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Off-Pump Coronary Artery Bypass Grafting with Malignant Tumor Resection Involving Different Organs: The Comparison of Long-Term Prognosis and Risk Factor Analysis Related to Survival

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ABSTRACT

Background: This study aimed to analyze the influence of the primary site of tumor location on off-pump coronary artery bypass grafting (OPCABG) surgery combined with concurrent tumor resection and to identify factors affecting the long-term survival.

Methods: Fifty-seven patients with coronary artery disease (CAD) and malignancy who underwent simultaneous surgery were retrospectively enrolled. The primary sites of tumor location and cancer stages were used as the basis for grouping. The long-term survival among the subgroups was compared, and the risk factors related to survival were analyzed.

Results: The median follow-up period was 40 months. The 5-year cumulative survival rate of patients undergoing OPCABG with concurrent tumor resection was 74%. There was no significant difference in long-term survival among the four oncological location subgroups ($P = 0.8$), while significant difference was found between the two cancer stage subgroups ($P = 0.0076$). On multivariable Cox regression analysis, only cancer stage was an independent predictor of the long-term mortality rate (hazard ratio 5.42, $P = 0.007$).

Conclusion: For patients with potentially curable cancer and surgically correctable CAD, the safety of simultaneous surgery is confident. The primary site of tumor location does not significantly affect the long-term survival of these patients. The long-term survival rate strongly correlates with tumor stage.

INTRODUCTION

Coronary artery disease (CAD) and malignant tumor are two of the most common diseases [Collaborators 2017], of which incidence increase with age, and malignancies are usually found in patients with CAD [Suzuki 2017]. The SHIP (Sakakibara Health Integrative Profile) cohort study [Suzuki 2017] concluded that cancer prevalence and mortality were >2-fold higher in patients with atherosclerotic cardiovascular disease than in patients with nonatherosclerotic cardiovascular diseases. For concomitant diseases patients who progress to severe CAD, coronary revascularization should be the priority to reduce the risk of myocardial infarction that is a medical emergency with high mortality [Guha 2020; Takahashi 1995; Potts 2019].

Coronary artery bypass grafting (CABG) is the surgical intervention method to revascularize vasculopathy for patients with severe CAD, such as three-branch lesions. It was conducted first for patients with CAD and malignant tumor, and then oncological surgery was carried out. The strategy of staged approach was recently described by Garatti et al. [Garatti 2020]. They performed CABG first, and then cancer resection was scheduled 4 or 6 weeks later. Unsatisfactorily, the 5- and 10-year survival rates were significantly lower in patients with concomitant diseases compared with patients with CAD alone [Garatti 2020]. Carrying out alone CABG surgery first inevitably resulted in postponed tumor resection, which may influence the long-term survival of patients with both CAD and malignancy. Because of this, simultaneous procedures to revascularize vasculopathy and resect tumors attracted a fair amount of attention and became the mainstream, which may be beneficial for long-term survival of these patients.

Many studies have explored the feasibility and safety of simultaneous surgery in patients suffering from both CAD and tumor, and the off-pump CABG (OPCABG) was considered the first choice in this approach. Most of the reported simultaneous surgeries were confined to chest procedures, such as CABG combined with lung cancer or esophageal cancer resection surgery, and the surgical method was demonstrated to be safe and feasible [Tourmousoglou 2014; Wang 2021; Ding 2021; Liu 2017]. Besides, a recent meta-analysis also revealed that combined CABG and lung tumor resection had lower mortality rate and acceptable complication rate [Cheng 2021]. This kind of simultaneous surgery could only affect the thoracic organs, however, cardiac operation combined with non-thoracic surgery, such as gastroenteric, urinary and other solid tumor resection surgeries, need extra surgical incisions and may affect the organ function of the corresponding system, while it was

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poorly reported [Zhao 2017; Dedeilias 2010]. Additionally, the comparison of long-term survival about simultaneous surgery being conducted in CAD patients suffering from malignant tumor involving different organs is also rarely reported.

Our team has confirmed that OPCABG with simultaneous non-cardiac surgery did not significantly deteriorate the major perioperative outcomes compared with isolated off-pump bypass [Dong 2021; Yang 2016]. In this study, we compared the long-term survival among patients undergoing OPCABG combined with simultaneous malignant tumor resection involving different organ systems and analyzed the risk factors that affected the long-term survival of these patients.

MATERIALS AND METHODS

Population: Of the 1240 CAD patients who underwent first-time OPCABG in Peking University First Hospital between January 2013 and December 2020, 1178 patients (95%) had isolated OPCABG conducted and 62 cases (5%) underwent OPCABG combined with simultaneous noncardiac surgery. Of the 62 patients undergoing simultaneous surgery, there were 57 cases (91.9%) of OPCABG combined with simultaneous tumor resection and five cases with non-tumor resection, including one case of superior mediastinum mass resection (mediastinal goiter), one case of retrosternal partial thyroidectomy (nodular goiter), one case of right internal carotid endarterectomy (right carotid atherosclerosis), one case of laparoscopic cholecystectomy (chronic cholecystitis with gallstone), and one case of open cholecystectomy with laparoscopic common bile duct exploration and T-tube drainage (cholecystitis with cholangiolithiasis). According to the type of primary neoplasms, the enrolled 57 patients were divided into four major subgroups: lung neoplasms (25 cases, 43.9%), urinary neoplasms (17 cases, 29.8%), gastroenteric neoplasms (10 cases, 17.5%), and other solid neoplasms (five cases, 8.8%). Demographic information and perioperative characteristics were collected from the electronic medical record system.

Ethics: The protocol of the study was approved by The Human Ethics Committee of Peking University First Hospital. All patients were given a verbal and written explanation of the study, and no personal information was recorded during the research. Written informed consent was obtained from all enrolled patients. This study was conducted in accordance with the Declaration of Helsinki.

Preoperative diagnosis and surgical indications: For patients with CAD and malignant tumor, simultaneous surgery is considered if they meet the following indications: 1) preoperative evaluation indicates the malignancy in early or middle stage without distant metastasis, combining with severe coronary artery three-branch lesions or complications after myocardial infarction which need surgical intervention; 2) patients with severe CAD and advanced renal cancer and inferior vena cava tumor emboli; 3) CAD patients with advanced malignancy need to undergo CABG and they have to receive palliative surgery due to tumor obstruction, such as progressive gastrointestinal tract obstruction or urinary tract obstruction that cause severe clinical symptoms.

Surgical technique and oncological staging: All subjects underwent OPCABG first, and the key operation procedure can be briefly described as follows: median thoracotomy approach was conducted, followed by half-dose (1mg/kg) heparinization, and coronary artery anastomosis was completed by using Octopus heart stabilizer as cardiac surface fixation. Then, the subsequent procedures were selected based on the surgical characteristics of different tumor types to complete the tumor resection operations.

Tumor tissues were examined by routine pathological microscopy, and the malignancies were accurately staged according to the histopathological classification postoperatively. Based on the classification method that Hirose et al. [Hirose 2000] reported, these patients were divided into two subgroups: stage I or II were defined as early stage (37 patients, 64.9%) and stage III or IV were considered as advanced stage (20 patients, 35.1%). Further treatment, checkup, and follow-up also depended on the postoperative histopathological classification of tumors.

Follow-ups: Follow-up information was obtained from telephone follow-up or outpatient clinic visits. Routine postoperative follow-up was conducted at 1 month, 3 months, 6 months after surgery, and then 6 months thereafter. Primary endpoint events were defined as dying of major adverse cardiovascular events (MACEs) and cardiac sudden death or tumor-related death. MACEs mainly include acute myocardial infarction, acute congestive heart failure, acute stroke, and so on. Cardiac sudden death is defined as sudden and unexpected death, which means sudden consciousness loss with circulatory and respiratory arrest shortly after symptoms appear [Fan 2015]. Tumor-related death is defined as the death from any causes associated with cancer.

Statistical analyses: The normality of continuous variables was tested and validated by the Shapiro-Wilk test. The variable that was normally distributed was presented as mean±standard deviation, while non-normally distributed continuous variable was presented as median and interquartile range. One-way ANOVA analysis or Kruskal–Wallis test were performed for multiple comparisons. The $\chi 2$ or Fisher's exact test were used to compare the difference between categorical variables. A *P*-value <0.05 (two sides) was considered statistically significant.

Survival curves were calculated starting from the date of simultaneous surgery. Multivariable comparison of survival curves was estimated with the log-rank test. Survival probabilities were derived from the Cox regression predicted survival curves, holding the other covariates constant.

Univariable Cox regression was used to preliminarily evaluate the predictors of long-term mortality rate, then the multivariable Cox regression was conducted. The Schoenfeld residuals test was used to check the proportional hazard assumption for all categorical covariates. All data was analyzed using the SPSS 26.0 statistical software package (SPSS, Inc., Chicago, IL).

RESULTS

Baseline characteristics: The average age of the patients with severe CAD and tumors was 66.06±8.15 years, and there were 49 cases (86.0%) of male patients. The incidence of hypertension was 68.4% (39 cases). Forty-three cases (75.4%) of patients were diagnosed as three-branch lesions of coronary artery. There were no significant differences in terms of demographics or comorbidities among cancer type groups (Table 1). The percentage of left main stenosis in the advanced stage subgroup was higher than that in the early stage subgroup (80.0% vs. 51.4%, $P = 0.047$). The remaining demographic characteristics and comorbidities among the cancer stage subgroups can be seen in Table 2.

The common pathological patterns of tumors were lung squamous cell carcinoma (11 cases), renal clear cell carcinoma (10 cases), lung adenocarcinoma (seven cases), colon adenocarcinoma (six cases), and vesical papillary transitional cell carcinoma (four cases). Further details can be found in Table 3.

Perioperative outcomes: The common oncological operation strategies were lobectomy (19 cases), radical nephrectomy (10 cases), hemicolectomy (six cases), wedged lobectomy (four cases), and radical esophagectomy (three cases).

The median amount of coronary artery grafts among all patients was two. The median number of grafts was the most in patients with gastroenteric tumors, while it was the least in other solid tumors (3.00 [2.25, 4.00] vs. 1.00 [1.00, 2.00], $P = 0.009$). OPCABG with simultaneous urinary neoplasm resection required the least mean procedure duration (283.18±55.10 min). Of these patients, the proportion of perioperative blood product use was higher in the cases who underwent simultaneous operation with gastroenteric neoplasms (10 cases, 100%) than others. In addition, the patients in the gastroenteric neoplasm subgroup required a longer median hospitalization length of stay (31.5 [28.25, 46.00] day). More details of perioperative characteristics categorized according to cancer type are shown in Table 4. The perioperative characteristics categorized according to cancer stage are shown in Table 5. Also, there were no statistically significant differences in perioperative data between the two subgroups of cancer stage.

There was no perioperative death among the patients. After the simultaneous surgery, two patients underwent reoperations due to abdominal incision infection and acute hemothorax, and one patient reentered the intensive care unit after thoracotomy hemostasis, three patients suffered postoperative myocardial infarction and made a recovery after conservative treatment, one patient had a stroke and made a recovery after conservative treatment, two patients had conducted dialysis after surgery due to chronic kidney disease, and nine

Table 1. Baseline characteristics in cancer type subgroups

	All (*N* = 57)	Lung Neoplasm (*N* = 25)	Urinary Neoplasm (*N* = 17)	Gastroenteric Neoplasm (*N* = 10)	Other Solid Tumors (*N* = 5)	*P*-value
Age (years), mean±SD	66.06±8.15	66.18±7.60	68.09±8.83	64.03±8.73	62.66±7.66	0.478
Male, n (%)	49 (86.0)	24 (96.0)	14 (82.4)	7 (70.0)	4 (80.0)	0.140
BMI (kg/m^2), median [IQR]	24.49 [22.79, 26.75]	24.91 [23.18, 26.79]	24.16 [22.68, 26.74]	24.64 [22.53, 26.54]	23.42 [20.57, 26.30]	0.891
Hypertension, n (%)	39 (68.4)	14 (56.0)	13 (76.5)	8 (80.0)	4 (80.0)	0.410
Type II Diabetes, n (%)	24 (42.1)	9 (36.0)	8 (47.1)	5 (50.0)	2 (40.0)	0.861
COPD, n (%)	6 (10.5)	4 (16.0)	2 (11.8)	0 (0.0)	0 (0.0)	0.589
Liver disease, n (%)	2 (3.5)	2 (8.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.734
CKD, n (%)	1 (1.8)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	0.263
Smoking, n (%)	37 (64.9)	20 (80.0)	10 (58.8)	4 (40.0)	3 (60.0)	0.114
Heart valve disease, n (%)	9 (15.8)	2 (8.0)	4 (23.5)	3 (30.0)	0 (0.0)	0.219
Previous PCI, n (%)	5 (8.8)	3 (12.0)	1 (5.9)	1 (10.0)	0 (0.0)	0.903
Previous acute MI, n (%)	10 (17.5)	4 (16.0)	3 (17.6)	2 (20.0)	1 (20.0)	1.000
Previous stroke, n (%)	9 (15.8)	3 (12.0)	2 (11.8)	3 (30.0)	1 (20.0)	0.547
LVEF (%), median [IQR]	65.10 [56.10, 71.70]	66.90 [57.00, 73.20]	64.40 [53.00, 69.60]	65.45 [57.55, 72.85]	64.00 [56.00, 70.00]	0.566
Stenosis of LAD, n (%)	7 (12.3)	4 (16.0)	0 (0.0)	3 (30.0)	0 (0.0)	0.072
Stenosis of left main, n (%)	35 (61.4)	13 (52.0)	13 (76.5)	7 (70.0)	2 (40.0)	0.316
Three-branch lesions (coronary artery), n (%)	43 (75.4)	19 (76.0)	13 (76.5)	9 (90.0)	2 (40.0)	0.351

SD, standard deviation; BMI, body mass index; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; PCI, percutaneous transluminal coronary intervention; MI, myocardial infarction; LVEF, left ventricular ejection function; LAD, left anterior descending

Table 2. Baseline characteristics in cancer stage subgroups

	Cancer (*N* = 57)	Early stage (*N* = 37)	Advanced stage (*N* = 20)	*P*-value
Age (years), mean±SD	66.06±8.15	66.00±8.69	66.18±7.26	0.936
Male, n (%)	49 (86.0)	31 (83.8)	18 (90.1)	0.699
BMI (kg/m^2), median [IQR]	24.49 [22.79, 26.75]	24.91 [23.23, 26.85]	23.74 [21.42, 26.45]	0.155
Hypertension, n (%)	39 (68.4)	26 (70.3)	13 (65.0)	0.769
Type II diabetes, n (%)	24 (42.1)	15 (40.5)	9 (45.0)	0.784
COPD, n (%)	6 (10.5)	3 (8.1)	3 (15.0)	0.654
Liver disease, n (%)	2 (3.5)	2 (5.4)	0 (0.0)	0.536
CKD, n (%)	1 (1.8)	0 (0.0)	1 (5.0)	0.351
Smoking, n (%)	37 (64.9)	26 (70.3)	11 (55.0)	0.263
Heart valve disease, n (%)	9 (15.8)	5 (13.5)	4 (20.0)	0.705
Previous PCI, n (%)	5 (8.8)	4 (10.8)	1 (5.0)	0.647
Previous acute MI, n (%)	10 (17.5)	5 (13.5)	5 (25.0)	0.298
Previous stroke, n (%)	9 (15.8)	7 (18.9)	2 (10.0)	0.298
LVEF (%), median [IQR]	65.10 [56.10, 71.70]	66.80 [61.00, 73.00]	64.65 [50.67, 70.27]	0.165
Stenosis of LAD, n (%)	7 (12.3)	4 (10.8)	3 (15.0)	0.687
Stenosis of left main, n (%)	35 (61.4)	19 (51.4)	16 (80.0)	0.047
Three-branch lesions (coronary artery), n (%)	43 (75.4)	30 (81.1)	13 (65.0)	0.407

SD, standard deviation; BMI, body mass index; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; PCI, percutaneous transluminal coronary intervention; MI, myocardial infarction; LVEF, left ventricular ejection function; LAD, left anterior descending

Table 3. Subgroups and pathological patterns of tumors

Tumor subgroups	Pathological patterns
Lung cancer (25 cases)	Squamous cell carcinoma (11 cases, 44%), Adenocarcinoma (7 cases, 28%), Large cell cancer (3 cases, 12%), Neuroendocrine carcinoma (3 cases, 12%), Small cell carcinoma (1 case, 4%)
Urinary cancer (17 cases)	Vesical papillary transitional cell carcinoma (4 cases, 24%), Ureteral urothelium carcinoma (1 case, 6%), Renal clear cell carcinoma (10 cases, 59%), Chromophobe renal cell carcinoma (1 case, 6%), Renal oxyphilic cell carcinoma (1 case, 6%)
Gastroenteric cancer (10 cases)	Colon adenocarcinoma (6 cases, 60%), Rectal adenocarcinoma (1 case, 10%), Gastric adenocarcinoma (1 case, 10%), Small intestinal carcinoma (1 case, 10%), Gastric small cell carcinoma (1 case, 10%)
Other solid cancer (5 cases)	Esophageal squamous cell carcinoma (2 cases, 40%), Liver cell carcinoma (1 case, 20%), Adenocarcinoma of the esophagogastric junction (1 case, 20%), Breast adenocarcinoma (1 case, 20%)

patients suffered from postoperative atrial fibrillation. There was no case of newly developed renal failure.

Long-term outcomes: There were eight cases (14%) of withdrawal, and the follow-up of the other patients was completed. The median follow-up period was 40 months. During the follow-up period, there were 14 observational deaths in these patients with 24.6% overall mortality. Of them, eight patients' deaths were cancer-related, and six cases were cardiac-related. The overall 1- and 5-year survival rates of these patients were 97% and 74%, respectively. There was no significant difference in the 5-year survival rate among the four subgroups of cancer types (Figure 1, Log-rank *P* = 0.8). The 5-year survival rate of gastroenteric neoplasms, urinary neoplasms, lung neoplasms, and other solid neoplasms were 80%, 77%, 65%, and 80%, respectively. Furthermore, the 5-year survival rate of patients with malignancy in early stage was 86.7% (95% CI 74.9-100%), and the prognosis was much better than that of advanced stage (51.1%, 95% CI 31.8-82%) (Figure 2, Log-rank *P* = 0.0076).

On univariable Cox regression analysis, after preliminary screening, we found that whether suffering COPD or not (HR 3.6, 95%CI 1.1-12, *P* = 0.032), whether suffering CKD or not (HR 5.2, 95%CI 1.1-23, *P* = 0.033), and tumor stage (HR 2.3, 95%CI 1.1-4.7, *P* = 0.014) were the variables that might be the predictors of long-term survival in these patients. On multivariable Cox regression analysis, we concluded that only

Table 4. Perioperative characteristics in cancer type subgroups

	All (*N* = 57)	Lung Neoplasm (*N* = 25)	Urinary Neoplasm (*N* = 17)	Gastroenteric Neoplasm (*N* = 10)	Other Solid Tumors (*N* = 5)	*P*-value
Total grafts, median [IQR]	2.00 [2.00, 3.00]	2.00 [2.00, 3.00]	3.00 [2.00, 3.00]	3.00 [2.25, 4.00]	1.00 [1.00, 2.00]	0.009
Operation time (min), mean±SD	344.79±106.66	360.16±111.33	283.18±55.10	379.50±97.95	408.00±159.83	0.025
Blood loss (ml), median [IQR]	430.00 [300.00, 600.00]	500.00 [300.00, 800.00]	430.00 [250.00, 500.00]	440.00 [300.00, 650.00]	300.00 [150.00, 400.00]	0.336
Perioperative blood products, n (%)	27 (47.4)	7 (28.0)	7 (41.2)	10 (100.0)	3 (60.0)	<0.001
Tumor stage, n (%)	-	-	-	-	-	0.327
Early	37 (64.9)	19 (76.0)	10 (58.8)	5 (50.0)	3 (60.0)	
Advanced	17 (29.8)	6 (24.0)	6 (35.3)	4 (40.0)	1 (20.0)	
Metastasis	3 (5.3)	0 (0.0)	1 (5.9)	1 (10.0)	1 (20.0)	
Auxiliary ventilation time (h), median [IQR]	11.50 [7.00, 19.00]	11.00 [7.00, 20.00]	8.00 [6.50, 15.00]	17.50 [9.25, 19.50]	24.00 [13.00, 25.00]	0.116
ICU stay time (h), median [IQR]	66.00 [43.00, 111.00]	66.00 [41.00, 89.00]	62.00 [43.00, 68.00]	117.00 [74.00, 136.75]	64.00 [46.00, 159.00]	0.063
HLOS (d), median [IQR]	23.00 [21.00, 29.00]	22.00 [20.00, 24.00]	22.00 [21.00, 28.00]	31.50 [28.25, 46.00]	23.00 [20.00, 28.00]	0.017
Postoperative hospitalization days (d), median [IQR]	14.00 [13.00, 15.75]	14.00 [13.00, 14.00]	14.00 [13.00, 15.00]	17.00 [13.00, 20.50]	14.00 [13.00, 15.00]	0.268

IQR, interquartile range; SD, standard deviation; ICU, intensive care unit; HLOS, hospitalization length of stay

Table 5. Perioperative characteristics in cancer stage subgroups

	Cancer (*N* = 57)	Early stage (*N* = 37)	Advanced stage (*N* = 20)	*P*-value
Total grafts, median [IQR]	2.00 [2.00, 3.00]	3.00 [2.00, 3.00]	2.00 [1.75, 3.00]	0.642
Operation time (min), mean±SD	344.79±106.66	358.03±110.13	320.30±97.85	0.205
Blood loss (ml), median [IQR]	430.00 [300.00, 600.00]	400.00 [300.00, 600.00]	500.00 [250.00, 700.00]	0.663
Perioperative blood products, n (%)	27 (47.4)	15 (40.5)	12 (60.0)	0.178
Tumor type, n (%)	-	-	-	0.426
Lung Neoplasm	25 (43.9)	19 (51.4)	6 (30.0)	
Gastroenteric Neoplasm	10 (17.5)	5 (13.5)	5 (25.0)	
Urinary Neoplasm	17 (29.8)	10 (27.0)	7 (35.0)	
Other Solid Tumors	5 (8.8)	3 (8.1)	2 (10.0)	
Auxiliary ventilation time (h), median [IQR]	11.50 [7.00, 19.00]	11.50 [7.00, 19.00]	10.50 [7.00, 18.50]	0.834
ICU stay time (h), median [IQR]	66.00 [43.00, 111.00]	66.00 [44.00, 86.00]	53.50 [41.75, 112.50]	0.639
HLOS (d), median [IQR]	23.00 [21.00, 29.00]	23.00 [20.00, 28.00]	27.00 [22.00, 29.50]	0.190
Postoperative hospitalization days (d), median [IQR]	14.00 [13.00, 15.75]	14.00 [13.00, 16.00]	14.00 [12.75, 15.00]	0.601

IQR, interquartile range; SD, standard deviation; ICU, intensive care unit; HLOS, hospitalization length of stay the stage of cancer was an independent predictor of the long-term mortality (HR 5.42, 95% CI 1.58–18.56; P = 0.007). More detailed information about Cox regression analysis is available in Table 6.

DISCUSSION

In this study, we enrolled 57 patients suffering from both severe CAD and tumor and carried out long-term follow-up. There was no significant difference in long-term survival among the patients who suffered OPCABG with concurrent malignant tumor resection involving different organ systems. Besides, we found that the perioperative results of these patients was satisfactory, and significant difference was found in long-term survival between different tumor stage subgroups. It is well known that surgery is one of the most effective treatments for tumors, and it is a kind of semi-elective operation that should be considered as early as possible for patients with cancer. In this study, we found that only tumor stage was the independent risk factor influencing the long-term survival of patients undergoing OPCABG and simultaneous tumor resection, while the primary location of cancer didn't have significant influence on the long-term survival of these patients.

Due to a lack of patients undergoing staged approach in our institution, the published results were used to contrast with our results. Although the heterogeneity among different studies is inevitable, the comparison can also provide some clues. One hundred and three patients undergoing on-pump CABG and tumor resection were enrolled by Garatti and his colleagues [Garatti 2020]. They concluded that the perioperative mortality of patients suffering from both CAD and malignancy was 4.9%, and 5-year survival of these patients was about 60%. Cheng et al.'s [Cheng 2021] meta-analysis in 2021 enrolled 536 cases of patients undergoing combined heart surgery (on-pump and off-pump CABG) and lung tumor resection from 29 studies to evaluate the perioperative mortality of combined surgery, and they concluded that the proportion of operative mortality was 1% (95% CI: 0%-3%). Another meta-analysis was conducted by Bablekos et al. [Bablekos 2016], and they reported that the 30-day mortality in the combined operation group was about 5.49% (95% CI: 3.51%-8.12%), and the five-year survival probability was 52.03% (95% CI: 34.71%–69.11%). Based on the results of the aforementioned studies, we could conclude that the perioperative outcome of our study was non-inferior, and the long-term safety was confident.

In the staged approach, heart surgery was performed to recover the coronary artery blood supply first, and then tumor resection was carried out 4 weeks to 3 months later [Garatti 2020]. It was established as the most prudent action, due to the inability of patient's general condition. However, taking the timing and priority of each operation into account, dilemma rises for this procedure due to cancer resection may be postponed by a delayed recovery from CABG [Darwazah 2011]. And the perturbations from cardiac operation may drive tumor progression and eventually metastatic disease [Darwazah 2011].

The use of cardiopulmonary bypass (CPB) in cardiac surgery is suspected as a cause that leads to cancer metastasis. It has been well documented that the immune system can be severely suppressed after extracorporeal circulation [Knudsen 1990]. Pessimistic results were also obtained by some clinical

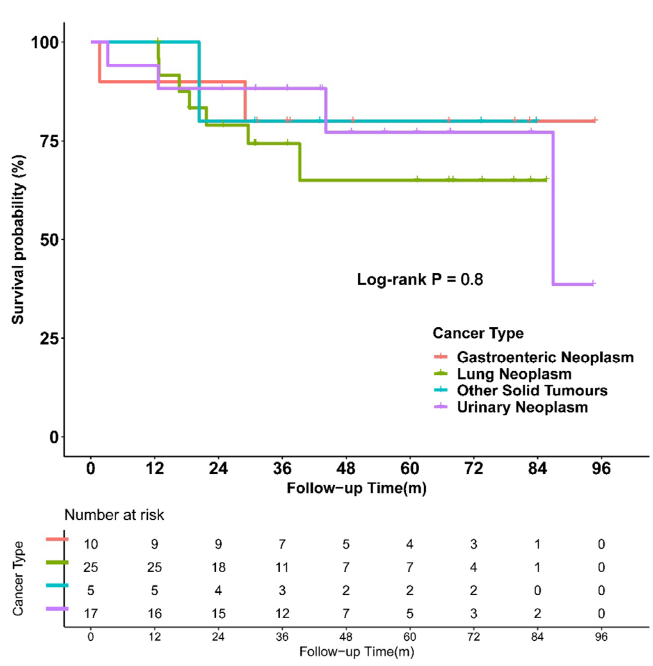

Figure 1. Long-time survival in different subgroups of cancer subtypes

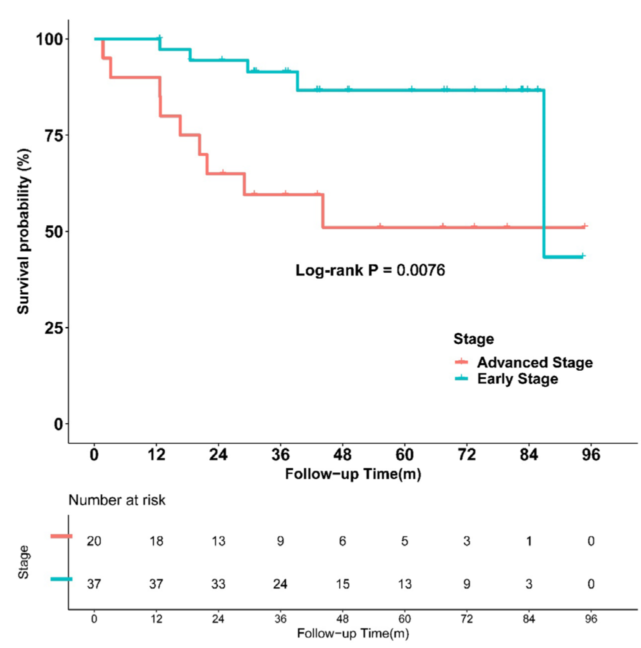

Figure 2. Long-time survival in different subgroups of cancer stage

Table 6. Univariable and multivariable Cox regression analysis

Variable name	Univariable Cox regression analysis					Multivariable Cox regression analysis	
	beta	HR	(95% CI for HR)	Wald test	*P*-value	HR	*P*-value
Age	0.036	1	(0.98-1.1)	1.4	0.25	-	
Male=Y	18	8.5e+07	(0-Inf)	0	1	-	
BMI>24kg/m^2	-0.79	0.45	(0.16-1.3)	2.2	0.14	-	
Hypertension=Y	-0.3	0.74	(0.25-2.2)	0.28	0.59	-	
Type II diabetes=Y	-0.92	0.4	(0.13-1.3)	2.4	0.12		
COPD=Y	1.3	3.6	(1.1-12)	4.6	0.032	3.76 [0.97, 14.63]	0.056
Liver disease=Y	0.73	2.1	(0.27-16)	0.49	0.48	-	
CKD=Y	1.6	5.2	(1.1-23)	4.6	0.033	2.80 [0.33, 23.60]	0.343
Smoking=Y	-0.13	0.88	(0.31-2.5)	0.06	0.81	-	
Heart valve disease=Y	0.49	1.6	(0.46-5.9)	0.57	0.45		
Previous PCI=Y	-18	1.3e-08	(0-Inf)	0	1	-	
Previous acute MI=Y	0.26	1.3	(0.41-4.1)	0.2	0.65	-	
Previous stroke=Y	-0.62	0.54	(0.11-2.6)	0.61	0.43	-	
Hemoglobin concentration <120g/L	1	2.8	(1-8)	3.9	0.05	-	
LVEF<50%	0.75	2.1	(0.66-6.8)	1.6	0.2	-	
Stenosis of LAD=Y	-0.4	0.67	(0.088-5.1)	0.15	0.7	-	
Stenosis of left main=Y	0.16	1.2	(0.39-3.5)	0.09	0.77	-	
Three-branch lesions=Y	-0.062	0.94	(0.45-2)	0.03	0.87	-	
Total grafts	0.038	1	(0.59-1.8)	0.02	0.89	-	
Operation time>300min	-0.13	0.88	(0.31-2.4)	0.06	0.8	-	
Blood loss>500ml	0.37	1.4	(0.51-4.1)	0.47	0.49	-	
Perioperative blood products=Y	0.59	1.8	(0.64-5.1)	1.3	0.26	-	
Tumor stage	1.4	4	(1.3-12)	6.1	0.014	5.42 [1.58, 18.56]	0.007
Lung neoplasm=Y	0.54	1.7	(0.58-5.2)	0.95	0.33	-	
Gastroenteric neoplasm=Y	-0.37	0.69	(0.15-3.1)	0.24	0.63	-	
Urinary neoplasm=Y	-0.27	0.76	(0.23-2.5)	0.2	0.65	-	
Other solid tumors=Y	-0.23	0.79	(0.1-6.1)	0.05	0.83	-	
Thoracic operation=Y	0.43	1.5	(0.53-4.5)	0.63	0.43	-	
Auxiliary ventilation time(h)	-0.016	0.98	(0.94-1)	0.62	0.43	-	
ICU stay time(h)	0.0049	1	(1-1)	1.2	0.28	-	
HLOS>30 days	0.37	1.4	(0.49-4.3)	0.46	0.5	-	
Postoperative hospitalization days>15 days	0.59	1.8	(0.64-5.1)	1.2	0.27	-	

HR, hazard ratio; CI, confidence interval; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; PCI, percutaneous transluminal coronary intervention; MI, myocardial infarction; LVEF, left ventricular ejection function; LAD, left anterior descending; ICU, intensive care unit; HLOS, hospitalization length of stay studies. Darwazah et al. found two patients developed distant metastasis after on-pump bypass [Darwazah 2011]. However, there was also some contrasting evidence, which showed that CPB did not consequentially contribute to distant metastasis of tumors after surgery [Darwazah 2011; Nguyen 2015]. In Chen's study [Chen 2021], no difference was found in the postoperative distant metastasis between the patients with and without CPB. The evidence is mixed for the effect of CPB on postoperative cancer prognosis, and this discrepancy undermines the confidence of using CPB for patients involving CAD and malignancy.

To be cautious, CPB should be avoided as much as possible among patients with combined CAD and malignant tumor. Our results showed that the off-pump bypass with sequential malignant tumor resection fully reflected its therapeutic advantages for these patients, neither resulting in the immune perturbation nor in delaying earlier resection of the malignant tumor. Additionally, the results of simultaneous operations involving OPCABG and tumor resection was favored by abundant literatures in the past decades [Dedeilias 2010; Darwazah 2011]. Earlier resection of malignant tumor might be beneficial for patient's survival, corresponding with our result that cancer stage was a factor that affected the long-term survival of patients with the two diseases.

Our results verified the feasibility of implementing simultaneous procedure of OPCABG and tumor resection involving different organs. The primary tumor site did not affect long-term survival of patients involving CAD and malignant tumor, while the cancer stage was the independent risk factor for mortality. Hence, early diagnosis and treatment are critical for these patients. We believe that off-pump bypass with concurrently combined tumor resection may be the preferred modality of surgical management to remove the tumor and revascularize the myocardium for most patients.

However, the strategy of simultaneous corrections is not always the best treatment method for CAD patients with malignancy, and staged operation is not useless. The decision should be made to use either a staged or simultaneous approach based on the urgency of surgery, surgical risk of simultaneous corrections, and the specific conditions of each case, not routinely [Darwazah 2012]. Besides, tumor resection should even come first for some special kinds of malignancies that can obviously influence the systemic condition, such as phaeochromocytoma. Significant amounts of catecholamine can be released from tumor cells deriving from neuroectoderm tissues in the patients with phaeochromocytoma. They require rigorous pre- and intra-operative drug therapy to prevent vascular instability induced by unpredictable catecholamine release. Although To and his colleagues reported two successful cases of CABG combined with phaeochromocytoma excision [To 2007], the staged approach with preferential correction of the endocrine tumor may be beneficial to maintain perioperative circulation stability in the later surgical coronary revascularization.

Our study has some limitations. First, this was a retrospective single-center study with limited number of patients, meaning the research conclusions still must be determined by further prospective studies involving more cases. Second, there were some censored data when the study ended, which means we should go on follow-up in the future in order to obtain more accurate data. Third, we did not group according to the number of grafting vesssels and compare the long-term outcomes among the subgroups. Lastly, our study only included patients undergoing OPCABG combined with simultaneous tumor resection.

CONCLUSION

Simultaneous surgery is feasible and safe for patients with severe CAD and malignancy. The short-term curative effect is quite satisfactory with low peri-operative mortality and morbidity. The primary site of tumor location does not significantly affect the long-term survival of CAD patients who suffer malignancies. The long-term survival of these patients mainly depends on cancer stage.

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