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Prognosis of patients with active cancer undergoing transcatheter aortic valve implantation: An insight from Japanese multicenter registry

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ABSTRACT

Background: Malignancy is common in older adults undergoing transcatheter aortic valve implantation (TAVI), and may affect prognosis. The present study aimed to examine whether active cancer affects all-cause mortality rates among patients undergoing TAVI.

Methods: This retrospective study examined data from 1,114 consecutive patients treated between April 2010 and June 2019. Patients with life expectancy of <1 year due to non-cardiac causes were excluded.

Results: Active cancer was defined as cancer under treatment or cured within 1 year, and was recognized in 62 patients (5.6%) with (n = 17) and without (n = 45) metastases. In multivariate analysis, being female (hazard ratio [HR] 0.55, 95% confidence interval [CI] 0.39–0.77, p < 0.001), body mass index (BMI) (HR = 0.92 per 1 kg/m^2 increase, 95% CI 0.87–0.97, p = 0.001), New York Heart Association (NYHA) class III/IV (HR = 1.53, 95% CI 1.06–2.20, p = 0.022), atrial fibrillation (HR = 2.40, 95% CI 1.70–3.38, p < 0.001), albumin levels (HR = 0.41 per 1-g/dl, 95% CI 0.30–0.57, p < 0.001), and cancer metastasis (HR = 5.28, 95% CI 1.86–14.9, p = 0.001) were associated with all-cause mortality after TAVI.

Conclusion: In patients undergoing TAVI, being female, high BMI, NYHA class III/IV, atrial fibrillation, albumin levels, and cancer metastasis were factors associated with mortality. Meanwhile, active cancer without metastasis was not associated with increased mortality rates. These findings would help clinical decision-making by patients and physicians.

Clinical trial registration: UMIN000031133.

1. Introduction

Several clinical trials have shown that transcatheter aortic valve implantation (TAVI) is as effective as surgical aortic valve replacement (SAVR) in every-risk patients with aortic stenosis (AS) [1–3]. Real-world data have revealed that most patients undergoing TAVI are the elderly aged ≥70 years [4]. Clinical trials and guidelines on TAVI exclude cohorts with limited life expectancy [1–3]. Malignancies are common among older adults, as is calcified AS; several TAVI candidates have cancer that is either active or in remission [5–9]. Stachon et al. preoperatively screened 374 patients with severe AS using computed tomography (CT) and found that 70 (19%) patients presented with signs of cancer [10]. Among them, 28 (40%) patients had findings that affected prognosis, such as cancer metastasis, enlarged lymph nodes, multiple metastases, and bone melting. History of active cancer is conventionally considered a comorbidity limiting patient prognosis; however, progress

Abbreviations: TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; AS, aortic stenosis; CT, computed tomography; HR, hazard ratio; CI, confidence interval; NYHA, New York Heart Association.

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in oncology has turned several malignant tumor types into partially or fully remitted disease [11,12]. However, whether active cancer affects the prognosis of patients with AS undergoing TAVI remains controversial [5–9]. The present study aimed to investigate whether active malignancy affects patient prognosis after TAVI.

2. Methods

2.1. Study design and patients

This was a multicenter prospective observational study. It included 1,114 consecutive patients that underwent TAVI at Sakakibara Heart Institute, Juntendo University Hospital, Mie University Hospital, or Yamagata University Hospital between April 2010 and June 2019. Patient data was prospectively registered in a dedicated database, and retrospectively analyzed. We compared demographic and clinical characteristics, procedural details, and prognosis between patients with and without active cancer. Active cancer was diagnosed before or during the pre-screening of TAVI. In patients with active cancer, malignancy characteristics were also investigated (i.e., primary site, distant metastasis status, therapy type). Post-TAVI follow-up was conducted by outpatient visit, telephone call or postcard at 30 days, 6 months, 12 months, and yearly thereafter. The study protocol was approved by the ethics committee of Sakakibara Heart Institute (number: 17-048) and each institution. The study adhered to the Declaration of Helsinki and other ethical guidelines on medical research involving humans. According to the policy of respective ethical committees, patient's consent was obtained by opt-out or written informed consent.

2.2. Definition of active cancer

Cancer types included were carcinoma and sarcoma, and the diagnosis was confirmed by an oncologist. Active cancer was defined as disease undergoing treatment or treatment planning concurrent with TAVI or completed within 1 year before TAVI. Therapy aiming to extend survival was defined as radical therapy, and that aiming to alleviate symptoms was defined as palliative therapy.

2.3. TAVI procedure

TAVI candidates were patients with symptomatic severe AS or bioprosthetic valve dysfunction of intermediate, high, or prohibitively high surgical risk. Patients with chronic renal failure requiring dialysis or life expectancy of <1 year due to non-cardiac disease were not eligible for TAVI. All patients underwent screening contrast-enhanced CT scans of the trunk and magnetic resonance imaging scans of the head. Patients with anemia due to suspected intestinal bleeding underwent upper gastrointestinal endoscopy and fecal occult blood tests. Based on the findings of these assessments, patients were referred to a cancer specialist to confirm that their life expectancy was of >1 year. In patients with active cancer, especially those having metastasis, the multidisciplinary hear team had decided the therapeutic policy considering their procedural risk, symptomatic burden due to aortic valve dysfunction, and expected life expectancy. The details of TAVI protocol have been described elsewhere [13].

2.4. Endpoint and definition

The primary endpoint was all-cause mortality after TAVI. The secondary endpoint was 30-day complication listed in combined endpoint. The definition of outcome was based on the Valve Academic Research Consortium-2 criteria [14].

2.5. Statistical analysis

Categorical variables have been reported as counts (%). Continuous variables have been reported as means ± standard deviations or medians (interquartile range), depending on the type of data distribution. The normality of distribution of continuous variables was evaluated with the Shapiro-Wilk test. The Chi-square and Fisher exact tests were used to compare categorical variables. To compare continuous variables, we used the unpaired Student *t*-test or Mann-Whitney *U* test, as suitable. The Kaplan-Meier survival curve was used to examine survival outcomes after TAVI; survival estimates were compared with the log-rank test. A univariate and multivariate Cox regression model was used to identify factors associated with survival. P-values of <0.05 were considered indicative of statistically significant findings, and a Bonferroni correction was applied in a multiple comparison. Factors of which P-value <0.05 on an univariate analysis were entered into a multivariate analysis with consideration for multicollinearity and clinical plausibility. Active cancer with or without metastasis were separately tested based on the result of preceding studies [5,10]. All analyses were performed in Easy R (ver. 3.6.1; http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html).

3. Results

3.1. Baseline characteristics

A total of 1,114 cases were included, with the median age of 85 years; two-thirds of the patients were women. Active cancer was confirmed in 62 (5.6%) patients. The primary cancer sites were breast (n = 11, 18%), colon (n = 11, 18%), stomach (n = 11, 18%), prostate (n = 10, 16%), and lung (n = 7, 11%) (Table 1). A total of 17 (27%) patients had metastatic cancer, and were treated as presented in Fig. 1. Forty-two of 45 (93%) patients without distant metastases were treated with radical therapy; in contrast, only nine (53%) patients with distant metastases were treated with the same approach. The characteristics of patients with and without active cancer were similar, except for the mean age (83 vs. 85 years, p = 0.003) and hemoglobin level (10.5 vs. 11.6 g/dl, p = 0.018) (Table 2).

3.2. Procedural details

Procedural characteristics were similar among patients with or without active cancer (Table 3). In the assessment of procedural outcomes, 30-day mortality, life-threatening bleeding rates, and combined endpoint estimates were similar in both groups. Treatment for active cancer was administered before, after, and both before and after TAVI in 19 (31%), 30 (48%), and 13 (21%) patients, respectively. Among patients undergoing radical treatment, 26 (51%) patients received it after TAVI.

3.3. Prognosis after TAVI

The overall median follow-up period was 19 months. There were 152 deaths during the follow-up period. The causes of death included

Table 1
Primary site of active cancer.

Patients with active cancer (n = 62)	
Breast cancer	11 (18%)
Colon cancer	11 (18%)
Gastric cancer	11 (18%)
Prostate cancer	10 (16%)
Lung cancer	7 (11%)
Renal cancer	4 (6.5%)
Liver cancer	3 (4.8%)
Bladder cancer	2 (3.2%)
Lymphoma	1 (1.6%)
Malignant soft tissue tumor	1 (1.6%)
Pancreatic cancer	1 (1.6%)

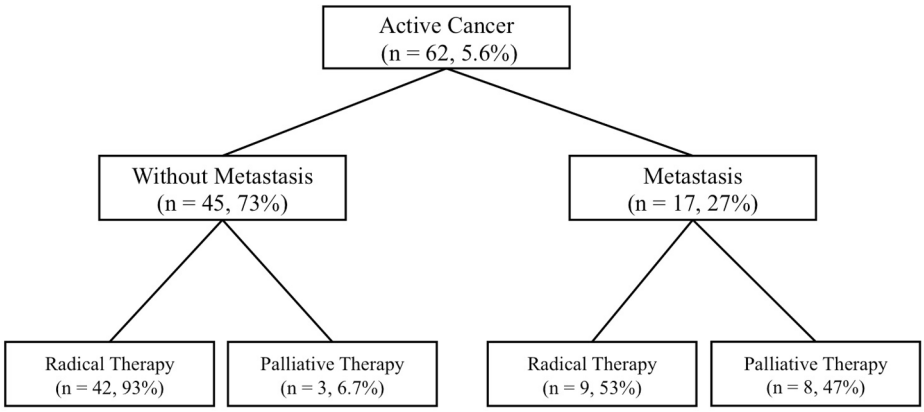

Fig. 1. . Treatment policy of patients with active cancer. Therapy aiming to extend survival was defined as radical therapy, and that aiming to alleviate symptoms was defined as palliative therapy.

Table 2
Baseline characteristics of patients with or without active cancer.

	Active cancer (n = 62)	Non-active cancer (n = 1,052)	P value
Age (years)	83 (79–86)	85 (82–88)	0.003
Female	37 (60%)	727 (69%)	0.12
Height (cm)	152 (146–161)	150 (144–157)	0.058
Weight (kg)	53 (45–59)	50 (43–58)	0.24
BSA (m^2)	1.4 (1.4–1.6)	1.4 (1.3–1.6)	0.12
BMI (kg/m^2)	22 (20–24)	22 (20–25)	0.85
Frailty*			0.43
Frail	33 (53%)	618 (59%)	
Non-frail	29 (47%)	434 (41%)	
DM	20 (32%)	239 (23%)	0.084
HT	42 (68%)	823 (78%)	0.054
NYHA class III/IV	25 (40%)	547 (52%)	0.074
Previous MI	7 (11%)	54 (5.1%)	0.075
Previous CABG	5 (8.1%)	62 (5.9%)	0.42
Previous PCI	11 (18%)	196 (19%)	0.86
AF/AFL	15 (24%)	253 (24%)	0.98
PAD	15 (24%)	170 (16%)	0.099
COPD	4 (6.5%)	102 (9.7%)	0.40
Stroke	3 (4.8%)	123 (12%)	0.098
STS score (%)	5.2 (3.4–7.3)	5.8 (3.9–8.2)	0.15
EuroSCOREII (%)	3.9 (2.2–7.3)	4.3 (2.7–6.8)	0.37
Hemoglobin (g/dL)	10.9 (10.0–12.1)	11.6 (10.5–12.7)	0.018
Platelet (×10,000/uL)	18 (16–23)	17 (14–22)	0.26
Albumin (g/dL)	3.7 (3.3–4.0)	3.8 (3.5–4.1)	0.080
eGFR ($ml/min/1.73\ m^2$)	51 (37–63)	53 (41–65)	0.53
AVA (cm^2)	0.68 (0.53–0.86)	0.67 (0.55–0.79)	0.66
Mean transvalvuar PG (mmHg)	51 (40–60)	48 (38–62)	0.65
LVEF (%)	63 (58–66)	63 (57–67)	0.89

*Frail was defined as clinical frailty scale was five or more.
BSA, body surface area; BMI, body mass index; DM, Diabetes mellitus; HT, hypertension; NYHA, New York Heart Association; MI, myocardial infarction; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; AF, atrial fibrillation; AFL, atrial flutter; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; STS, Society of Thoracic Surgeons; eGFR, estimated glomerular filtration rate; AVA, aortic valve area; PG, pressure gradient; LVEF, left ventricular ejection fraction.

cardiovascular disease (n = 52, 34%), infection (n = 36, 24%), malignant tumor (n = 16, 11%), and respiratory failure (n = 8, 5.3%).

In the active cancer group, 15 (24%) patients died during the follow-up period (1- and 2-year mortality rates of 9.7% and 15%, respectively); malignant tumor was the primary cause of death (n = 11, 73%). In patients without active cancer, 137 (13%) patients died during the follow-up, and 7 of 137 (5.1%) were derived from malignant tumor.

The Kaplan-Meier analysis revealed that survival was poorest among patients with metastatic cancer; while, survival among patients with non-metastatic cancer and those without active cancer was similar

Table 3
Procedural characteristics and outcome.

	Active cancer (n = 62)	Non-active cancer (n = 1,052)	P value
TF Approach	55 (89%)	961 (91%)	0.50
THV generation			0.13
First generation	20 (32%)	249 (24%)	
Second generation	42 (68%)	803 (76%)	
Balloon expandable valve (vs. self-expandable valve)	50 (71%)	760 (72%)	0.19
Anesthesia			0.54
General	32 (52%)	501 (48%)	
Local	30 (48%)	551 (52%)	
Device success	57 (92%)	990 (94%)	0.41
Thirty-day survival	62 (100%)	1044 (99%)	1.0
All stroke	1 (1.6%)	36 (3.4%)	0.72
Life-threatening bleeding	1 (1.6%)	24 (2.3%)	1.0
AKI stage 2 or 3	3 (4.8%)	22 (2.1%)	0.16
Coronary obstruction requiring intervention	1 (1.6%)	6 (0.6%)	0.33
Major vascular complication	0 (0%)	29 (2.8%)	0.40
Valve-related dysfunction requiring repeat procedure	0 (0%)	2 (0.2%)	1.0
Requiring PMI	2 (3.2%)	96 (9.1%)	0.11
Length of stay after TAVI (days)	8.5 (6.0–14.8)	9.0 (6.0–13)	0.85
Home discharge	57 (92.0%)	965 (91.7%)	1.0

TF, transfemoral; THV, transcatheter heart valve; AKI, acute kidney injury; PMI, pacemaker implantation; TAVI, transcatheter aortic valve implantation.

(Fig. 2). The median survival estimates of the non-metastatic and metastatic cancer groups were 22.2 and 16.5 months. In the metastatic group, only one of nine (11%) patients died after receiving radical therapy; meanwhile, all patients (n = 8) receiving palliative therapy died during the follow-up period.

The multivariate Cox regression analysis revealed that being female (hazard ratio [HR] = 0.55, 95% confidence interval [CI] 0.39–0.77, p < 0.001), body mass index (HR = 0.92 per 1-kg/m^2 increase, 95% CI 0.87–0.97, p = 0.001), New York Heart Association (NYHA) class III/IV (HR = 1.53, 95% CI 1.06–2.20, p = 0.022), atrial fibrillation and flutter (HR = 2.40, 95% CI 1.70–3.38, p < 0.001), serum albumin levels (HR = 0.41 per 1-g/dl increase, 95% CI 0.30–0.57, p < 0.001), and cancer metastasis (HR = 5.28, 95% CI 1.86–14.9, p = 0.001) were factors independently associated with mortality (Table 4). In contrast, active cancer without metastasis was not associated with all-cause mortality after TAVI.

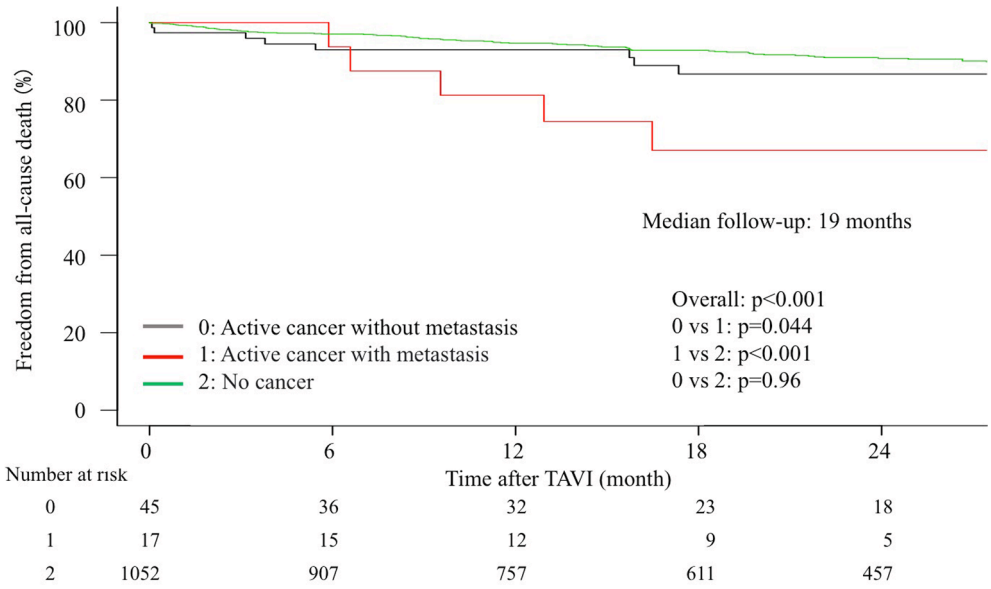

Fig. 2. . Patient survival estimates, stratified by cancer status: non-metastatic cancer vs. metastatic cancer vs. non-cancer group. TAVI indicates transcatheter aortic valve implantation.

Table 4
Predictors of survival after transcatheter aortic valve implantation.

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age	1.02	0.99–1.05	0.21			
Female	0.53	0.38–0.72	<0.001	0.55	0.39–0.77	<0.001
BMI	0.92	0.88–0.97	0.001	0.92	0.87–0.97	0.001
DM	1.14	0.79–1.65	0.47			
HT	0.67	0.46–0.94	0.030	0.76	0.51–1.12	0.16
NYHA class III/IV	1.87	1.34–2.60	<0.001	1.53	1.06–2.20	0.022
Previous MI	1.17	0.63–2.16	0.63			
Previous CABG	1.39	0.82–2.35	0.22			
Previous PCI	1.02	0.68–1.52	0.93			
AF/AFL	2.20	1.59–3.06	<0.001	2.40	1.70–3.38	<0.001
PAD	1.77	1.23–2.57	0.002	1.39	0.93–2.06	0.11
COPD	1.60	0.96–2.66	0.070			
Stroke	1.65	1.06–2.55	0.026	1.53	0.94–2.50	0.09
Hemoglobin (per 1-g/dl increase)	0.92	0.82–1.02	0.12			
Albumin (per 1-g/dl increase)	0.37	0.28–0.48	<0.001	0.41	0.30–0.57	<0.001
eGFR	0.99	0.98–1.00	0.060			
LVEF(per 1% increase)	0.98	0.97–1.00	0.016			
Active cancer without metastasis	1.72	1.01–2.94	0.046	0.93	0.46–1.89	0.84
Metastasis	5.16	2.52–10.6	<0.001	5.28	1.86–14.9	0.001

HR, hazard ratio; CI, confidence interval; BMI, body mass index; DM, diabetes mellitus; HT, hypertension; NYHA, New York Heart Association; MI, myocardial infarction; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; AF, atrial fibrillation; AFL, atrial flutter; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration ratio; LVEF, left ventricular ejection fraction.

4. Discussion

The present study investigated the prognosis of patients with cancer undergoing TAVI; 5.6% of consecutive patients undergoing TAVI had active malignancy. TAVI was safely performed despite malignancy. Distant metastasis was associated with patient prognosis after TAVI; in contrast, malignant tumor without distant metastasis did not affect patient prognosis.

4.1. Candidates of TAVI and active cancer

TAVI is becoming more common, and most candidates for this procedure are adults aged ≥70 years [4]. Aging is a major risk factor for several malignancies, and thus it is likely that the number of TAVI candidates with a concurrent malignancy will increase over time. Present guidelines recommend that patients have life expectancy of >1 year to qualify for TAVI [15]. Malignant tumors significantly restrict life expectancy, and are thus among the exclusion criteria in clinical trials [2]. Evidence on mid- or long-term prognosis of cancer patients undergoing TAVI is limited. Previous observational studies reported that 2.9–6.3% of patients undergoing TAVI had concurrent active malignant tumors [5,6,8,9]; the present study estimate was 5.6%. Previous studies have shown that patients undergoing TAVI had prostate, breast, hematological, and colon cancer diagnoses [5–9]. In the present study, the colon (n = 11, 18%), breast (n = 11, 18%), and stomach (n = 11, 18%) were the primary sites of comorbid cancer.

4.2. AS therapy and active cancer

Patients with active cancer may develop vascular fragility, which may be caused by anti-cancer drugs or radiation therapy [16]. Active cancer is found to be a bleeding risk in an antithrombotic therapy, and aspirin monotherapy may be preferable post-TAVI [17]. In addition, the immune system function may be reduced by anti-cancer treatment, the malignancy itself, or cardiopulmonary bypass used in SAVR [18–20]. Louis et al. reported that cardiac surgery in patients with leukemia was associated with a high incidence of infection, blood transfusion, and long-term hospitalization [19]. In addition, Armin et al. reported that cardiopulmonary bypass induced tumor necrosis factor-α and interleukin-10 production, which may trigger abnormal immune responses [20].

Recovery from cardiac surgery may delay cancer treatment. One of the advantages of TAVI is its minimal invasiveness. Mangner et al. and Landes et al. reported that periprocedural mortality and major complication rates were equivalent in patients with and without active cancer [6,7]. In the present study, there was no between-group difference in 30-day complication rates. The presence of cancer did not affect the duration of hospitalization after TAVI. TAVI does not require a median

sternotomy or a cardiopulmonary bypass, and may be performed under local anesthesia, which reduces the overall time required to complete the procedure, benefiting patients with malignant tumors.

The European Society of Cardiology position paper on cancer treatment and cardiovascular toxicity states that drugs used in chemotherapy should be reduced, modified, or discontinued in patients with cardiac dysfunction and heart failure due to drug cardiotoxicity [21]. Severe AS may disrupt chemotherapy in patients with malignant tumors. The guidelines recommend that symptomatic severe AS be treated ahead of elective non-cardiac surgery [15]; however, malignant tumors are among the leading causes of declining rates of SAVR in patients with severe AS [22,23]. Considering the safety and short recovery time associated with TAVI, this approach may be suitable for older adults with severe AS and malignancies. In the present study, approximately half the patients receiving radical therapies were treated after undergoing TAVI. TAVI had played a role as a bridge to definite therapy of active cancer.

4.3. Prognosis after TAVI

It remains under discussion whether active cancer affects patient prognosis after TAVI [5–9]. This controversy may be due to the differences in cancer type and definitions used in different studies. In the present study, cancer metastasis was associated with mid-term prognosis after TAVI; meanwhile, active cancer without metastasis was not associated with patient prognosis. Effective prognostication is paramount in patients with cancer metastasis. Previous studies have shown that patients with metastasis may not be eligible for TAVI [7,23]; however, prognostic inaccuracies were present in these studies [23]. For patients with life expectancy of approximately 1 year, the risk-benefit analysis should be carefully performed. In the present study, TAVI was performed in patients with cancer metastasis and life expectancy of >1 year. Among the nine patients with cancer metastasis undergoing radical treatment, only one (11%) patient died during the follow-up period. TAVI could be a possible treatment option even in patients with metastasis; multidisciplinary management by oncology and cardiovascular experts is recommended for such cases. If the life expectancy is undetermined or less than 1 year, balloon aortic valvuloplasty is a viable option as a bridge to definitive therapy or a palliative procedure [24].

5. Limitations

This study has some limitations that should be considered when interpreting its findings. Specifically, the number of patients with active malignancy and the follow-up period were limited. The respective outcome in different active cancer and prognostic factors of cancer patients could not be analyzed. Our results should be carefully generalized in a different setting. Because of the nature of observational study, there are possible random errors including referral bias.

6. Conclusions

In summary, in the present study, active malignancies were recognized in 5.6% of the patients undergoing TAVI. TAVI was safely performed; cancer treatment was subsequently administered, as required. Cancer metastasis was negatively associated with mid-term survival; active malignancy without metastasis did not affect survival. A multidisciplinary management including the oncologist and cardiovascular experts should be needed for optimal therapeutic decision making in patients with active cancer.

Declaration of Competing Interest

Dr Takamisawa is a clinical proctor of Edwards Lifesciences and Medtroic. The other authors have no conflict of interest regarding this article.

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Author contributions

All authors contributed to the study conception and design. Data analysis was performed by Yoshimasa Kojima. The first draft of the manuscript was written by Yoshimasa Kojima and Ryosuke Higuchi, and all authors commented on the manuscript. All authors read and approved the final manuscript.

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