**INTRODUCTION**

Cardiovascular diseases in cancer patients are currently attracting attention from both cardiologists and oncologists worldwide (1-3). Recent developments in therapy have improved the prognosis of patients with cancer. Along with this progress, patients with concomitant cancer and cardiovascular diseases are increasing. Specifically, coronary artery disease (CAD) often coexists with cancer, as some risk factors (e.g., smoking) are common in both atherosclerosis and cancer. However, available evidence on CAD treatment in patients with cancer is insufficient.

Irrespective of type, cancer induces a prothrombotic state, potentially leading to cancer-associated thrombosis (4, 5). Furthermore, patients with cancer have higher bleeding risks when treated with anti-thrombotic drugs for venous thromboembolism (6). An increased risk of bleeding due to anticoagulation therapy with direct oral anticoagulants (DOAC) or warfarin has been reported (7-11). Percutaneous coronary intervention (PCI) with stent implantation, which requires extended treatment with dual-antiplatelet therapy (DAPT) followed by single-antiplatelet therapy (SAPT), is often performed as treatment for CAD in these patients. A few studies have reported that patients with cancer experience a higher bleeding rate after PCI (12, 13). Nevertheless, the long-term prognostic bleeding risk of DAPT or SAPT in these patients has been rarely reported in the past, and the actual bleeding risk following PCI procedures is unknown. Therefore, we investigated the risk factors for clinically relevant bleeding events in patients with cancer after PCI with stent implantation.

**METHODS**

**PATIENTS AND METHODS**

**Study Population**

The present study was conducted in accordance with the Declaration of Helsinki and ethical standards; the study protocol was approved by the local ethics committee of Osaka International Cancer Institute (approval no. 19046). The requirement for acquisition of informed consent was waived owing to the retrospective nature of the study.

Patients who were diagnosed with qualifying cancer and who received PCI from 2013 to 2018 at Osaka International Cancer Institute were enrolled in this study. Patients (1) who had undergone either PCI with stent implantation or coronary artery bypass grafting before 2013, (2) who died of cancer within 1 month and did not have bleeding events, or (3) who had been treated with DAPT prior to the index PCI were excluded. Baseline clinical data and outcomes were obtained from medical records. Patients were followed-up up to 3 years after the index PCI. All PCI procedures were performed by experienced interventionists.

Chronic kidney disease was defined as an estimated glomerular filtration rate of < 60 mL/min/1.73 m² for > 3 months. Overweight was defined as body mass index > 25 kg/m².

**Definitions of Primary and Secondary Endpoints**

The primary endpoint of the study was bleeding events, which were categorized into Bleeding Academic Research Consortium (BARC) types 2, 3, and 5 (14). Bleeding events included intracranial bleeding and gastrointestinal or colorectal bleeding requiring endoscopic hemostasis, as well as any bleeding requiring blood transfusion, hospitalization, or medical care or death caused by bleeding. Only patients with clinically proven ischemia underwent PCI with stent implantation. Evidence of
cardiac ischemia was determined by fractional flow reserve, myocardial scintigraphy, or angiographical stenosis ≥ 90% according to the American Heart Association classification. As the secondary endpoint, 3-point major adverse cardiovascular events (3P-MACEs) were defined as cardiac death, nonfatal myocardial infarction (MI), and nonfatal stroke.

Definition of Active Cancer and Non-active Cancer

For individuals with multiple primary cancers, the most recently diagnosed cancer was considered. The cancer's activity status was categorized according to the operability by radical surgery. The non-active cancer group included patients who had already undergone radical surgery or endoscopic cancer resection, as well as those who had planned radical surgery within 3 months after and 5 years before the index PCI. Active cancer was determined as cancer currently treated with chemotherapy and/or radiation therapy with no indication for radical surgery for any reason. One reason for this group categorization was that operable patients could have similar characteristics to patients without cancer after radical surgery. In addition, we included patients who had planned to have radical surgery “within 3 months” because the current guidelines recommend 3 months of DAPT for high bleeding risk patients, such as those with cancer.

Data Analysis

Continuous data are reported as means ± standard deviation, and prevalence is expressed as percentage (%). Categorical data were compared using the chi-squared test or Fisher’s exact test. DAPT duration data were not normally distributed and were compared using the Wilcoxon signed-rank test. Event-free survival (EFS) relative to bleeding, all-cause death, and 3P-MACE were assessed using Kaplan-Meier survival analysis, and differences between the groups were compared using the log-rank test. The risks of developing bleeding events and 3P-MACE were estimated by hazard ratio (HR) and their 95% confidence intervals (CI) based on Cox proportional hazards models. Variables with P < 0.1 in the univariate analysis were included in a multivariate model to identify independent risk factors. For statistical analysis, P < 0.05 was considered statistically significant. Due to the small sample size, some factors could not be assessed by Cox regression hazards models and were indicated as “NA.” All statistical analyses were performed using JMP version 11.0 (SAS Inc., Tokyo, Japan).

RESULTS

Baseline Characteristics of the Study Participants

The data of 236 patients subjected to PCI with stent implantation from 2013 to 2018 were collected. Of these, 84 patients without cancer and 50 patients who underwent PCI with stent implantation before 2013 were excluded. Patients with malignant lymphoma and leukemia, those who died of cancer within 1 month after PCI, and those who received DAPT before PCI for any reasons were also excluded. Finally, 89 patients were categorized into either the active cancer group (n = 45) or the non-active cancer group (n = 44) (Figure 1). Within the non-active cancer group, 17 of 44 patients underwent radical surgery at < 3 months after the index PCI, 19 underwent radical surgery at < 6 months, 2 at < 12 months, and 6 at < 5 years before PCI. During the follow-up period, 11 bleeding events, 8 3P-MACEs, and 18 all-cause deaths occurred.

The baseline characteristics of all patients and for each group are summarized in Table I. The prevalence of acute coronary syndrome (ACS) and atrial fibrillation (AF), average left ventricular ejection fraction, and oral anticoagulant use were significantly different between groups. The percentage of drug-eluting stent (DES) implantation over bare metal stent (BMS) was not significantly different between groups. For prognostic assessment, the median follow-up period was 2.2 years [interquartile range (IQR): 0.7–3.0 years] for the primary endpoint and 2.5 years [IQR: 0.7–3.0] for the secondary endpoint. Kaplan-Meier analysis for all-cause death, as the preferred indicator of prognosis for these two groups, is shown in Figure 2. The all-cause death rate in 3 years was much higher in the active than in the non-active cancer group (log-rank test, P = 0.018), most likely due to differences in cancer stages, as indicated by the prevalence of metastasis in Table I.
Table I. Baseline characteristics

|                          | All patients (n = 89) | Non-active cancer (n = 44) | Active cancer (n = 45) | P value |
|--------------------------|-----------------------|----------------------------|------------------------|---------|
| Age                      | 71 ± 7.4              | 72 ± 7.0                   | 71 ± 7.8               | 0.548   |
| Male sex                 | 76 (85)               | 38 (86)                    | 38 (84)                | 1.000   |
| ACS                      | 12 (13)               | 1 (2)                      | 11 (24)                | 0.004   |
| Drug eluting stent       | 57 (64)               | 29 (66)                    | 28 (62)                | 0.826   |
| Atrial fibrillation      | 9 (10)                | 1 (2)                      | 8 (18)                 | 0.030   |
| Multi-vessel disease     | 26 (29)               | 13 (30)                    | 13 (29)                | 1.000   |
| Number of implanted stents | 1.3 ± 0.7             | 1.3 ± 0.5                  | 1.4 ± 0.1              | 0.287   |
| Total length of the stent (IQR) (s) | 28 (20-39)           | 28 (20-40)                 | 28 (24-40)             | 0.263*  |
| LAD PCI                  | 56 (63)               | 28 (64)                    | 28 (62)                | 1.000   |
| DAPT duration, median (IQR) (m) | 9 (3-12)             | 10 (3-12)                  | 8 (3-12)               | 0.558*  |
| Chronic kidney disease   | 26 (29)               | 14 (32)                    | 12 (27)                | 0.646   |
| Hypertension             | 59 (66)               | 28 (64)                    | 31 (69)                | 0.658   |
| Dyslipidemia             | 50 (56)               | 25 (57)                    | 25 (56)                | 1.000   |
| Diabetes mellitus        | 39 (44)               | 17 (39)                    | 22 (49)                | 0.395   |
| Current smoking          | 14 (16)               | 7 (16)                     | 7 (16)                 | 1.000   |
| Overweight               | 12 (13)               | 4 (9)                      | 8 (18)                 | 0.353   |
| History of              |                       |                            |                        |         |
| Cerebral infarction      | 10 (11)               | 3 (7)                      | 7 (16)                 | 0.315   |
| Intracranial bleeding    | 2 (2)                 | 0 (0)                      | 2 (4)                  | 0.495   |
| Myocardial infarction    | 10 (11)               | 3 (7)                      | 7 (16)                 | 0.315   |
| Congestive heart failure | 9 (10)                | 3 (7)                      | 6 (13)                 | 0.485   |
| Echocardiography         |                       |                            |                        |         |
| LVEF (%)                 | 65 ± 9                | 66 ± 7.5                   | 63 ± 10.0              | 0.085   |
| LV end diastolic diameter (mm) | 46 ± 5              | 46 ± 4.7                   | 45 ± 5.2               | 0.873   |
| LV end systolic diameter (mm) | 29 ± 5              | 29 ± 4.8                   | 30 ± 5.5               | 0.404   |
| Mitral regurgitation ≥ type 3 | 2 (2)              | 1 (2)                      | 1 (2)                  | 1.000   |
| Medication               |                       |                            |                        |         |
| Oral anti-coagulant      | 9 (10)                | 1 (2)                      | 8 (18)                 | 0.030   |
| β-blocker                | 43 (48)               | 21 (48)                    | 22 (49)                | 1.000   |
| ACE-I / ARB              | 28 (31)               | 11 (25)                    | 17 (38)                | 0.255   |
| Diuretics                | 5 (6)                 | 1 (2)                      | 4 (9)                  | 0.361   |
| Statins                  | 70 (79)               | 35 (80)                    | 35 (78)                | 1.000   |
| Proton-pump inhibitor    | 6 (7)                 | 5 (11)                     | 1 (2)                  | 0.110   |
| Cancer type              |                       |                            |                        |         |
| Digestive tract          | 33 (37)               | 24 (55)                    | 9 (20)                 |         |
| Urinary organs, prostate | 16 (18)               | 7 (16)                     | 9 (20)                 |         |
| Head, neck               | 5 (6)                 | 1 (2)                      | 4 (9)                  |         |
| Breast                   | 6 (7)                 | 3 (7)                      | 3 (7)                  |         |
| Liver, bile, pancreas    | 14 (16)               | 4 (9)                      | 10 (22)                |         |
| Lung, bronchus           | 13 (15)               | 3 (7)                      | 10 (22)                |         |
| Bone, muscle             | 2 (2)                 | 2 (5)                      | 0 (0)                  |         |
| Metastasis               | 23 (24)               | 0 (0)                      | 23 (53)                | < 0.001 |

Data are presented as means ± standard deviation or n (%). P-values are for non-active cancer group vs. active cancer group. Continuous data were analyzed by two-sided Student t-tests. Categorical data were analyzed by Fisher's exact test. *Wilcoxon signed-rank test.

ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; LAD, left anterior descending artery; DAPT, dual anti-platelet therapy; LVEF, left ventricular ejection fraction; ACE-I, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker.
Eleven patients presented with bleeding of BARC types 2, 3, and 5 after PCI. The characteristics are shown in Tables II and III. All patients were males, and the cancer types varied. Intracranial bleeding occurred in 2 of 11 patients, whereas gastrointestinal bleeding was identified in 8 of 11 patients.

The antiplatelet therapies used when the events occurred are indicated in Table III. Bleeding events were observed not only during DAPT but also during SAPT regardless of anticoagulant intake. Among 45 patients with active cancer, 8 received DOAC; of these, 2 (25%) patients experienced bleeding events at <3 years. Furthermore, among the remaining 57 patients with active cancer who did not receive DOAC, 5 (14%) experienced bleeding events during DAPT and 3 (8%) had bleeding events during SAPT (Tables II and III). All 8 patients who had gastrointestinal bleeding events received proton pump inhibitors since introduction of DAPT.

As the primary endpoints, the EFS and rate of bleeding events categorized as BARC types 2, 3, and 5 were assessed. The occurrence rates of events during the follow-up period (median, 2.2 years) were 2% and 22% for the non-active and active cancer groups, respectively. As shown in Figure 3a, the bleeding rate was lower in the non-active than in the active cancer group (log-rank test, P = 0.002). The risk of BARC types 2, 3, and 5 bleeding in the non-active cancer group was low, with only 1 of 11 patients in this group experiencing a bleeding event. Among them, 5 patients had bleeding events during chemotherapy. However, only 1 patient had a low platelet count (48,000/µL), which might have been due to the bleeding, whereas the others had a platelet count of more than 100,000/µL (Table II). None of them had a diagnosis of disseminated intravascular coagulation when they had bleeding events. Case number 4 and 6 in Table II were related to endoscopic treatment, which were ulcers following endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR), while case number 9 was related to the endoscopic retrograde biliary drainage (ERBD) procedure.

Next, we assessed significant clinical prognostic factors for bleeding (Table IV). The presence of active cancer (HR, 1.7; 95% CI, 1.1-2.8) was an independent predictor of bleeding (P = 0.04). The risk of BARC types 2, 3, and 5 bleeding in the non-active cancer group was low, with only 1 of 11 patients in this group experiencing a bleeding event. Among them, 5 patients had bleeding events during chemotherapy. However, only 1 patient had a low platelet count (48,000/µL), which might have been due to the bleeding, whereas the others had a platelet count of more than 100,000/µL (Table II). None of them had a diagnosis of disseminated intravascular coagulation when they had bleeding events. Case number 4 and 6 in Table II were related to endoscopic treatment, which were ulcers following endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR), while case number 9 was related to the endoscopic retrograde biliary drainage (ERBD) procedure.

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Table II. Characteristics of the Patients with Bleeding Events

| Case # | Age | Sex | Primary cancer | Stage | BARC type | ACS | OAC | DAPT duration (months) | PCI to bleeding event (days) | Bleeding during DAPT | Active cancer | Platelet count (x10^4/µL) | Bleeding site |
|--------|-----|-----|----------------|-------|-----------|-----|-----|------------------------|---------------------------|------------------|--------------|----------------|-------------|
| 1      | 73  | M   | NSCLC          | III   | 3         | -   | +  | 11                     | 659                       | -                | +            | 2.36         | Intracranial |
| 2      | 58  | M   | Pancreas       | IV    | 3         | -   | -  | 8                      | 224                       | +                | +            | 1.62         | Intracranial |
| 3      | 80  | M   | Gastric        | IV    | 3         | -   | -  | 1                      | 13                        | +                | +            | 5.31         | Gastric tumor |
| 4      | 77  | M   | NSCLC          | II    | 3         | -   | -  | 34                     | 414                       | +                | +            | 1.37         | Gastric ulcer |
| 5      | 76  | M   | Pharyngeal     | I     | 3         | -   | -  | 8                      | 112                       | +                | +            | 2.09         | Duodenum ulcer |
| 6      | 68  | M   | Laryngeal      | III   | 2         | -   | +  | 12                     | 576                       | -                | +            | 1.62         | Colon ulcer |
| 7      | 63  | M   | Renal          | IV    | 3         | +   | -  | 19                     | 1189                      | -                | +            | 2.86         | Small intestine |
| 8      | 54  | M   | Gastric        | IV    | 3         | -   | -  | 3                      | 216                       | -                | +            | 4.21         | Gastric tumor |
| 9      | 68  | M   | Pancreas       | IV    | 5         | -   | -  | 3                      | 108                       | -                | +            | 0.43         | Biliary tract |
| 10     | 78  | M   | Pancreas       | II    | 3         | -   | -  | 2                      | 83                        | -                | +            | 2.90         | Esophagus |
| 11     | 81  | M   | NSCLC          | IV    | 3         | -   | -  | 4                      | 72                        | +                | +            | 1.35         | Unknown |

ACE, acute coronary syndrome; DAPT, dual-antiplatelet therapy; NSCLC, non-small cell lung cancer; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; ESD, endoscopic submucosal dissection.

Table III. Relationship between OAC, Antiplatelet Therapy, and Event Rates

|                  | Non-active cancer (n=44) | Active cancer (n=45) |
|------------------|--------------------------|----------------------|
|                  | DAPT                     | SAPT                 | DAPT                     | SAPT                 | DAPT                     | SAPT                 |
| BARC types 2, 3, and 5 | 0 (0)                   | 0 (0)                | 1 (2.3)                  | 0 (0)                | 2 (25.0)                | 5 (13.5)            |
| 3P-MACE          | 0 (0)                   | 0 (0)                | 2 (4.7)                  | 0 (0)                | 1 (12.5)                | 2 (25.0)            |

BARC, Bleeding Academic Research Consortium; DAPT, dual-antiplatelet therapy; MACE, major adverse cardiovascular event; OAC, oral anticoagulant; SAPT, single-antiplatelet therapy.
Figure 3. Kaplan-Meier analysis of the primary and secondary endpoints after PCI. (A) Survival free from bleeding of BARC types 2, 3, and 5 was compared between the active cancer group (n = 45) and the non-active cancer group (n = 44). (B) Survival free from 3P-MACE was compared between the active cancer group (n = 45) and the non-active cancer group (n = 44). 3P-MACE comprised cardiovascular death, nonfatal death, and nonfatal MI.

PCI, percutaneous coronary intervention; BARC, Bleeding Academic Research Consortium; 3P-MACE, 3-point major adverse cardiovascular events

Table IV. Cox Regression Hazards Model Analysis for Bleeding Events of BARC Types 2, 3, and 5

|                              | Univariate analysis |                              |          | Multivariate analysis |                             |
|------------------------------|---------------------|------------------------------|----------|-----------------------|-----------------------------|
|                              | HR [95% CI]         | P value                      | HR [95% CI] | P value               |
| Age                          | 1.00 [0.92–1.08]    | 0.979                        | 9.03 [1.33–176.69] | 0.023                  |
| Male sex                     | NA                  | NA                           | NA       |                        |
| Multi-vessel disease         | 2.29 [0.66–7.63]    | 0.185                        |          |                       |
| Number of implanted stents   | 1.41 [0.53–2.82]    | 0.440                        |          |                       |
| Total length of the stent(s) | 1.01 [0.99–1.03]    | 0.266                        |          |                       |
| Active cancer                | 12.81 [2.44–235.57] | 0.001                        | 9.03 [1.33–176.69] | 0.023                  |
| ACS                          | 0.89 [0.05–4.70]    | 0.914                        |          |                       |
| Drug-eluting stent           | 0.69 [0.21–2.40]    | 0.545                        |          |                       |
| Atrial fibrillation          | 1.04 [0.06–5.45]    | 0.969                        |          |                       |
| LAD PCI                      | 1.46 [0.42–6.68]    | 0.563                        |          |                       |
| DAPT duration (months)       | 0.99 [0.91–1.04]    | 0.711                        |          |                       |
| Chronic kidney disease       | 0.97 [0.21–3.36]    | 0.966                        |          |                       |
| Hypertension                 | 0.88 [0.27–3.36]    | 0.840                        |          |                       |
| Dyslipidemia                 | 0.42 [0.11–1.38]    | 0.154                        |          |                       |
| Diabetes mellitus            | 1.18 [0.34–3.94]    | 0.781                        |          |                       |
| Current smoker               | 1.84 [0.40–3.37]    | 0.392                        |          |                       |
| Obesity                      | 0.56 [0.03–2.93]    | 0.548                        |          |                       |
| Previous cerebrovascular infarction | NA | NA | NA |                       |
| Previous myocardial infarction | 2.59 [0.36–9.50] | 0.314                        |          |                       |
| Congestive heart failure     | 1.50 [0.07–7.03]    | 0.810                        |          |                       |
| LVEF (%)                     | 0.96 [0.90–1.04]    | 0.307                        |          |                       |
| LV end diastolic diameter (mm) | 0.97 [0.85–1.09] | 0.572                        |          |                       |
| LV end systolic diameter (mm) | 1.02 [0.89–1.14] | 0.796                        |          |                       |
| Mitral regurgitation ≥ grade 3 | NA | NA | NA |                       |
| Oral anticoagulant           | 1.87 [0.28–7.25]    | 0.455                        |          |                       |
| β-blocker                    | 0.54 [0.14–1.80]    | 0.321                        |          |                       |
| ACE-I / ARB                  | 0.45 [0.07–1.75]    | 0.269                        |          |                       |
| Diuretics                    | 1.63 [0.09–8.53]    | 0.664                        |          |                       |
| Statin                       | 0.38 [0.11–1.44]    | 0.142                        |          |                       |
| Metastasis                   | 5.23 [1.54–18.50]   | < 0.01                       | 2.02 [0.57–8.00] | 0.277                  |

Statistically undetermined values are described as “NA.” No bleeding was observed in women and those who had previous coronary intervention or mitral regurgitation > type 3.

ACE-I, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; BARC, Bleeding Academic Research Consortium; DAPT, dual-antiplatelet therapy; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; HR, hazards ratio; CI, confidence interval.
Cancer activity and bleeding events post-PCI

12.81; 95% CI, 2.44–235.57; P = 0.001) and the prevalence of metastasis (HR, 5.23; 95% CI, 1.54–18.50; P < 0.001) were significant prognostic factors in Cox proportional hazards models. Other clinical characteristics, such as history of coronary risk factors, cardiac function, CAD-related medications, and PCI-related factors were not significant. Further, DAPT duration and stent type (DES or BMS) were not significant prognostic factors for bleeding events. Multivariate analysis revealed that only active cancer was a significant independent risk factor for bleeding events (HR, 9.03; 95% CI, 1.33–176.69; P = 0.023).

Risk Assessment for 3P-MACE

We also assessed the 3P-MACE rate as a secondary endpoint in the two groups. There were no significant differences in DAPT duration, percentage of ACS, and history of previous MI or cerebral infarction between the groups (Table I). The occurrence rates of events during the follow-up period (median, 2.5 years) were 2% and 6% for the non-active and active cancer group, respectively. Overall, 3P-MACE was present in 9% of the patients, and Kaplan-Meier analysis did not show significant differences between the two groups (Figure 3b). Additionally, Cox proportional hazards models did not indicate active cancer as a significant prognostic factor (Table V). ACS, number of stents, total length of stents, and left ventricular ejection fraction tended to be related to 3P-MACE (P < 0.10). Furthermore, multivariate analysis showed that these factors were not significant risk factors for 3P-MACE.

Table V. Cox Regression Hazards Model Analysis for 3P-MACEs

|                         | Univariate analysis | Multivariate analysis |
|-------------------------|---------------------|-----------------------|
|                         | HR [95% CI]         | P value               | HR [95% CI]         | P value               |
| Age                     | 0.97 [0.97–1.00]    | 0.456                 | 0.98 [0.92–1.05]    | 0.629                 |
| Male sex                | NA                  | NA                    | NA                  |                       |
| Active cancer           | 2.40 [0.63–11.42]   | 0.202                 | 5.81 [0.87–37.06]   | 0.068                 |
| ACS                     | 4.39 [0.92–16.83]   | 0.062                 |                       |                       |
| Drug-eluting stent      | 0.45 [0.11–1.72]    | 0.239                 |                       |                       |
| Atrial fibrillation     | 2.71 [0.40–11.25]   | 0.261                 |                       |                       |
| Residual coronary stenosis | 2.40 [0.63–9.71] | 0.192                |                       |                       |
| Multi-vessel disease    | 2.13 [0.53–8.08]    | 0.273                 |                       |                       |
| Number of implanted stents | 1.98 [0.92–3.63]   | 0.0754                | 2.98 [0.23–32.05]   | 0.386                 |
| Total length of the stent(s) | 1.02 [0.99–1.04]  | 0.0830                | 0.98 [0.92–1.05]    | 0.629                 |
| LAD PCI                 | 1.09 [0.29–5.17]    | 0.902                 |                       |                       |
| DAPT duration (months)  | 0.93 [0.92–1.02]    | 0.171                 |                       |                       |
| Chronic kidney disease  | 2.15 [0.53–8.14]    | 0.265                 |                       |                       |
| Hypertension            | 0.39 [0.10–1.46]    | 0.157                 |                       |                       |
| Dyslipidemia            | 0.61 [0.15–2.32]    | 0.467                 |                       |                       |
| Diabetes mellitus       | 1.12 [0.28–4.23]    | 0.871                 |                       |                       |
| Current smoker          | 1.38 [0.21–5.72]    | 0.698                 |                       |                       |
| Obesity                 | NA                  | NA                    | NA                  |                       |
| Previous cerebral infarction | 2.33 [0.35–9.66] | 0.332                |                       |                       |
| Previous myocardial infarction | 1.38 [0.07–7.74] | 0.774                |                       |                       |
| Congestive heart failure| 4.26 [0.62–18.37]   | 0.122                 |                       |                       |
| LVEF (%)                | 0.93 [0.87–1.00]    | 0.052                 | 0.96 [0.89–1.04]    | 0.309                 |
| Mitral regurgitation ≥ type 3 | NA                  | NA                    | NA                  |                       |
| Oral anticoagulant      | 4.32 [0.91–16.40]   | 0.064                 |                       |                       |
| β-blocker               | 1.27 [0.34–5.14]    | 0.718                 |                       |                       |
| ACE-I / ARB             | 1.13 [0.24–4.29]    | 0.863                 |                       |                       |
| Diuretics               | NA                  | NA                    | NA                  |                       |
| Statin                  | 1.97 [0.36–36.62]   | 0.485                 |                       |                       |
| Metastasis              | 1.22 [0.18–9.17]    | 0.812                 |                       |                       |

Statistically undetermined values are described as “NA.” No 3P-MACE was observed in those who were obese or took diuretics. ACE-I, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; DAPT, dual-antiplatelet therapy; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; HR, hazards ratio; CI, confidence interval.
DISCUSSION

The key findings of our study are as follows: (i) patients with non-active cancer, based on our definition, have significantly lower bleeding rates than those with active cancer; (ii) bleeding after PCI may occur during both DAPT and SAPT; and (iii) most bleeding sites involve the gastrointestinal tract.

In our definition of non-active cancer, patients scheduled for radical surgery within 3 months were included, in addition to patients who had already received interventions. In the real-world clinical setting, CAD is often diagnosed during preoperative examination for cancer surgery; at this time, cardiologists and oncologists make difficult decisions regarding when to perform PCI. It was reported that, historically, patients with cancer experience fewer in-hospital bleeding events than do current patients with prostate, colon, and lung cancer (15). As patients with cancer are known to have a higher bleeding risk, a better stratification of risk for these patients is needed. As indicated in the European Society of Cardiology guidelines (16), the recommended DAPT duration after PCI for stable CAD in patients with high bleeding risk is 3 months. Thus, we defined “PCI <3 months before planned radical surgery” as non-active cancer for further stratification of bleeding risk. Nonetheless, active cancer is sometimes difficult to define. However, whether the patients are eligible for or have already had radical surgery could be an easy and clear indicator of risk stratification. Accordingly, we chose the criteria for “active” and “non-active” cancer.

One of the major differences in the baseline characteristics of the two groups was the prevalence of ACS, which was higher in the active than in the non-active cancer group. This finding is reasonable since ACS should be treated with primary PCI even in cases of active cancer; more patients with non-active cancer underwent PCI for stable CAD because of their relatively better prognosis.

Impact of Cancer Activity on Bleeding Event Rates After PCI

Several studies have reported bleeding risks after PCI largely in patients with ischemic heart disease but without cancer. For example, the 1-year outcomes of bleeding of BARC types 2 and 3 were observed in 3.6% and 1.8% of patients, respectively (17). Another study reported the bleeding risk in patients treated for 3 months with DAPT (ticagrelor and aspirin), followed by randomized assignment to the ticagrelor plus placebo group or DAPT continuation group. The risk of BARC type 3 or 5 bleeding at 1 year was reported to be 1.0% for the placebo group and 2.0% for the DAPT group (18). Furthermore, in the AFIRE study, the bleeding risk was the safety endpoint of rivaroxaban monotherapy or single antiplatelet plus rivaroxaban for patients with AF and those who underwent PCI at >1 year earlier (19). The study reported bleeding event rates of 1.62% and 2.76% per patient-year for the rivaroxaban monotherapy group and the single antiplatelet plus rivaroxaban group, respectively. When considering patients with cancer, it is easy to imagine that those with advanced cancer have more bleeding events. Nevertheless, available evidence for bleeding events after PCI is limited. In one of the few studies involving patients with cancer who underwent PCI, the prevalence of cancer was an independent determinant of the cumulative incidence of hospitalization for bleeding (12).

Another important study reported the bleeding risks of DAPT among 9240 patients with ACS on DAPT with a median follow-up period of 17 months; 1.8% of the patients had a confirmed neoplasm event, and the rate of Global Use of Strategies to Open Occluded Coronary Arteries severe/moderate bleeding was higher in those with than in those without neoplasms (11.2 vs. 1.5%) (13). Considering the follow-up period, the bleeding event rate of 11.2% was similar to that for our active cancer group (22%). Our results and those of previous studies indicate that patients with non-active cancer experience lower rates of BARC types 2, 3, and 5 bleeding events (2%), which is similar to the results of previous studies mostly involving non-cancer patients. Conversely, patients with active cancer had a relatively higher bleeding rate (22%) than those without a cancer history but had a consistent bleeding rate compared to those with neoplasms, as reported previously.

In our data, 3 of 10 bleeding events in active cancer patients were related to endoscopic treatments, such as ESD, EMR, and ERBD. Therefore, the gastrointestinal bleeding events were not always due to proton pump inhibitor-resisted ulcers. We should recognize that active cancer patients often need these cancer-related treatments. Moreover, we should be aware of the fact that a minor bleeding could progress to a major bleeding when active cancer patients on anti-platelet therapy undergo invasive clinical procedures.

Impact of Cancer Activity on 3P-MACE Rates After PCI

As the secondary endpoint, we assessed the 3P-MACE rate in the two groups. There was no difference between the active and non-active cancer groups according to both Kaplan-Meier and Cox regression hazards model analyses. The rates of 3P-MACE were 5% and 13% in the non-active and active cancer groups, respectively, after a median follow-up period of 2.5 years. According to the AFIRE study (19), the rate of MACE, including stroke, MI, unstable angina requiring PCI, and all-cause death, was 4.14% per year for the DOAC monotherapy group and 5.75% per year for the DOAC plus SAPT group. Patients after PCI with hypertension had significantly higher 2-year rates of MACE (cardiac death, MI, or stent thrombosis) than did patients without hypertension (7.0% vs. 4.4%) (20). Additionally, in the AUGUSTUS study, AF patients who underwent elective PCI experienced 5.6% and 5.4% of death and ischemic events (stroke, MI, stent thrombosis, and urgent revascularization), respectively, when treated with apixaban or vitamin K antagonist plus P2Y12 inhibitor over at least a 6-month follow-up period (21). The composite endpoint of cardiovascular death, MI, and stroke was reported to occur more frequently in patients with neoplasms than in those without (18.2% vs. 13.5%) (13). Compared to that in previous studies, the 3P-MACE rate in our study seemed to be reasonable and was not higher than the rate in studies that included mostly non-cancer patients.

Implications for Patients Undergoing PCI

In the real-world clinical setting, it is difficult for cardiologists to decide on the timing of PCI and cancer surgery. Furthermore, DAPT duration after PCI is controversial. In our study, patients with BMS received 1 month of DAPT and those with DES received 6 to 12 months of DAPT. As reported in the STOPDAPT-2 study, a short DAPT duration significantly reduces bleeding events after PCI; thus, DAPT duration has been reduced for PCI in non-cancer patients. However, bleeding events during SAPT were also detected during the 3-year follow-up period. In addition, although bleeding was mostly from the digestive tract, the primary cancers also included the lung, renal, larynx, and pharynx.

There are two major risk stratifications of bleeding after PCI, the PRECISE DAPT score (22) and the Academic Research Consortium High Bleeding Risk (ARC-HBR) criteria (23). The former may not provide additional information on cancer patients, as the scores and criteria include the white blood cell count, hemoglobin, and platelet levels, which are unstable in patients undergoing chemotherapy. Although the ARC-HBR criteria include the presence of cancer as a bleeding risk factor, further
risk stratification of patients with cancer is needed, considering accumulated evidence showing that these patients have a higher bleeding risk than cancer-naïve patients. However, our study may contribute to the improvement of decision-making with respect to indications for PCI in patients with cancer.

LIMITATIONS

This was a retrospective observational study with a relatively small sample size; thus, it was underpowered for the evaluation of clinical outcomes such as bleeding or MACEs. As our institute does not have an emergency room, and all patients who come to our institute have cancer, the number of PCI procedures was relatively low. However, all PCI procedures were performed by well-trained and certified interventionists. Another limitation is that the effects of cancer type, which was different between the groups, could not be considered due to the small sample size. Furthermore, as the event rate was very low, some factors could not be correctly assessed by Cox regression hazards model analysis.

CONCLUSIONS

In the present study, we demonstrated that non-active cancer patients had a significantly lower rate of bleeding event after PCI compared to that in the active cancer group. In addition, the rate of 3P-MACE was not different between active and non-active groups.

In summary, our study suggests that post-PCI bleeding in patients with non-active cancer may not be a cause for concern; however, closer attention should be paid on bleeding events during SAPT to the same degree as during DAPT in those with active cancer.

CONFLICT OF INTEREST

None declared.

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