

Outcomes of Coronary Artery Bypass Surgery in Patients with Malignancy

Kayo Sugiyama*, Hirotaka Watanuki, Masato Tochii, Katsuhiko Matsuyama

Department of Cardiac Surgery, Aichi Medical University Hospital, Nagakute, Japan

Email: *kayotaro3@gmail.com

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Abstract

Objective: In patients with severe coronary artery disease (CAD), the risk of tumor surgery under general anesthesia is high, and whether coronary revascularization should be prioritized remains debatable, considering tumor prognosis. We aimed to analyze surgical outcomes for severe CAD with malignancy. **Materials and Methods:** We analyzed 20 patients with malignant tumors and 256 who underwent coronary artery bypass graft surgery (CABG) at our hospital to investigate early and long-term outcomes. We also conducted propensity score analysis. **Results:** No significant differences were observed in preoperative background. Patients with malignancy had significantly fewer lesions and bypass grafts. There was no significance in postoperative complications or cardiac events. After propensity score matching, results were similar. Treatment for malignancy was performed safely post-CABG. However, two patients could not undergo scheduled treatment because of change in their clinical condition after CABG. **Conclusion:** CABG in patients with malignancy was safely performed and prevented postoperative cardiac events. Because postoperative status can be changeable, cancer team management should be considered for all CABG cases with malignancy.

Keywords

Coronary Artery Bypass Surgery, Malignant Tumor, Multidisciplinary Cancer Team

1. Introduction

With an aging population and improved diagnostic techniques, a significant increase in the number of patients with malignancy combined with coronary artery disease (CAD) has been observed. Perioperative cardiac complications are a major cause of death in patients undergoing non-cardiac surgery with severe CAD, and

the treatment strategy for patients with malignancy combined with CAD remains a challenge for cardiac surgeons [1]. Patients with cardiovascular disease have higher cancer risk compared with individuals from the general population. “Reverse cardio-oncology” has started to attract more attention and called for awareness among physicians for the increased cancer risk in patients with cardiovascular disease [2]. Cancer prevalence and mortality were >2-fold higher in patients with atherosclerotic cardiovascular disease than in patients with nonatherosclerotic cardiovascular diseases [3]. These findings suggest atherosclerosis as a risk factor for cancer and a marker of poor prognosis [3]. Accordingly, there have been some reports describing the association between cardiovascular disease and cancer, however, most of them have not reported the relation of cancer stages. Moreover, the relation of CABG for cardiovascular disease with cancer stage has rarely presented.

In patients with CAD, myocardial revascularization before malignant tumor therapy could allow for subsequent safe malignant surgery, chemotherapy, or both and potentially improve long-term survival [4]. Other studies have also shown that initial myocardial revascularization can ensure the safety of subsequent treatments for malignancy [5] [6]. In critically ill patients with left main coronary artery or three-vessel disease, coronary artery bypass surgery has significant advantages in terms of reducing the incidence of adverse cardiac events during oncological surgery and preventing thrombosis. As reported in previous studies [4] [7], long-term survival was mainly driven by the prognosis of malignancy and was only secondarily related to CAD. These findings justify the indication to perform coronary surgery, at least in patients with early-stage malignancy.

Conversely, the appropriate timing for cancer treatment can be missed because of CABG. European guidelines state that coronary artery revascularization should not be performed in cases where a prognosis of 12 months cannot be expected [8]. However, determining a 12-month prognosis is not easy. There are classifications for determining cancer treatment based on its stage, but these do not accurately reflect the prognosis.

This study aimed to analyze surgical treatment outcomes for severe CAD in combination with malignancy and to evaluate their cancer treatment after CABG.

2. Materials and Methods

All consecutive adult patients with CAD who underwent surgery at our institution between August 2015 and September 2022 were included in this study. CABG was considered in patients with malignancy who were expected a prognosis of at least 12 months. During this period, 276 adult patients underwent CABG; of these, 20 (7%) had malignancy, and 256 (93%) did not. We evaluated preoperative factors and postoperative course. Patients who underwent procedures such as valve replacement or repair, left ventricular aneurysmectomy, congenital heart disease, or aortic surgery were excluded to ensure homogeneity of patients. Patients with malignancy who had already completed cancer treatment were also excluded.

As previously reported [4], for safe hemodynamic maintaining, we recommend

prioritizing the surgical treatment of cardiac disease followed by subsequent treatment of the neoplasm, either by surgical resection or radiation and oncological therapies. In patients with concomitant neoplastic and cardiac diseases, a staged approach is normally used: heart surgery performed first and then cancer resection scheduled 4 or 6 weeks later [4]. Only lung cancer or other mediastinum cancer were resected concomitantly with CABG.

Clinical data were collected from the medical records, and multiple variables were recorded for each patient. Data on age, sex, hypertension, diabetes mellitus, dyslipidemia, present smoking, past smoking, chronic respiratory disease, chronic kidney disease, hemodialysis, peripheral artery disease, chronic atrial fibrillation, left ventricular ejection fraction, history of coronary artery intervention, and history of cerebral infarction were included. Information on the severity of CAD was obtained from angiography reports. Intraoperative factors, including the number of diseased vessels, use of cardiopulmonary bypass (CPB), and number of distal anastomoses were recorded.

Conventional on-pump arrest, on-pump beating, or off-pump CABG was performed based on the patient's condition and surgeon's preference. On-pump beating or conventional CABG is currently preferred, particularly in patients with hemodynamic instability, whereas off-pump CABG is preferred for patients with severe atherosclerotic changes. For patients with malignancy, we attempted to complete CABG without CPB (off-pump CABG) due to concerns about potentially compromising the patient's immune system or causing metastasis as a result of the CPB. All-cause mortality was the primary endpoint. An up-to-date clinical follow-up was obtained by telephone interview with patients or their family. All major adverse cardiac and cerebrovascular events after hospital discharge, defined as sudden death, recurrent angina, myocardial infarction, congestive heart failure, percutaneous coronary intervention, repeat coronary operation, or cerebrovascular accident, were recorded. Patency of the grafts was checked multidetector computed tomography or standard coronary angiography in all patients after surgery or in patients with symptoms of ischemia.

Statistical procedures

Continuous variables are expressed as mean \pm standard deviation or median (range), and categorical variables are expressed as the number (%) of patients. Categorical variables were analyzed using Fisher's exact test. Continuous variables were compared using Student's t-test, whereas non-parametric variables were analyzed using the Mann-Whitney U-test. Survival curves were constructed using the Kaplan-Meier method and compared using the log-rank test. All data analyses were performed using the JMP 16.1 software (SAS Institute, Cary, NC, USA). Statistical significance was defined by $p < 0.05$.

We conducted a 1:1 propensity score analysis to match patients without malignancy, using JMP 16.1 software (SAS Institute, Cary, NC, USA). The nearest neighbor technique was adopted to match each case to a control which is closest in terms of the calculated propensity score. The propensity score was calculated

from the following 15 matching variables: age, sex, hypertension, diabetes mellitus, dyslipidemia, present smoking, past smoking, chronic respiratory disease, chronic kidney disease, hemodialysis, peripheral artery disease, chronic atrial fibrillation, left ventricular ejection fraction, history of coronary artery intervention, and history of cerebral infarction.

Ethics approval

All procedures were performed in accordance with the tenets of the Declaration of Helsinki. The Ethics Committee of Aichi Medical University Hospital approved this study on October 26th, 2023 (approval number, 2023-522). All patients provided written consent for the use of their clinical data for scientific presentation or publication.

3. Results

Patient characteristics are listed in **Table 1**. Although patients with malignancy tended to be older than those without malignancy ($p = 0.052$) and were less likely to have a smoking habit ($p = 0.052$), all factors including age, sex, history of hypertension, diabetes mellitus, dyslipidemia, chronic respiratory disease, chronic kidney disease, hemodialysis, peripheral artery disease, chronic atrial fibrillation, left ventricular ejection fraction, history of coronary artery intervention, and history of cerebral infarction did not differ significantly between the two groups.

Table 1. Characteristics of patients.

	Total, 276	Patients with cancer 20 (7%)	Patients without cancer 256 (93%)	p value
Age (y)	71 (36 - 85)	73 (62 - 85)	70 (36 - 85)	0.052
Sex (male, %)	239 (87)	15 (75)	214 (84)	0.32
Hypertension (%)	188 (68)	15 (75)	173 (68)	0.49
Diabetes (%)	169 (61)	13 (65)	156 (61)	0.72
Dyslipidemia (%)	162 (59)	9 (45)	153 (60)	0.20
Present smoking (%)	31 (11)	1 (5)	30 (12)	0.36
Past smoking (%)	112 (41)	4 (20)	108 (42)	0.052
Chronic respiratory disease (%)	39 (14)	2 (10)	37 (14)	0.58
Chronic kidney disease (%)	71 (26)	5 (25)	66 (26)	0.94
Hemodialysis (%)	36 (13)	4 (20)	32 (13)	0.34
Peripheral artery disease (%)	42 (15)	2 (10)	40 (16)	0.50
Chronic atrial fibrillation (%)	15 (5)	1 (5)	14 (5)	0.93
Left ventricular ejection fraction (%)	56 (16 - 83)	61 (30 - 77)	56 (16 - 83)	0.36
History of coronary artery intervention (%)	53 (19)	3 (15)	50 (20)	0.62
History of cerebral infarction (%)	48 (17)	4 (20)	44 (17)	0.75

Table 2. Characteristics of patients in the matched cohort.

	Total, 40	Patients with cancer 20 (50%)	Patients without cancer 20 (50%)	p value
Age (y)	73 (62 - 85)	61 (30 - 77)	74 (65 - 83)	0.47
Sex (male, %)	33 (83)	15 (75)	18 (90)	0.21
Hypertension (%)	33 (83)	15 (75)	18 (90)	0.21
Diabetes (%)	22 (55)	13 (65)	9 (45)	0.20
Dyslipidemia (%)	24 (60)	9 (45)	15 (65)	0.051
Present smoking (%)	1 (3)	1 (5)	0	0.23
Past smoking (%)	9 (23)	4 (20)	5 (25)	0.70
Chronic respiratory disease (%)	7 (18)	2 (10)	5 (25)	0.21
Chronic kidney disease (%)	11 (28)	5 (25)	6 (30)	0.72
Hemodialysis (%)	6 (15)	4 (20)	2 (10)	0.37
Peripheral artery disease (%)	7 (18)	2 (10)	5 (25)	0.21
Chronic atrial fibrillation (%)	1 (3)	1 (5)	0	0.23
Left ventricular ejection fraction (%)	62 (26 - 83)	61 (30 - 77)	62 (26 - 83)	0.73
History of coronary artery intervention (%)	5 (13)	3 (15)	2 (10)	0.63
History of cerebral infarction (%)	7 (18)	4 (20)	3 (15)	0.68

After propensity matching analysis, our main cohort included 20 cases with malignancy and 20 cases without malignancy (**Table 2**). There were no significant different factors in the matched cohort.

Figure 1(a) shows the details of tumors in patients with malignancy. There were seven cases of gastroenteric tumors (35%), seven of urinary tumors (35%), three of lung tumors (15%), and three of others (15%). **Figure 1(b)** shows the staging of each malignancy at the time of CABG. Eight patients (40%) had stage I cancer, three (15%) had stage II, two (10%) had stage III, six (30%) had stage IV, and one (5%) was unknown.

Table 3 presents procedural and intraoperative data. There were no significant differences in urgent or emergency CABG, left main trunk disease, and use of CPB. Triple vessel disease was significantly rarer ($p = 0.0010$), and the number of vessels with significant stenosis and number of vessels bypassed were significantly fewer ($p = 0.0019$ and 0.0014) in patients with malignancy. The mean numbers of vessels with significant stenosis were 2.20 ± 0.62 and 2.62 ± 0.57 in patients with malignancy and those without, while the mean numbers of vessels bypassed were 2.45 ± 1.28 and 3.29 ± 1.10 in patients with malignancy and those without, respectively. There were no significant differences in intensive care unit stay, hospital stay, 30-day mortality, reoperation due to postoperative bleeding, paroxysmal atrial fibrillation, sternal infection, cerebrovascular event, and cardiac death. The

30-day mortality was detected in three cases without malignancy who experienced ST elevated myocardial infarction (1.1%): all cause of death in these patients was heart failure. In the matched cohort, triple vessel disease was significantly rarer ($p = 0.025$), the number of vessels with significant stenosis and number of vessels bypassed were significantly fewer ($p = 0.015$ and $p = 0.016$), and postoperative sternal infection occurred significantly rarer ($p = 0.036$) in patients with malignancy (**Table 4**).

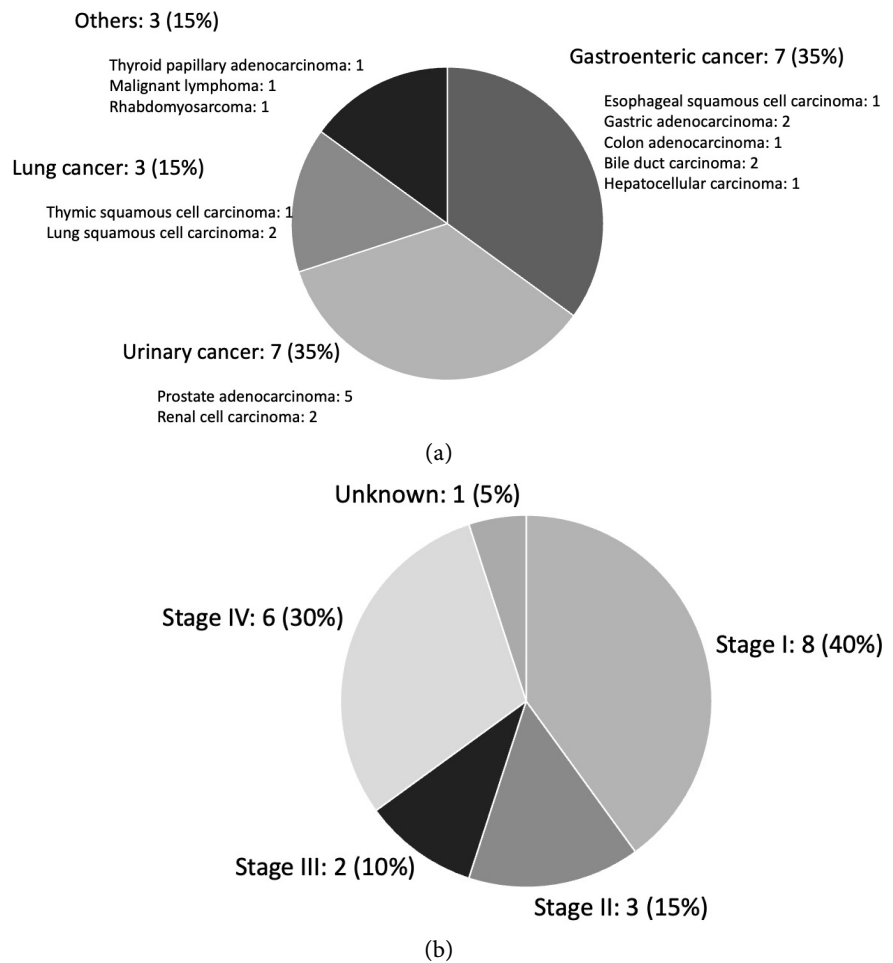


Figure 1. (a) Subgroups and phenotype classifications; (b) Staging of malignancy.

Sixteen patients with malignancy received definitive treatment for malignancy after CABG; nine underwent tumor resection, and seven received chemotherapies, including hormone therapy for malignant lymphoma or prostate adenocarcinoma. Two patients received palliative treatment, as scheduled. The remaining two patients could not undergo their planned cancer surgery owing to changes in the patients' condition. One patient withdrew his request for surgical treatment for his cancer because of decreased physical strength following CABG. The other patient with esophageal cancer could not undergo definitive treatment owing to poor nutritional status after CABG.

Table 3. Operative procedures and outcomes.

	Total, 276	Patients with cancer 20 (7%)	Patients without cancer 256 (93%)	p value
Urgent or emergency CABG	74 (27)	4 (20)	70 (27)	0.48
Left main coronary artery disease (%)	75 (27)	4 (20)	71 (28)	0.45
Triple vessel disease (%)	177 (64)	6 (30)	171 (67)	0.0010
Mean number of vessels with significant stenosis	2.59 ± 0.59	2.20 ± 0.62	2.62 ± 0.57	0.0019
Use of CPB (%)	90 (33)	5 (25)	85 (33)	0.45
Mean number of vessels bypassed	3.23 ± 1.14	2.45 ± 1.28	3.29 ± 1.10	0.0014
ICU stay	2 (1 - 33)	3 (1 - 8)	2 (1 - 33)	0.52
Hospital days	14 (1 - 270)	17 (6 - 29)	14 (1 - 270)	0.76
Reoperation for bleeding (%)	3 (1)	0	3 (1)	0.63
Paroxysmal atrial fibrillation (%)	52 (19)	4 (20)	48 (19)	0.89
Sternal infection (%)	12 (4)	0	12 (5)	0.32
Cerebrovascular event (%)	13 (5)	1 (5)	12 (5)	0.95
30-day mortality (%)	3 (1)	0	3 (1)	0.63
Cardiac death (%)	8 (3)	1 (5)	7 (3)	0.56

CABG, coronary artery bypass graft surgery; CPB, cardiopulmonary bypass; ICU, intensive care unit.

Table 4. Operative procedures and outcomes in the matched cohort.

	Total, 40	Patients with cancer 20 (50%)	Patients without cancer 20 (50%)	p value
Urgent or emergency CABG	8 (20)	4 (20)	4 (20)	1.00
Left main disease (%)	13 (33)	4 (20)	9 (45)	0.088
Triple vessel disease (%)	19 (48)	6 (30)	13 (65)	0.025
Mean number of vessels with significant stenosis	2.43 ± 0.59	2.20 ± 0.62	2.65 ± 0.49	0.015
Use of CPB (%)	9 (23)	5 (25)	4 (20)	0.7
Mean number of vessels bypassed	2.88 ± 1.14	2.45 ± 1.28	3.30 ± 0.80	0.016
ICU stay	3 (1 - 9)	3 (1 - 8)	3 (2 - 9)	0.78
Hospital days	17 (6 - 60)	17 (6 - 29)	17 (11 - 60)	0.081
Reoperation for bleeding (%)	0	0	0	
Paroxysmal atrial fibrillation (%)	7 (18)	4 (20)	3 (15)	0.68
Sternal infection (%)	3 (8)	0	3 (15)	0.036
Cerebrovascular event (%)	2 (5)	1 (5)	1 (5)	1.00
30-day mortality (%)	0	0	0	
Cardiac death (%)	1 (3)	1 (5)	0	0.31

CABG, coronary artery bypass graft surgery; CPB, cardiopulmonary bypass; ICU, intensive care unit.

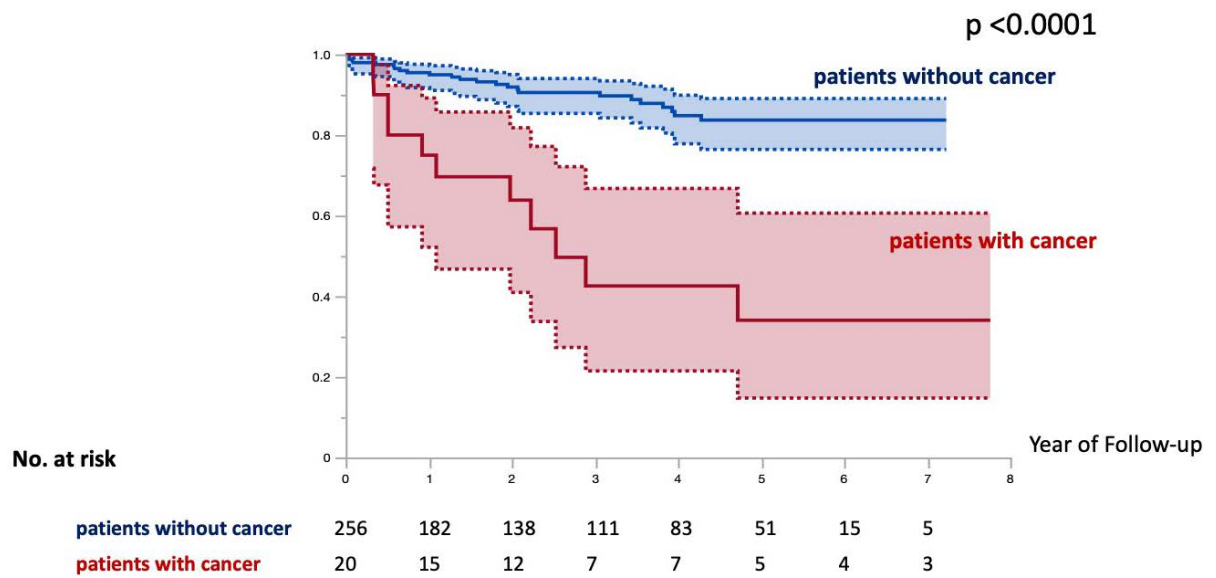


Figure 2. Cumulative survival of all patients.

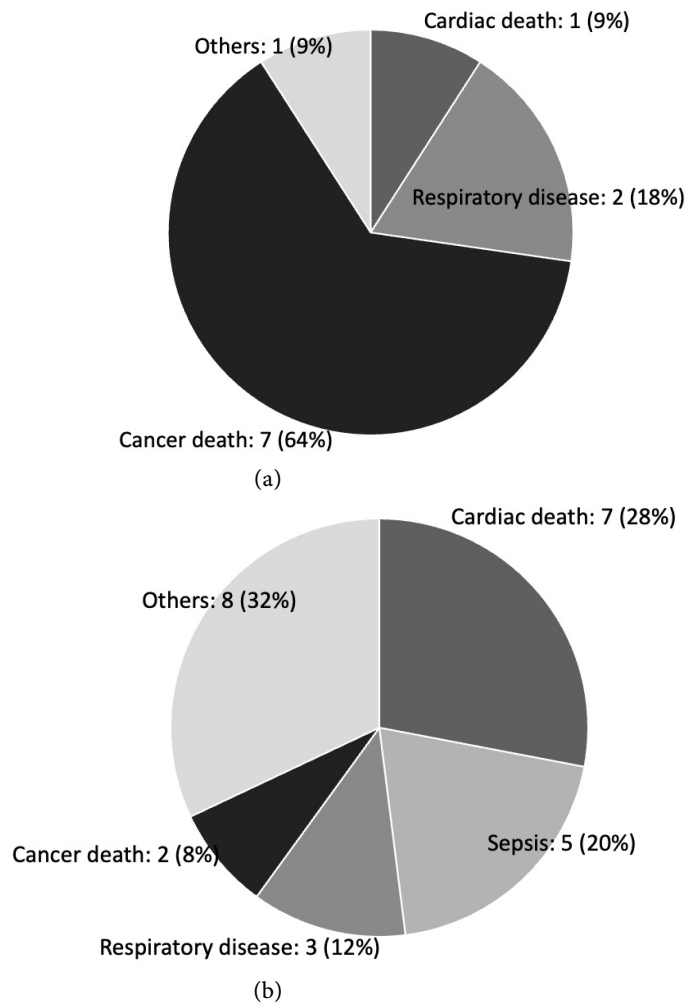


Figure 3. (a) Causes of mortality in patients with malignancy; (b) Causes of mortality in patients without malignancy.

The Kaplan-Meier curve in **Figure 2** shows the survival. We observed 15 deaths (5%): five (25%) in patients with malignancy and 10 (4%) in those without malignancy in the year after CABG. In total, we observed 36 deaths (13%): 11 (55%) in patients with malignancy and 25 (10%) in those without malignancy. Significantly poorer outcomes were observed in patients with malignancy who underwent CABG ($p < 0.0001$). The causes of death in patients with and without malignancy are shown in **Figure 3(a)** and **Figure 3(b)**, respectively. Most patients ($n = 7$, 64%) with malignancy died of recurrence or worsening of malignancy, whereas patients without malignancy died mainly of cardiovascular events ($n = 7$, 28%). In four patients of rhabdomyosarcoma, prostate adenocarcinoma, and renal cell carcinoma, metastasis of primary cancer was detected during follow up period. Patients ($n = 7$, 64%) with malignancy who died of recurrence or worsening of malignancy were two of stage IV gastric cancer, one of stage III esophageal cancer, one of stage I cholangiocellular carcinoma, one of stage IV rhabdomyosarcoma, one of stage I lung cancer, and one of stage IV prostate adenocarcinoma. Patients with stage IV cancer could not survive in the late phase.

Although the evaluation of patients' activity is difficult, all patients with malignancy could walk to the hospital as an outpatient till the end of the follow-up. Graft occlusion was not found in patients with malignancy after CABG.

4. Discussion

In the present study, CABG was safely performed in patients with malignancy. Even after propensity matching analysis, there was no significance in postoperative complications and cardiac events. Further, in the present study, patients with stage IV malignancy died in the late phase, however, only one of them died from cardiac causes. Therefore, because cancer did not affect the prognosis of CABG, CABG appeared effective in reducing adverse cardiac events in patients with malignancy. Guha *et al.* reported that among patients undergoing CABG, the prevalence of comorbid malignancy has steadily increased [9]. They observed that apart from major bleeding, these patients shared similar outcomes with those of patients without malignancy, indicating that CABG utilization should not be declined in patients with malignancy, when otherwise indicated.

In the majority of cancer patients, mortality was mainly due to cancer rather than cardiac death [10] [11]. In the presence of metastases, prostate, breast, colon, and lung cancers were independently associated with mortality, PCI complications, and major bleeding [12] [13]. Moreover, patients with metastatic cancer also had an increased risk of all-cause mortality and long-term noncardiac death compared with patients with limited cancer [14] [15]. In this study, we identified metastasis of primary cancer in four cases, but only one case, a case of rhabdomyosarcoma, resulted in late death. Depending on the histological type of the primary cancer, treatment of metastatic lesions may be possible. Even in cases with metastatic lesions, indication of CABG should be considered based on the histological type of the primary cancer. Conversely, the stage of cancer was related to

the mortality; no patients with stage IV cancer survived in the late phase. Stage 4 advanced cancer cases generally have a poor prognosis, and even if a case is considered suitable for CABG, careful judgment should be made based on individual clinical backgrounds.

In accordance with Darwazah *et al.*, patients with tumors undergoing staged CABG and tumor surgery had the advantage of a low incidence of adverse cardiovascular events, the interval between the two procedures ranged from 5 to 60 days, and there was no significant correlation between the recurrence or metastasis of the tumor and no correlation to the time between staged procedures [5]. In the present study, however, two patients were dropped out after CABG from surgery for malignancy because of worsening activity, and nutritional status. Suzuki *et al.* reported that an independent association of polyvascular disease with the incidence of cancer in patients with CAD was found, implying the possibility that the severity of atherosclerosis could play a pivotal role in cancer development [3]. Numerous factors such as the presence of active cancer, current oncologic treatment, and cancer-related co-morbidities (frailty, anemia, thrombocytopenia, nutritional/performance status) require the clinician to personalize the management plan with the help of a multidisciplinary team comprising of a cardiologist, interventional cardiologist, and an oncologist [16]. In our hospital, post-surgical conference in intensive care unit including cardiac surgeons, anesthesiologists, nurse practitioners, pharmacists, and nurses are held every day after cardiac surgery. This meeting includes nutrition staff, rehabilitation staff, and social workers, if necessary. After transport to the general ward, these meetings are held weekly or more. For patients who need meticulous care, these supports should be given before CABG.

Garatti *et al.* proposed that, instead of PCI, CABG should not be withheld from patients with solid organ tumors owing to concerns about a poorer prognosis or reduced graft durability [4]. In the present study, patients with malignancy had significantly fewer lesions and, therefore, received fewer bypass grafts. CABG via left small thoracotomy with single-vessel bypass was commonly seen in patients with malignancy. This could be because catheter intervention requiring dual antiplatelet therapy was avoided. Moreover, there were no patients with malignancy who developed graft occlusion in the present study. The reason why postoperative sternal infection occurred significantly rarer in patients with malignancy might be these fewer bypass grafts and difference in approach. For oncology surgeons, it is preferable that patients underwent CABG than PCI demanding dual antiplatelet therapy. Minimally invasive CABG enables less intraoperative bleeding, avoidance of respiratory complications and sternal infection, and prompt postoperative recovery [17] [18]. In the future, if minimally invasive or robotic CABG develops dramatically and becomes popular, the waiting time until the next cancer surgery may be shortened.

Limitation

This study has some limitations. First, it was a retrospective study with a small

sample size. Guha *et al.* reported that 8.6% of cancer patients were found in total CABG patients; this number is similar to our ratio [9].

Recall bias during the clinical course cannot be ruled out. To confirm these clinical data, more cases of malignant diseases combined with CAD are required. Second, the distribution of diseases in this study was varied, including gastrointestinal, respiratory, urinary, and thymic malignancies, and malignant lymphoma; further classification studies are challenging. The value of tumor staging in the selection of treatment strategies for patients with malignancy combined with CAD requires further research. Third, some patients with advanced cancer denied aggressive coronary evaluation and revascularization, so we could not include these high-risk patients.

5. Conclusion

CABG could be safely performed in patients with malignancy, contributing to avoid cardiac events in the late phase. Further, even after successful CABG, sequential support by multidisciplinary team is essential for a safe cancer treatment.

Author Contributions

Study conception: KS; Data collection: KS; Analysis: KS, KM; Investigation: KS; Writing: KS; Funding acquisition: KS; Critical review and revision: all authors; final approval of the article: all authors; accountability for all aspects of the work: all authors.

Ethics Approval and Consent to Participate

All procedures were performed according to the tenets of the Declaration of Helsinki, and the Ethics Committee of Aichi Medical University Hospital approved the study on September 28th, 2021 (approval number, 2021-412). All patients provided written consent for the use of their clinical data for scientific presentation or publication.

Consent for Publication

The patients provided permission to publish the study results. The patient's identity is protected.

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Conflicts of Interest

The authors declare that they have no competing interests.

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