</td>
<td>36 (24.3)</td>
<td>155 (45.2)</td>
<td>191</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>112 (75.7)</td>
<td>188 (54.8)</td>
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<td>&lt;0.001</td>
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<td>BMI, n(%)</td>
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</tr>
<tr>
<td>&lt;30 kg/m^2</td>
<td>145 (98.0)</td>
<td>335 (97.7)</td>
<td>480</td>
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</tr>
<tr>
<td>≥30 kg/m^2</td>
<td>3 (2.0)</td>
<td>8 (2.3)</td>
<td>11</td>
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<tr>
<td>Performance status, n(%)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td>141 (95.3)</td>
<td>333 (97.1)</td>
<td>474</td>
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</tr>
<tr>
<td>3.4</td>
<td>7 (4.7)</td>
<td>10 (2.9)</td>
<td>17</td>
<td>0.419</td>
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<td>ASA score, n(%)</td>
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<td>1.2</td>
<td>70 (47.5)</td>
<td>301 (87.8)</td>
<td>371</td>
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<tr>
<td>3.4</td>
<td>78 (52.7)</td>
<td>42 (12.2)</td>
<td>120</td>
<td>&lt;0.001</td>
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<td>Diabetes mellitus, n(%)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>51 (34.5)</td>
<td>43 (12.5)</td>
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</tr>
<tr>
<td>No</td>
<td>97 (65.5)</td>
<td>300 (87.5)</td>
<td>397</td>
<td>&lt;0.001</td>
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<td>History of CI/TIA, n(%)</td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>45 (30.4)</td>
<td>10 (2.9)</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>102 (68.9)</td>
<td>333 (97.1)</td>
<td>435</td>
<td>&lt;0.001</td>
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<td>Current Hemodialysis/PD, n(%)</td>
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<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>11 (7.4)</td>
<td>2 (0.6)</td>
<td>13</td>
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<tr>
<td>No</td>
<td>137 (92.6)</td>
<td>341 (99.4)</td>
<td>478</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of CHF, n(%)</td>
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<td></td>
<td></td>
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<td>Yes</td>
<td>44 (29.7)</td>
<td>16 (4.7)</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>104 (70.3)</td>
<td>327 (95.3)</td>
<td>431</td>
<td>&lt;0.001</td>
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<tr>
<td>History of PCI, n(%)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>78 (52.7)</td>
<td>0 (0)</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>70 (47.3)</td>
<td>343 (100)</td>
<td>413</td>
<td>&lt;0.001</td>
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<tr>
<td>Anticoagulation used, n(%)</td>
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<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>23 (15.5)</td>
<td>18 (5.2)</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>125 (84.5)</td>
<td>325 (94.8)</td>
<td>450</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 2 Background characteristics of patients in the cohort.
**Table 3** Perioperative characteristics of patients in the cohort.

| Variables                                      | APT (n = 148) | non-APT (n = 343) | Total (n = 491) | P  
---|---|---|---|---  
Type of surgery, n(%)  
Colon  | 98 (66.2) | 220 (64.1) | 318 |  
Rectum  | 50 (33.8) | 123 (35.9) | 173 | 0.682  
Laparoscopic surgery, n(%)  
Yes  | 46 (31.1) | 145 (42.3) | 191 |  
No  | 102 (68.9) | 196 (57.7) | 300 | 0.021  
TNM Stage, n(%)  
0-II  | 94 (63.5) | 228 (66.5) | 322 |  
III  | 54 (36.5) | 115 (33.5) | 169 | 0.536  
Grade of lymphadenectomy, n(%)  
D1  | 17 (11.5) | 25 (7.3) | 42 |  
D2  | 79 (53.4) | 169 (49.3) | 248 |  
D3  | 52 (35.1) | 149 (43.4) | 201 |  
Perioperative chemotherapy, n(%)  
Yes  | 29 (19.6) | 101 (29.4) | 130 |  
No  | 119 (80.4) | 241 (70.6) | 360 | 0.026  
Estimated blood loss, n(%)  
<1000 ml  | 147 (99.3) | 337 (98.3) | 484 |  
≥1000 ml  | 1 (0.7) | 6 (1.7) | 7 | 0.68  
Intraoperative RBC transfusion, n(%)  
Yes  | 20 (13.5) | 19 (5.5) | 39 |  
No  | 128 (86.5) | 242 (94.5) | 370 | 0.006  
Bleeding complications, n(%)  
Yes  | 1 (0.7) | 3 (0.9) | 4 |  
No  | 147 (99.3) | 340 (99.1) | 487 | 1  
Thromboembolic complications, n(%)  
Yes  | 1 (0.7) | 0 (0) | 1 |  
No  | 147 (99.3) | 343 (100) | 490 | 0.301  

APT: antiplatelet therapy, RBC: red blood cell.

**Table 4** Cause of death in the cohort.

|   | APT (n=148) | non-APT (n=343) |   |   |   |    
|---|---|---|---|---|---|---  
Stage |   |   |   |   |   |    
0 | 5 | 0 (0%) | 0 (0%) |   |   |    
I | 33 | 2 (6.1%) | 2 (6.1%) |   |   |    
II | 56 | 3 (5.4%) | 12 (21.4%) |   |   |    
III | 54 | 8 (14.8%) | 5 (9.3%) | | |  

APT: antiplatelet therapy, RBC: red blood cell.

**Table 5** Univariate analysis for DFS and OS.

| Variables | Number | DFS events | P  | DFS events | P  
---|---|---|---|---|---  
Age  
<75yo  | 312 | 53 (17.0) | 0.624 | 42 (13.5) | 0.093  
≥75yo  | 179 | 34 (19.0) | 35 (19.6) |   |    
Gender  
Female  | 191 | 45 (23.6) | 0.008 | 38 (18.3) | 0.205  
Male  | 300 | 42 (14.0) | 42 (14) | |  
Performance status  
0-2  | 474 | 87 (18.4) | 0.053 | 69 (14.6) | 0.002  
3  | 17 | 0 (0) | 8 (47.1) | |    
ASA score  
1-2  | 371 | 63 (17.0) | 0.492 | 49 (13.2) | 0.013  
3  | 120 | 24 (20.0) | 28 (23.5) | |    
Diabetes mellitus  
Yes  | 94 | 14 (14.9) | 0.548 | 14 (14.9) | 0.876  
No  | 397 | 73 (18.4) | 63 (15.9) | |  
History of CI/TIA  
Yes  | 55 | 11 (20.0) | 0.708 | 8 (14.5) | 1  
No  | 435 | 76 (17.5) | 69 (15.9) | |  
Current Hemodialysis/PD  
Yes  | 13 | 1 (7.9) | 0.481 | 8 (58.6) | 0.036  
No  | 478 | 86 (18.3) | 72 (15.1) | |  
History of CHF  
Yes  | 60 | 13 (21.7) | 0.372 | 20 (33.3) | <0.001  
No  | 431 | 74 (17.2) | 57 (13.2) | |  
History of PCI  
Yes  | 78 | 17 (21.8) | 0.332 | 23 (29.5) | 0.001  
No  | 413 | 70 (16.9) | 54 (13.1) | |  
Anticoagulation used  
Yes  | 41 | 7 (17.1) | 1 (7.1) | 0.822  
No  | 450 | 80 (17.7) | 70 (15.6) | |  
APT used  
Yes  | 148 | 27 (18.2) | 0.898 | 32 (21.7) | 0.021  
No  | 343 | 60 (17.5) | 45 (13.1) | |  
Cancer Stage  
0-II  | 322 | 34 (10.6) | <0.001 | 35 (10.9) | <0.001  
III  | 169 | 53 (31.4) | 42 (24.9) | |  
Estimated blood loss  
<1000ml  | 484 | 84 (17.4) | 0.11 | 75 (15.5) | 0.302  
≥1000ml  | 7 | 3 (42.9) | 2 (28.6) | |  
Intraoperative RBC transfusion  
Yes  | 39 | 13 (33.3) | 0.014 | 13 (33.3) | 0.004  
No  | 452 | 74 (16.4) | 64 (14.2) | |  
Perioperative therapy  
Yes  | 130 | 47 (36.2) | <0.001 | 28 (22.3) | 0.024  
No  | 360 | 40 (11.1) | 48 (13.3) | |  

**Table 6** Multivariate analysis for DFS and OS.

| Variables | P value | Hazard Ratio | 95% CI | P value | Hazard Ratio | 95% CI  
---|---|---|---|---|---|---  
Female gender  | 0.003 | 2.099 | 1.342 to 3.283 | - | - | -  
Performance status ≥ 3  | - | - | - | 0.001 | 4.006 | 1.772 to 9.054  
Current Hemodialysis/PD  | 0.605 | 1.171 | 0.643 to 2.133 | 0.057 | 2.773 | 0.971 to 7.923  
History of CHF  | - | - | - | 0.006 | 2.382 | 1.282 to 4.428  
History of PCI  | - | - | - | 0.02 | 2.562 | 1.163 to 5.644  
Cancer Stage III  | 0.005 | 2.141 | 1.253 to 3.663 | 0.01 | 2.086 | 1.195 to 3.650  
Intraoperative RBC transfusion  | 0.003 | 2.499 | 1.366 to 4.571 | 0.005 | 2.477 | 1.308 to 4.693  
APT  | 0.207 | 1.377 | 0.838 to 2.262 | 0.213 | 0.605 | 0.273 to 1.333  

Hazard Ratio and 95% CI for the hazard ratio are presented. APT: antiplatelet therapy.
With the widespread use of antiplatelet agents for secondary prevention following coronary stent implantation, bypass surgery, non-cardiogenic ischemic stroke or TIA \([1,14,15]\), it is not uncommon that patients with APT undergo a surgical procedure. Approximately 5% to 15% of patients receiving coronary stent implantation are estimated to undergo a surgical procedure within 2 years \([4,6]\). Berger PB, et al \([12]\) reported more than 4% of patients required a major non-cardiac surgery in the year after placement of DES.

Bleeding and thromboembolic complications are major perioperative concerns in patients with APT. Interruption of APT may cause thromboembolic events, whereas continuation of antiplatelet agents is associated with an increased risk of bleeding \([12,17]\). Some clinical studies have shown no increase in the risk of perioperative bleeding 5-7 days following the withdrawal of antiplatelet agents \([18,20]\). Therefore, if the risk of thromboembolism is low, interruption of APT one week before surgery should be adequate. However, if the thromboembolic risk is high, perioperative continuation of APT should be considered. Particularly in patients with coronary stent, continuation of dual antiplatelet therapy (DAPT) with both aspirin and clopidogrel for at least 1 month after BMS implantation, and for at least 6 months after DES implantation is recommended \([1]\). Premature discontinuation of antiplatelet agents is one of risk factors of late stent thrombosis, which is uncommon but life-threatening complication with the mortality rate of between 9% and 45% \([1,4,6]\).

Dealing with such conflicting problems is challenging. Following the expansion of APT indication, the question of their influence on long-term outcomes of surgery is raised. Is not the surgical radicality limited in order to avoid perioperative complications? Due to the limitation of study evidence, however, the effect of APT on surgical outcome in patients receiving surgery for malignancy still remains largely unknown. Some recent reports showed favorable short-term outcomes of surgical procedures on patients with APT \([20,21,26]\). Nevertheless, there are no specific reports relating to the effect of APT on both short-term and long-term outcome after surgery for malignancy. We have previously demonstrated that using a perioperative antithrombotic management protocol ("Kokura Protocol"), both open and laparoscopic abdominal surgery can be performed safely and satisfactorily in patients with APT \([19,27]\). In addition, the current study also showed that the Kokura Protocol is valid and feasible even in the setting of colorectal cancer surgery, resulting in neither increased perioperative complications nor decreased DFS/OS of colorectal cancer patients receiving APT.

Interestingly the HR for OS showed a low value of 0.6 (95% CI, 0.275 to 1.333), which suggests that APT was rather a potential improving factor of OS, although it was not significant. It might be because APT was effective for severe underlying disease and prevented death from cardiovascular and/or cerebrovascular events. It has been known that regular aspirin use reduces the risk of fatal colon cancer \([27]\). Randomized trials designed to assess the cardiovascular benefits of aspirin demonstrated that allocation to aspirin reduced the risk of cancer metastasis including colorectal cancer \([28]\), and recent cohort study showed aspirin use after colon cancer diagnosis was associated with improved survival if tumors expressed HLA class I antigen \([27]\). Although our data showed no significant difference in recurrence rates, aspirin may reduce the risk of colorectal cancer recurrence and extend OS.

This study has some limitations. It is a retrospective review from a single center, which lessens the efficacy of the statistical analysis and conclusion. This limitation will be mitigated in a later follow-up study or in a multi-institutional, prospective study. Furthermore, it is uncertain if our perioperative management can be applied to Western populations. Despite these limitations, the current study provides important evidence about management of high thromboembolic risk patients undergoing colorectal cancer surgery.

**CONCLUSION**

This is the first study to examine the effects of APT on both short-term and long-term outcomes in patients undergoing surgery for colorectal cancer. Under rigorous Kokura Protocol including single APT continuation in high thromboembolic patients, operations were performed safely and satisfactory long-term outcome was achieved without any decrease of surgical radicality even for patients with APT.
Figure 3 Disease free survival (DFS) and overall survival (OS) in each cancer stage. (A) 5-year DFS rates of patients with stage I colorectal cancer (CRC) were 89.2% and 95.7% in APT and non-APT groups, respectively. (B) 5-year DFS rates of patients with stage II CRC were 80.3% and 77.2% in APT and non-APT groups, respectively. (C) 5-year DFS rates of patients with stage III CRC were 61.9% and 63.6% in APT and non-APT groups, respectively. (D) 5-year OS rates of patients with stage 0 CRC were 100% and 87.5% in APT and non-APT groups, respectively. (E) 5-year OS rates of patients with stage I CRC were 82.4% and 94.4% in APT and non-APT groups, respectively. (F) 5-year OS rates of patients with stage II CRC were 58.4% and 88.9% in APT and non-APT groups, respectively. (G) 5-year OS rates of patients with stage III CRC were 69.4% and 63.2% in APT and non-APT groups, respectively.
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The authors declare that they do not have conflict of interests.

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