Prognosis of Cancer Patients with Aortic Stenosis Under Optimal Cancer Therapies and Conservative Cardiac Treatments

A Single Cancer Center Study with 92 Consecutive Patients

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Summary

Aortic stenosis (AS) is a life-threatening comorbidity of cancer patients. Aortic valve replacement (AVR) should be considered for some cancer patients, but neither the characteristics nor prognosis under conservative therapy is well known.

We searched our echocardiography log (years 2005-2014) for cancer patients with AS, and 92 patients (54% female) were included in the study. To compare the survival curves, 470 control patients without AS were selected from our cancer registry.

Mean age ($\pm$ SD) was 77.6 ± 6.7 years for males and 81.6 ± 6.3 years for females. Mean aortic valve area (AVA) was 1.0 ± 0.3 cm². Stomach, blood, and urinary bladder cancers were the major sites of current cancer. During the 5-year follow-up period, 44 patients with AS (48%) died; 26 (59%) due to cancer progression, 10 (23%) heart failure, and 4 (9%) stroke. Heart-failure death was significantly higher for patients with AS than for control patients ($P < 0.001$). Kaplan-Meier survival estimates were worse for stage I or II patients with AVA < 0.75 cm² than for control patients ($P = 0.016$). Older age, advanced stages, absence of dyslipidemia, recent syncope, and chronic heart failure or AVA < 0.75 cm² were significantly and independently associated with poor survival.

Although the majority of cancer patients with AS died of cancer, a quarter died of heart failure. Careful follow-up is needed because cancer patients at earlier stages with symptomatic AS or AVA < 0.75 cm² should be considered for AVR.

(Int Heart J 2018; 59: 750-758)

Key words: Prognosis, Cardio-oncology, Cancer stage

Cancer and cardiovascular disease are the two major causes of death in developed countries.¹⁻³⁾ Aging, smoking, diabetes, obesity, and physical inactivity are risk factors for both cancer and cardiovascular disease.²⁻⁴⁾ Therefore, cancer patients often have cardiovascular comorbidities, and patients with cardiovascular diseases often have cancer.

Aortic stenosis (AS) is the most common valvular heart disease in the elderly population. Aortic valves that are calcified, thickened, and have reduced openings are often observed in adults of advanced age (2-12% of the population > 65 years old).^{5,6)} Severe AS is common among the elderly; the prevalence was reported to be 3%.⁷⁾ AS is occasionally diagnosed in cancer patients undergoing treatment.

Cancer patients with AS are generally elderly, and

their prognosis is limited.^{8,9)} Aortic valve replacement (AVR) is currently the only treatment that effectively improves survival in non-cancer patients with AS;⁵⁻¹¹⁾ this procedure, however, may not be beneficial for cancer patients with AS, because the life expectancy of a patient with advanced cancer may already be too short to justify treatment of AS.^{8,9)}

The appropriate application of AVR to AS patients with cancer is important for both patients and healthcare practitioners because the benefit to patients and limited medical resources must be balanced. Prognosis and prognostic factors of patients with AS and cancer are necessary for choosing an appropriate therapy, e.g., whether AS or cancer should be treated first and which cancer therapy should be attempted (surgery, chemotherapy, or radiation therapy). However, there are few reports about patients

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Received for publication June 11, 2017. Revised and accepted October 25, 2017.

Released in advance online on J-STAGE June 6, 2018.

doi: 10.1536/ihj.17-320

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with both AS and cancer. Cancer stages and the severity of AS have never been evaluated collectively. Therefore, to clarify the prognosis and prognostic factors of cancer patients with AS, we conducted a retrospective study at our cancer center hospital.

Methods

Patient selection: In our hospital, systemic screening is performed before cancer therapy. All patients in our hospital go through a physical examination, 95% of the patients have electrocardiograms, and 53% of the patients undergo chest radiography. If necessary, cancer patients are referred to cardiologists (Y.O., T.T., K.O.), and 23% of the patients undergo transthoracic echocardiography. We searched our echocardiography log for cancer patients with AS between 2005 and 2014, and 92 patients (54% female) were included in the study. To compare the survival curves, 470 control patients without AS were selected from our cancer registry. AS was defined through two-dimensional imaging as thickened leaflets with reduced systolic opening associated with an increased velocity across the aortic valve (> 3.0 m per second) or a mean gradient > 25 mmHg, or an aortic valve area (AVA) < 1.5 cm². Moderate to severe aortic regurgitation was excluded.

Review of patients: All medical records of the selected patients were reviewed, and their clinical data were collected and summarized according to a predetermined protocol. If a patient had echocardiography recorded multiple times, only the record just before cancer therapy was chosen. For patients who underwent noncontrast chest computed tomography (CT) for cancer diagnosis, calcifications of the aortic valve were evaluated. The number of slices with valve calcification was counted in every 5 mm of slice thickness in the transverse plane.

Outcome measures: Our hospital maintains a cancer registry and regularly updates clinical information and the vital status of patients. The date of initial diagnosis, clinical stage at diagnosis, date of operation, and date of death were obtained from the registry. Date of AS diagnosis was obtained from medical records. The total number of cancer patients in our hospital during the research period was obtained from the hospital registry.

Control patient selection: To clarify the influence of AS on the survival of cancer patients, survival curves from the date of cancer therapy were compared between cancer patients with AS and their controls without AS. The choice of controls was made by cancer registrars (C.F. and T.S.) who did not know the purpose of this study. Registrars strictly followed a predefined protocol. Five control cancer patients without AS were selected for each cancer patient with AS, matched for age, gender, date of underlying cancer diagnosis, clinical stage of underlying cancer, histology, and therapy. Almost all patients had a physical examination and an electrocardiogram. To ensure that the control patients did not have AS, we checked echocardiography reports and chest CT, if available. We excluded any case for which the aortic valve had calcification in more than two slices in CT.

Statistical analysis: To estimate the approximate prevalence of AS, the proportion of AS in each gender and age

group was calculated using the following equation:

Number of cancer patients with AS/Total number of cancer patients $\times 100$ (%).

Baseline data were compared between the AVA < 0.75 cm² group and AVA ≥ 0.75 cm² group. Preliminarily, we stratified cancer patients with AS by quartiles of AVA: quartile 1, 0.42-0.74 cm²; quartile 2, 0.80-1.03 cm²; quartile 3, 1.09-1.25 cm²; quartile 4, 1.26-1.54 cm². Survival of quartile 1 was shorter than that of quartile 2 ($P = 0.003$), quartile 3 ($P = 0.101$), and quartile 4 ($P = 0.067$). Therefore, for the subsequent analyses we stratified the patients into a group with AVA < 0.75 cm² (quartile 1) and a group with AVA ≥ 0.75 cm² (quartiles 2, 3, and 4). Categorical variables are presented as numbers and percentages. Comparison of proportions was made by χ^2 or Fischer's exact test. Continuous variables are presented as the mean $\pm$ SD and were compared by Student's *t*-test or the Wilcoxon rank sum test. A two-tailed significance level of 0.05 was used. A Cox proportionate hazard regression model was used to identify the prognostic predictors of death. Simple univariate analysis was done first for each of the input variables against positive death outcome, and all the variables associated with it at $P \leq 0.1$ were then included in a multivariate forward stepwise Cox regression model. Data were analyzed with IBM SPSS statistics Version 23.0.

Ethical considerations: The study protocol was reviewed and approved by the Ethics Committee of Niigata Cancer Center.

Results

Characteristics of cancer patients with AS:

Demographic characteristics We identified 111 patients with AS from among 26,235 patients with cancer. Among these 111 patients, 15 were excluded because AS was diagnosed several years after completion of cancer therapy. Three patients who underwent AVR before cancer therapy owing to decompensated heart failure were also excluded. We excluded one female patient who had changed therapy from a conservative one to AVR. Ultimately, 92 cancer patients with AS diagnosed just before cancer therapy were included in the study. The majority (54%) were females (Table I), who were significantly older than the males (81.6 ± 6.3 versus 77.6 ± 6.7 years; $P = 0.006$).

Proportion of AS patients among cancer patients in relation to age and gender The proportion of AS patients among cancer patients ≥ 60 years old was 0.4% for males and 0.7% for females (Figure 1). This proportion increased sharply after the age of 80 years for females, reaching 2.2% for patients in their 80s.

Sites of current cancers and stages Stomach, blood, and urinary bladder cancers were the major sites of current cancer (Supplementary Table). Stomach, urinary bladder, and lung cancers were dominant in males, and breast, skin, blood, and stomach cancers were dominant in females (data not shown). Breast cancer was dominant in AS with AVA < 0.75 cm² than in AS with AVA ≥ 0.75 cm² ($P = 0.049$). Cancers were assessed with the TNM staging system and a stage of I, II, III, or IV was assigned. The number of patients with stage I, II, III, and

Table I. Comparison of Baseline Clinical Characteristics versus Aortic Valve Areas

	All patients with AS (n = 92)	AVA < 0.75 cm ² (n = 24)	AVA ≥ 0.75 cm ² (n = 68)	P
Age (years)	79.8 ± 6.8	79.7 ± 6.3	79.8 ± 7.0	0.802
Male gender	42 (45.7)	8 (33.3)	34 (50.0)	0.159
Height (cm)	152.4 ± 10.3	149.7 ± 12.8	153.5 ± 9.2	0.117
Weight (kg)	53.4 ± 11.1	50.5 ± 10.5	54.4 ± 11.2	0.144
BMI (kg/m ²)	22.9 ± 3.6	22.4 ± 2.7	23.1 ± 3.9	0.519
Systolic blood pressure (mmHg)	130.4 ± 20.7	129.9 ± 21.0	130.6 ± 20.7	0.887
Diastolic blood pressure (mmHg)	70.5 ± 11.2	68.6 ± 11.3	71.2 ± 11.2	0.322
Heart rate (/minute)	73.7 ± 13.3	74.7 ± 16.0	73.3 ± 12.2	0.923
Past history of cancer	39 (42.4)	8 (33.3)	31 (45.6)	0.218
Past history of cancer therapies				
Surgery	26 (28.3)	7 (29.2)	19 (27.9)	0.909
Chemotherapy	18 (19.6)	5 (20.8)	13 (19.1)	0.583
Radiation therapy	17 (18.5)	3 (12.5)	14 (20.6)	0.292
Current cancer	92 (100)	24 (100)	68 (100)	
I	32 (34.8)	5 (20.8)	27 (39.7)	0.095
II	11 (12.0)	4 (16.7)	7 (10.3)	0.310
III	17 (18.5)	4 (16.7)	13 (19.1)	0.529
IV	18 (19.6)	5 (20.8)	13 (19.1)	0.535
Not staged	14 (15.2)	6 (25.0)	8 (11.8)	0.121
Therapies for current cancer				
Surgery	59 (64.1)	14 (58.3)	45 (66.2)	0.491
Chemotherapy	23 (25.0)	8 (33.3)	15 (22.1)	0.344
Radiation therapy	15 (16.3)	4 (16.7)	11 (16.2)	0.591
Supportive care	10 (10.9)	2 (8.3)	8 (11.8)	0.487
Comorbidities				
Hypertension*	78 (84.8)	21 (87.5)	57 (83.8)	0.475
Diabetes mellitus†	30 (32.6)	8 (33.3)	22 (32.4)	0.930
Dyslipidemia‡	38 (41.3)	8 (33.3)	30 (44.1)	0.356
Atrial fibrillation§	17 (18.5)	4 (16.7)	13 (19.1)	0.529
Ischemic heart disease or angina¶	27 (29.3)	4 (16.7)	23 (33.8)	0.090
Chronic heart failure	24 (26.1)	11 (45.8)	13 (19.1)	0.010
Cerebrovascular disease**	25 (27.2)	8 (33.3)	17 (25.0)	0.430
Creatinine level > 2 mg/dL	7 (7.6)	2 (8.3)	5 (7.4)	0.589
Chronic obstructive pulmonary disease††	10 (10.9)	2 (8.3)	8 (11.8)	0.487
Liver cirrhosis‡‡	5 (5.4)	3 (12.5)	2 (2.9)	0.109
Osteoporosis§§	14 (15.2)	6 (25.0)	8 (11.8)	0.121
Recent syncope	6 (6.5)	2 (8.3)	4 (5.9)	0.496
Smoker (past or present)##	36 (39.1)	9 (37.5)	27 (39.7)	0.849
Laboratory data				
Total protein (g/dL)	7.0 ± 0.7	6.9 ± 0.6	7.0 ± 0.7	0.354
Albumin (g/dL)	3.7 ± 0.6	3.6 ± 0.7	3.7 ± 0.6	0.662
Total bilirubin (mg/dL)	0.9 ± 1.5	0.9 ± 0.6	0.9 ± 1.7	0.144
Hemoglobin (g/dL)	11.7 ± 2.0	11.2 ± 2.1	11.9 ± 2.0	0.108
Creatinine (mg/dL)	0.9 ± 0.3	0.9 ± 0.4	0.9 ± 0.3	0.982
Total cholesterol (mg/dL)	178.3 ± 33.7	168.2 ± 29.4	182.1 ± 34.7	0.080
LDL-cholesterol (mg/dL)	106.5 ± 23.1	98.4 ± 23.4	110.0 ± 22.5	0.115
Echocardiographic data				
Left atrial dimension (cm)	4.2 ± 0.8	4.2 ± 0.9	4.2 ± 0.8	0.926
Left ventricular diastolic dimension (cm)	4.6 ± 0.6	4.5 ± 0.6	4.7 ± 0.6	0.337
Interventricular septal thickness (cm)	1.1 ± 0.3	1.2 ± 0.3	1.1 ± 0.2	0.309
Posterior wall thickness (cm)	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2	0.520
Ejection fraction (%)	68.3 ± 9.4	69.2 ± 7.3	68.1 ± 10.1	0.957
E/e'	11.2 ± 4.4	12.5 ± 3.6	10.8 ± 4.6	0.040
Aortic valve area (cm ²)	1.0 ± 0.3	0.6 ± 0.1	1.2 ± 0.2	< 0.001
Max velocity (m/second)	3.0 ± 0.9	3.8 ± 0.8	2.7 ± 0.7	< 0.001
Max pressure gradient (mmHg)	39.3 ± 23.2	59.4 ± 28.2	31.6 ± 15.2	< 0.001
Mean pressure gradient (mmHg)	23.5 ± 16.2	37.8 ± 19.5	17.8 ± 10.3	< 0.001
Patients with calcified aortic valve on CT	69 (75.0)	19 (79.2)	50 (73.5)	0.400
Number of slices	3.3 ± 1.6	3.6 ± 1.8	3.3 ± 1.5	0.220

Values are mean ± SD or number of subjects and percentage. *P* value indicates difference in aforementioned variable between subjects with AVA < 0.75 cm² and those with AVA ≥ 0.75 cm². *Arterial blood pressure ≥ 140/90 mmHg or drug therapy. †Hemoglobin A1c ≥ 6.1% or drug therapy. ‡LDL cholesterol > 140 mg/dL or drug therapy. §Documented diagnosis by electrocardiography. ¶Diagnosis by cardiologists. **Diagnosis by neurologists with computed tomography or magnetic resonance imaging. ††Documented diagnosis with spirogram and images. ‡‡Documented diagnosis. §§Documented diagnosis or drug therapy. ##Self-reported.

Figure 1. The proportion of cancer patients with AS in different age groups. The number shown at the upper end of each bar represents the AS patient count, and the numbers below each age range along the horizontal axis represent the male and female cancer patients for that range.

IV were 32 (35%), 11 (12%), 17 (19%), and 18 (20%), respectively (Table I). Fourteen patients (15%) were not staged because of leukemia, lymphoma, sarcoma, unspecified primary sites, or other reasons.

Past history of cancer and cancer therapies Thirty-nine patients had past histories of cancer (Table I). Among the patients with AS, 28% had surgery, 20% had chemotherapy, and 19% had radiation therapy. Stomach and breast cancer were the major sites among all patients (Supplementary Table). Stomach, colon/rectum, and blood cancers were dominant in males, and breast and stomach cancers were dominant in females (data not shown).

Associated comorbidities Documented present or past histories of comorbidities are shown in Table 1. Hypertension, diabetes, and dyslipidemia were prevalent comorbidities (85%, 33%, and 41%, respectively). Chronic heart failure was more dominant in AS with AVA < 0.75 cm² than in AS with AVA ≥ 0.75 cm² (P = 0.010). Gender differences are not listed in the Tables; ischemic heart disease and chronic heart failure were more common in males (48% and 38%, respectively) than in females (14% and 18%, respectively). Notably, a history of smoking was substantially more prevalent in males (79%). Cerebrovascular diseases were common in both males (26%) and females (29%).

Echocardiographic data Mean AVA was 1.0 ± 0.3 cm² in all cancer patients with AS (Table I). A slightly thickened left ventricular (LV) wall, enlarged left atrium (LA), and elevated E/e' were often observed. E/e' was significantly larger in the AVA < 0.75 cm² group than in the AVA ≥ 0.75 cm² group (P = 0.040). In almost all patients, LV ejection fraction (EF) was preserved, and no significant difference was observed between two groups.

Calcification of the aortic valve in CT Among the 92 patients, 69 (75%) underwent chest CT for cancer diagnosis (Table I). All patients showed calcification of the aortic valve over several slices in 5-mm intervals.

Therapies for concurrent cancer with AS: Of the 92 patients, 59 (64%) had surgery, 23 (25%) had chemotherapy, and 15 (16%) had radiation therapy in addition to chemotherapy (Table I). Ten patients (11%) had supportive care but no therapeutic care. All patients had conservative therapy for AS.

Characteristics of controls: Five controls without AS were usually selected for each cancer patient with AS. In some cases, 4 or 6 controls without AS for each patient were selected. In the end, there were 470 patients who served as controls. Age (79.0 ± 6.3 years), male gender (46%), height (153.8 ± 9.2 cm), body weight (51.6 ± 9.8 kg), and hemoglobin (12.0 ± 2.2 g/dL) of the control patients were not significantly different from those of AS cases. Echocardiography was performed in 192 control patients (41%) and no AS was detected. LV and LA geometry was within normal limits (LV diastolic dimension 4.6 ± 0.6 cm, LA dimension 3.8 ± 0.8 cm, interventricular septal thickness 1.0 ± 0.2 cm, posterior wall thickness 1.0 ± 0.2 cm). Functionally, LVEF was 71.1 ± 9.2 % and E/e' was 8.9 ± 3.3. Among the 470 control cases, 331 (70%) underwent chest CT. The mean number of slices showing calcification of the aortic valve was 0.4 ± 0.7 in the control group, which was significantly less than in AS patients (P < 0.001). There were 74 control cases (16%) who had neither chest CT nor echocardiography.

Survival outcomes:

All patients and controls Forty-four patients with AS (48%) died during the 5-year follow-up period. The cause

Figure 2. Proportion of cause of death stratified by cancer stages and quartiles of AVA. The number shown in each bar represents the proportion (%) of each cause (pink, heart failure or sudden cardiac death; green, cancer; blue, stroke; and yellow, pneumonia or respiratory failure). AVA quartile 1 represents AVA < 0.75 cm², and quartiles 2-4 represent AVA 0.80-1.54 cm².

of death was established for all patients. The cause of death was attributed to cancer progression in 26 (59%), heart failure in 10 (23%) (2 due to cardiac sudden death), stroke in 4 (9%), pneumonia in 3 (8%), and respiratory failure in 1 (3%). Of the 10 heart failure deaths, 6 occurred in cancer patients with severe AS (AVA < 0.75 cm²). Among the cancer patients without AS (matched controls, $n = 470$), 213 deaths (45%) occurred during the 5-year follow-up: 179 (84%) were attributed to cancer progression and only 6 (3%) to cardiovascular issues. Heart failure-attributable death was significantly greater for patients with AS than for control patients without AS ($P < 0.001$). Figure 2 shows the proportions of causes of death stratified by cancer stage and quartile of AVA. Heart failure deaths were dominant in the stage I and II group, especially in AVA quartile 1. However, cancer death was dominant in the stage III and IV group, regardless of quartile.

The survival curves of cancer patients with AS and without AS (matched controls) are shown in Figure 3. The probability of overall survival was similar for cancer patients with AS and their matched controls ($P = 0.175$; Figure 3A). Cancer patients with AVA ≥ 0.75 cm² had survival similar to their matched controls ($P = 0.944$); however, cancer patients with AVA < 0.75 cm² had significantly worse prognoses than their matched controls ($P = 0.014$; Figure 3B).

Stage I or II, stage III or IV patients, and controls Stage I or II cancer patients with AVA ≥ 0.75 cm² had survival similar to their matched controls ($P = 0.392$); however, patients with AVA < 0.75 cm² had significantly worse prognoses than their matched controls ($P = 0.016$; Figure 3C). For patients with stage III or IV cancer, survival of

those with AVA < 0.75 cm² or those with AVA ≥ 0.75 cm² did not differ significantly from that of their controls (Figure 3D).

Patients and controls in their respective treatment groups

All cancer patients with AS underwent surgery, chemotherapy, radiation therapy, or supportive therapy for their cancer. Because AS increases perioperative risk, the surgeons, anesthesiologists, and cardiologists examined cancer patients with AS and discussed the indication and risk before surgery. For cancer patients who underwent surgery, the probability of overall survival was similar for cancer patients with AS and their matched controls ($P = 0.997$, data not shown); however, cancer patients with AVA < 0.75 cm² had significantly worse prognoses than their matched controls ($P = 0.039$; Figure 3E). For cancer patients who did not undergo surgery but had chemotherapy with or without radiation therapy, the probability of overall survival was similar for cancer patients with AS and their matched controls ($P = 0.462$, data not shown), and the survival of those with AVA < 0.75 cm² or AVA ≥ 0.75 cm² did not differ significantly from that of their controls (Figure 3F). Among cancer patients who did not undergo any therapeutic care but only had supportive care, cancer patients with AS had significantly worse prognoses than their matched controls ($P = 0.005$, data not shown); however, the subgroups in AVA were too small for reliable analysis.

Predictors of mortality: Older age at diagnosis, recent syncope, chronic heart failure, and AVA < 0.75 cm² were significantly associated with death; stage I or II, dyslipidemia, and relatively large AVA were inversely significantly associated with death (Table II). Owing to the high correlation between chronic heart failure and smaller AVA,

Figure 3. Kaplan-Meier estimates of overall survival in cancer patients with AS or without AS (matched controls). **A:** All cancer patients with AS and matched controls. **B:** All cancer patients with AS by AVA (1 and 3) and matched controls (2 and 4). **C:** Stage I or II cancer patients with AS by AVA (1 and 3) and matched controls (2 and 4). **D:** Stage III or IV cancer patients with AS by AVA (1 and 3) and matched controls (2 and 4). **E:** Cancer patients with AS (1 and 3) and matched controls (2 and 4) who underwent surgery for current cancer by AVA. **F:** Cancer patients with AS (1 and 3) and matched controls (2 and 4) who underwent chemotherapy or radiation therapy for current cancer by AVA.

these two pairs of variables were entered into the model as interaction terms (chronic heart failure or AVA < 0.75 cm²) to avoid collinearity. Ultimately, older age at diagnosis, advanced cancer stage, absence of dyslipidemia, recent syncope, and chronic heart failure or AVA < 0.75 cm² were significantly and independently associated with poor survival (Table II).

Hazard ratios for survival were calculated in the Cox proportionate hazard regression model. Eight subgroups were made from each AVA quartile and cancer stages I-II and III-IV. Each subgroup included AS patients and their matched controls. Hazard ratios of the presence of AS are presented in Table III. In the stage I-II cancer group, the hazard ratio of the presence of quartile 1 AS was 3.04

Table II. Variables Independently Associated with Mortality

	Univariate analysis			Multivariate analysis		
	HR	95% CI of HR	P	HR	95% CI of HR	P
Age (per 1 year increase)	1.05	1.00-1.11	0.032	1.07	1.01-1.13	0.014
Stage I or II	0.27	0.14-0.54	0.001	0.19	0.10-0.41	0.001
Dyslipidemia	0.52	0.27-0.99	0.045	0.44	0.22-0.89	0.021
Recent syncope	3.88	1.61-9.34	0.003	4.48	1.74-11.59	0.002
Chronic heart failure	2.31	1.23-4.35	0.009			
Aortic valve area (per 1 cm ² increase)	0.33	0.12-0.93	0.037			
Aortic valve area < 0.75 cm ²	2.22	1.22-4.04	0.009			
Chronic heart failure or aortic valve area < 0.75 cm ²	2.02	1.11-3.68	0.021	1.94	1.05-3.57	0.033

HR indicates hazard ratio; and CI, confidence interval.

Table III. Hazard Ratio of AS Presence for Mortality in Each Subgroup

Subgroups Cancer stages/AVA quartiles	Univariate analysis		P
	HR	95% CI of HR	
I-II			
1	3.04	1.18-7.84	0.021
2	1.49	0.50-4.43	0.477
3	0.31	0.04-2.32	0.255
4	0.35	0.05-2.57	0.299
III-IV			
1	1.44	0.59-3.50	0.421
2	0.88	0.11-7.24	0.907
3	1.23	0.50-5.44	0.520
4	0.82	0.40-1.68	0.587

AVA indicates aortic valve area; HR, hazard ratio; and CI, confidence interval. quartile 1, 0.42-0.74 cm²; quartile 2, 0.80-1.03 cm²; quartile 3, 1.09-1.25 cm²; quartile 4, 1.26-1.54 cm².

(95% CI 1.18-7.84, $P = 0.021$). However, for the other 7 subgroups, the presence of AS was not a significant predictor of poor survival.

Discussion

AS is the most common valvular heart disease in the elderly population.^{8,9} AVR is currently the only treatment for improvement of survival in non-cancer patients with AS.⁵ However, the majority of patients with severe AS do not undergo AVR. Bach, *et al* pointed out that many patients are not referred for surgical consultation despite being good candidates who are likely to benefit from AVR.^{10,11}

AS is also the most common valvular heart disease in cancer patients undergoing cancer treatment. Cancer patients with AS are generally elderly.^{8,9} Cancer treatment teams are often reluctant to recommend AVR to cancer patients with AS because of its invasiveness and the limited life expectancy of such patients. Cancer patients often decline immediate AVR for 3 reasons: they do not have symptoms of AS, AVR is a second priority after cancer therapy, or patients are of advanced age or frailty. Therefore, some cancer patients with AS might have been inappropriately denied access to AVR, which is a potentially life-saving therapy.

Recently, both the invasiveness of AVR and life expectancy with cancer have been improved.^{3,12} Transcatheter AVR (TAVR) has been rapidly established as the treat-

ment choice for AS patients with prohibitive conditions for surgical AVR (SAVR) because it is less invasive than SAVR.^{7,9} Furthermore, patients with earlier-stage cancers have better chances of survival that are similar to those for other chronic diseases.³ Thus, cancer patients should be considered for AVR and, therefore, it is important to clarify their prognosis and prognostic factors. However, AS associated with cancer is rare, and the characteristics of these patients and their prognoses are seldom reported.^{8,9}

Our Japanese cohort was older and had a higher proportion of females than the US cohort reported by Yusuf, *et al*.⁸ The high prevalence of hypertension, diabetes, dyslipidemia, ischemic heart disease, and heart failure in our cohort was consistent with those features of the US cohort. The high prevalence of these comorbidities was also observed in the Japanese registries OCEAN TAVI (AS associated with cancer, $n = 47$)⁹ and CURRENT AS (AS, $n = 1517$);¹³ however, the prevalence of these comorbidities was highest in our cohort. Although a precise comparison between these reports is not feasible because of the different methods of assessment, an elderly cohort with both cancer and AS, such as our cohort, may have a high prevalence of comorbidities. Common risk factors between cancer and atherosclerosis such as aging, smoking, dyslipidemia, and diabetes may have an important role in the accumulation of comorbidities in cancer patients with AS.^{3,5,14} A history of cancer therapy may partially cause progression of aortic valve sclerosis.^{15,16}

The prevalence of AS in the Asian population has never been reported. Hospital-based studies and registries have not reported their origins of population and numbers of patients in background.^{9,13,15} Therefore, we have never even speculated on the prevalence of AS. The prevalence in our study, i.e., 0.4% for males and 0.7% for females in cancer patients over 60 years old, was less than 3% of that of the general population in the United States.⁷ A comparison is not feasible because of the different methods of assessment. Not all cancer patients underwent echocardiography. Our prevalence did not calculate from total enumeration, therefore, it depended on the frequency of echocardiography. Among control patients (age 78.9 ± 6.3 ; the elderly population matched with our 92 AS patients), 41% of cancer patients underwent echocardiography. A crude estimate of the prevalence can be calculated by dividing the AS prevalence (e.g. 0.4 or 0.7%) by the frequency of echocardiography (e.g. 0.41). Accordingly,

we speculate that the approximate prevalence of AS in the cancer cohort in their late 70s might be 1% for males and 2% for females.

Our study revealed that patients with advanced stages of cancer had poor prognosis regardless of AVA. This was consistent with OCEAN TAVI, in which cancer metastasis was associated with increased mortality despite successful TAVI.⁹⁾ The life expectancy of a patient with advanced cancer was too short for problems associated with AS to manifest. In contrast to patients with advanced-stage cancers, early-stage patients with AVA < 0.75 cm² had significantly worse prognoses than their matched controls. AVA < 0.75 cm² has been reported to be a critical threshold for prognosis in non-cancer populations;¹⁷⁻²⁰⁾ we confirmed that this threshold is also critical in our cancer population.

Our results indicate that early-stage cancer patients may benefit from AVR. Oncologists at certain cancer centers often avoid prescribing SAVR immediately after cancer therapy. Cancer patients usually recover from therapy-associated disabilities and manage to adapt to post-treatment conditions;²¹⁻²³⁾ therefore, they are often unwilling to undergo SAVR in succession. However, the majority of our stage I patients did not reach the average life expectancy, and our prognostic factors coincided with those reported in the literature.²⁴⁻²⁶⁾ Therefore, we conclude that severe AS has a negative influence on prognosis, especially for our early-stage cancer patients, and thus AVR should be considered immediately after cancer therapy.

Our data reveal that cancer patients with AS who had high LDL-cholesterol or drug therapy had better survival. Most patients with dyslipidemia had taken statins. Nielsen, *et al* reported that statin use reduced cancer-related mortality in a large observational study.²⁷⁾ The favorable effects of statins for both cancer immunity and atherosclerosis might explain the benefit on survival of cancer patients with AS. However, selection biases such as healthy-user bias (patients who are expected to live a long time are preferably prescribed statins for prevention of cardiovascular events in the future) and survivor bias (patients who had taken statins are survivors of cardiovascular disease and have the potential to survive) also might have caused the benefit seen in our observational study.²⁸⁾ Therefore, our data do not prove the therapeutic benefit of statins for cancer patients with AS.

The present study has several limitations. First, the study was a retrospective and observational study.²⁹⁾ A prospective study is preferable for the precise assessment of AS burden on cancer patients. Second, we did compare cancer patients with AS and their matched controls without AS, but we could not compare cancer patients with AS according to AVA in each cancer. Therefore, we could not specify to which cancer type and stage our results applied. Third, selection bias by physicians exists. Cancer patients in the terminal stage may not have been recommended to undergo echocardiography and thus may have been inadvertently excluded from this study. In contrast, cancer patients at earlier stages were more likely to have undergone echocardiography and to have been included in this study. Fourth, the existence of AS may not have been completely excluded from the control group because echo-

cardiography was not conducted for all control cases. Instead, we evaluated chest CT and excluded AS by our own calcification scale. Chest CT has been reported to be highly sensitive for detection of AS.³⁰⁾ Eighty-four percent of control patients had undergone either echocardiography or chest CT. Furthermore, all patients had medical evaluations before cancer treatment. We believe that the existence of AS in the control group is unlikely. Fifth, the cause of death was based on that reported on the death certificate. Causes of death that were related to cancer and those that were not could not be consistently distinguished with high accuracy. Similarly, heart failures related to AS and those that were not might not have been distinguished properly. However, we had no way to judge the cause of death except by relying on information provided by the doctors who cared for the dying patients, and thus we believe that our method was fair.

We herein reported AS with cancer in our cancer center hospital. The patients were generally elderly and had frequent past histories of cancer and high comorbidities of atherosclerotic, cerebrovascular, and cardiovascular disease. Cancer patients at earlier stages may, on average, have shorter survival because they are generally not recommended for AVR. Careful follow-up is needed because symptomatic AS or AVA < 0.75 cm² were significantly and independently associated with death. Cancer care teams, cardiologists, surgeons, and patients and their families should be aware of the severity of AS and consider AVR if appropriate.

Acknowledgments

We thank Dr. Yoshinobu Okada for treating some of the cancer patients with AS, and Yoko Adachi, Emi Hasegawa, Keiko Henmi, Kumiko Kikuchi, Noriko Minabe, and Yukiko Suzuki for performing echocardiography for the cancer patients.

Disclosures

Conflicts of interest: The authors have read and understood the journal policy on the declaration of interests and have no relevant personal interests to declare.

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Supplemental Files

Supplemental Table

Please see supplemental files: <https://doi.org/10.1536/ihj.17-320>