Malignant Disease as a Comorbidity in Patients with Severe Aortic Stenosis: Clinical Presentation, Outcomes, and Management

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Abstract

Aim: To investigate the effect of malignancy on the outcomes of patients with severe aortic stenosis (AS) and the management strategy for AS with malignancy.

Methods: Using data of 3815 patients with severe AS in a retrospective multicenter registry (CURRENT AS registry), we compared 3-year clinical outcomes among three groups based on malignancy status: with malignancy currently under treatment including best supportive care (malignancy group), with a history of malignancy without any current treatment (past history group), or without history of malignancy (no malignancy group).

Results: Patients in the malignancy group (N=124) were more often men and had higher prevalence of low body mass index, recurrence of malignancy, anemia, and asymptomatic status, despite comparable surgical risks and echocardiographic parameters. The malignancy group or the past history group (N=389) had significantly higher risk for all cause death (HR: 2.49, 95%CI: 1.98-3.14; HR: 1.23, 95%CI: 1.04-1.46) and for malignancy-related death (HR: 16.2, 95%CI: 10.64-24.54; HR: 3.66, 95%CI: 2.43-5.52) than the no malignancy group (N=3302). The excess risk for aortic valve-related death was not observed in the malignancy group (HR: 0.79, 95%CI: 0.48-1.29) and was lower in the past history group (HR: 0.72, 95%CI: 0.53-0.96). In the malignancy group, the treatment strategy (surgery: N=16, conservative management: N=108) was determined based on the clinical status of AS or life expectancy.

Conclusions: Malignancy had marked effect on all-cause death and malignancy-related death in patients with severe AS. History of malignancy also had a smaller but significant effect on mortality.

(Contemporary Outcomes After Surgery and Medical Treatment in Patients With Severe Aortic Stenosis Registry; UMIN000012140)
https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000014041&language=E

Key words: Aortic stenosis; Malignancy; Cancer; Preoperative complications

Editorials

The prevalence of aortic stenosis (AS) and malignancy are both high in elderly people in developed countries. However, there is limited information on the influence of malignancy on outcomes of patients with severe AS; hence, there is no fixed treatment policy for patients with severe AS and malignancy. Thus, we investigated the effect of malignancy on the outcomes of patients with severe AS. We also investigated the management strategy for AS in patients with active malignancy.

The main findings of this study are as follows: 1) Not only the malignant disease but also history of malignancy has a significant risk for all-cause death and malignancy-related death in patients with severe AS. 2) In patients with active malignancy and severe AS, the main reasons behind selecting aortic valve replacement/transcatheter aortic valve implantation (AVR/TAVI) strategy were the presence of symptoms related to AS, as well as requirement of AVR before non-cardiac surgery, and very severe AS. The common reasons for the choice of conservative treatment strategy were absence of symptoms, limited life expectancy due to diseases unrelated to AS, and refusal for AVR/TAVI. 3) The rates of perioperative complications and mortality for malignancy surgery were low both in patients before or without AVR/TAVI and in patients who underwent AVR/TAVI prior to malignancy surgery. When we consider the treatment choices, the malignancy status is very important for the prognosis in patients with severe AS.

Introduction

With improvements in early detection and treatments for malignancy, patients with malignancy are living longer and more often with complete recovery from malignancy or with malignancy under control. As a result, malignancy is increasingly being recognized as a chronic disease. The growing cohort of survivors that exceeds 10 million was recently reported (1). The incidence of aortic stenosis (AS), which was accompanied with degenerative changes, is also increasing (2). The prevalence of severe AS may be up to 4.6% and 8.1% in people aged 75 or older and aged 85 or older, respectively(2-4). Thus, prolonged life expectancies of patients with malignant disease enabled simultaneous development of AS.

However, information on the influence of malignancy on outcomes of patients with severe AS (5-8) is limited. There have been few opportunities to study this topic because of the exclusion criterion of randomized controlled trial and the benefit from therapy to AS being blunted by malignancy-related death. Recently, we reported an observational registry which enrolled all consecutive patients who met the criteria of severe AS in a multicenter fashion (9-11). The aim of the present study was to investigate the effect of active and inactive malignancies on the outcomes of severe AS. Furthermore, we examined the reasons of the management strategies in patients with AS and malignancy as well as the perioperative complications of patients who underwent surgery for the malignancy.

Methods

Patients

We enrolled 3815 patients with severe AS from 27 centers in Japan between January 2003 and December 2011 in the CURRENT AS (Contemporary outcomes after sURgery and medical tREatmeNT in patients with severe Aortic Stenosis) registry (Supplementary Appendix) (9). Using the hospital database for transthoracic echocardiography, consecutive patients who met the definition of severe AS (peak aortic jet velocity [Vmax] > 4.0 m/s, mean aortic pressure gradient [PG] > 40 mm Hg, or aortic valve area [AVA] < 1.0 cm^2) for the first time during the study period were enrolled in this registry (9). When stratified according to the initial treatment strategies after the index echocardiography, the entire cohort was divided into the conservative management cohort (N=2618) and initial AVR cohort (N=1197). The decision of the initial treatment strategy was based on the physicians' discretion. Study design and patient enrollment in the registry have been previously described in detail (9).

The study protocol was approved by the institutional review board of each participating center. The requirement of written informed consent was waived due to the retrospective nature of the study. Patient records were anonymized prior to analysis.

Definitions of malignancy status and other conditions

The study subjects were divided into three groups based on the malignancy status.

We defined the malignancy group as those with a malignancy currently under treatment, for which treatment is planned, or the best possible supportive care is being provided, whereas the past history group was defined as those with a history of malignancy but without the need for current treatment. No malignancy group was defined as those without a history of malignancy (Figure 1). Malignancy types were classified according to anatomic and system primary involvement (12). The date of first malignancy diagnosis was identified from the hospital record. Reasons for selecting each treatment strategy were placed into one of various categories in the malignancy group; however, detailed reasons allowed for overlaps. We defined anemia according to the World Health Organization criteria (hemoglobin < 13.0 g/dL in men and < 12.0 g/dL in women). Results of two-dimensional transthoracic echocardiography were analyzed at index echocardiography. The left ventricular ejection fraction (LVEF) was measured using the Teichholz method or the modified Simpson's rule method.

Outcome measures

The primary outcome measure for the present analysis was all-cause death during the 3-year follow-up period. The secondary outcome measures were malignancy-related death and aortic valve-related death. The cause of death was classified according to the Valve Academic Research Consortium definitions and adjudicated by a clinical event committee

(11, 13, 14). Malignancy-related death was defined as death where malignancy was the primary causes for the deteriorating general condition. Aortic valve-related death included aortic procedure-related death, sudden death, death caused by heart failure potentially related to the aortic valve, and death due to aortic valve endocarditis. Sudden death was defined as death within 24 hours after the manifestation of symptoms, death during sleep, or unwitnessed death in patients who had been stable until then. When obvious non-cardiogenic causes were identified, the deaths were excluded from the definition of sudden death.

Statistical analysis

In the present analysis, 1) we compared the baseline characteristics and 3-year clinical outcomes among the three groups on the basis of malignancy status in the entire cohort and each treatment strategy, 2) we investigated reasons behind selecting each treatment strategy for AS in the malignancy group, and 3) we compared perioperative complications of the surgery for malignancy between those patients with or without AVR before malignancy surgery.

The categorical variables were expressed as numbers and percentages and were compared using a chi-square test or Fisher's exact test. Continuous variables were expressed as mean ± standard deviation or median with interquartile range (IQR). Based on their distribution, continuous variables were compared using the Student's t-test or the Wilcoxon

rank sum test between the two groups and the one-way analysis of variance or Kruskal-Wallis test across the three groups.

To compare the 3-year clinical outcomes among the three groups in the entire cohort and each treatment strategy, the probability of all-cause death was estimated using the Kaplan-Meier method; the log-rank test was used for univariate comparisons. Cumulative incidence rates of malignancy-related or aortic valve-related death were estimated by using the Gray method (15), accounting for the competing risk of death other than malignancy-related death or aortic valve-related death, respectively. To estimate the risk of the malignancy group and past history group relative to the no malignancy group during the entire follow-up period, a multivariable Cox proportional hazards model was developed for the all-cause death, and multivariable Cox proportional hazards models described by Fine and Gray subdistribution hazard model (16) were developed for the malignancy-related death and aortic valve-related death according for the competing risk of death other than malignancy-related death or aortic valve-related death, respectively. The results were expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). We selected 22 clinically relevant risk-adjusting variables (Table 1) by using dummy variables, with the center incorporated as the stratification variable. This was consistent with our previous study (9), except for the addition of admission for heart failure as a risk-adjusting variable. The subgroup analyses for the primary and secondary outcome measures were also performed in the conservative

management cohort and the initial AVR cohort according to the intention-to-treat principle, regardless of the actual performance of AVR.

All statistical analyses were conducted by a physician (E.M. or T.Kato) and a statistician (T.M.) using JMP 10.0.2 or SAS 9.4 (SAS Institute Inc., Cary, North Carolina). All the reported P values were two-tailed, and the level of statistical significance was set at $P < 0.05$.

Results

Baseline clinical and echocardiographic characteristics

Among the 3815 patients, 124 patients had malignancy currently under treatment, for which treatment was planned, or the best supportive care was being provided (malignancy group), 389 had a past history of malignancy (past history group), and 3302 patients had no history of malignancy (no malignancy group) (Figure 1). Regarding the baseline characteristics, patients in the malignancy group were more often male and had a higher prevalence of low body mass index, recurrence of malignancy, diabetes on insulin therapy, anemia, chest wall irradiation, and liver cirrhosis, while they had lower prevalence of hypertension, aortic/peripheral vascular disease, and symptoms related to AS (Table 1). Surgical risk scores were comparable among the three groups. All echocardiographic parameters except the left ventricular posterior wall thickness were comparable across the three groups. Initial AVR strategy was least often taken in the malignancy group (Table 1).

Clinical outcomes

The median follow-up duration after the index echocardiography was 1176 (IQR: 733-1618) days, with a 93% follow-up rate at 2 years. The cumulative 3-year incidence of AVR/TAVI was significantly lower in the malignancy group (24.4%) than in the past history group and no malignancy groups (past history group: 46.3%, no history group: 49.5%,

P<0.001) (Figure 2A). During the follow-up, 25 patients were undergoing AVR (n=24)/TAVI (n=1) in the malignancy group, 164 patients were undergoing AVR (n=159)/TAVI (n=5) in the past history group, and 1555 patients were undergoing AVR (n=1521)/TAVI (n=34) in the no history group. The proportion of patients undergoing TAVI to surgical AVR/TAVI was not different among the three groups (P=0.66). The cumulative 3-year incidence of the primary outcome measure (all-cause death) was markedly higher in the malignancy group and slightly but significantly higher in the past history group than in the no history group (64.9%, 39.0%, and 28.4%, P<0.001) (Figure 2B). The cumulative 3-year incidence of malignancy-related death was also markedly higher in the malignancy group than in the past history group and the no history group (36.4%, 8.6%, and 1.7%, P<0.001) (Figure 2C), while the cumulative incidence of aortic valve-related death did not differ significantly among the three groups (Figure 2D). After adjusting for confounders, the excess risk in the malignancy group and past history group relative to the no malignancy group for all-cause death remained significant (HR: 2.49, 95%CI: 1.98-3.14, P<0.001; HR: 1.23, 95%CI: 1.04-1.46, P=0.01, respectively, Supplementary Table 1). In malignancy-related death, the excess risks in the malignancy and past history groups relative to the no malignancy group were significant (HR: 16.2, 95% CI: 10.64-24.54, P<0.001 and HR: 3.66, 95% CI: 2.43-5.52, P<0.001, respectively) (Supplementary Table 1). For aortic valve-related death, the risk in the malignancy group was comparable to that in the no malignancy group (HR: 0.79, 95% CI:

0.48-1.29, P=0.35), while the risk of the past history group was lower than that in the no malignancy group (HR: 0.72, 95% CI: 0.53-0.96, P=0.03) (Supplementary Table 1).

Subgroup analysis according to the treatment strategy

In the conservative management cohort (N=2618, Supplementary Table 2), the results of cumulative 3-year incidence of the primary and secondary outcome measures among the three groups and the excess risk of the malignancy group were consistent with those in the entire cohort (Supplementary Figure 1A, 1B, 1C, and 1D, and Supplementary Table 3). In the initial AVR cohort (N=1197, Supplementary Table 4), the cumulative incidence of surgical AVR or TAVI did not differ among the three groups categorized by malignancy status (Supplementary Figure 2A). No patient had aortic valve-related death in the malignancy group (Supplementary Figure 2B, 2C and 2D, and Supplementary Table 5). The proportion of patients undergoing TAVI to surgical AVR/ TAVI did not differ among the three groups in the conservative management and initial AVR cohorts. (P=0.51, P=0.20, respectively) (Supplementary Table 6)

Reasons for selecting treatment strategies in the malignancy group

In the malignancy group, AVR was selected as the first-line treatment in 16 out of 124 patients (12.9%). In the past history group, AVR was selected for 114 out of 389 patients

(29.3%), while 1067 out of 3302 patients (32.3%) in the no malignancy group received AVR as the first-line treatment (Figure 1). In the malignancy group, the most common types of malignancies were prostate cancer (N=24; 19.4%), lung cancer (N=19; 15.3%), gastric cancer (N=13; 10.5%), hepatic cancer (N=8; 6.5%), and breast cancer (N=8; 6.5%) (Supplementary Table 7). The presence of metastasis was recognized in 38 patients. Seventy-eight patients were recognized as not having metastasis, and six patients were of unknown status. The cumulative incidence of AVR/TAVI was not statistically significant between the groups with and without metastasis (Supplementary Figure 3A), but the incidence of the overall mortality and malignancy-related death was higher in the group with metastasis (Supplementary Figure 3B, and 3C). Table 2 summarizes the reasons behind selecting conservative management or AVR/TAVI in the malignancy group. In the conservative management cohort, absence of symptoms was the most common reason, limited life expectancy due to diseases unrelated to AS was the second, and age was the third common reason behind selecting conservative management. Six patients declined the AVR/TAVI. In the AVR cohort, the reasons were symptomatic, as well as requirement of AVR before non-cardiac surgery, and very severe AS.

Perioperative complications of surgery for malignancy

Surgery for malignancy was performed in 35 patients with malignancy. We presented the characteristics and perioperative complications in patients undergoing surgery for

malignancy in Table 3. Surgery was performed on 30 patients for malignancy before or without AVR/TAVI and five patients after AVR/TAVI. Three patients (43%) who underwent surgery for malignancy after AVR/TAVI had very severe AS, while only one patient (3%) with surgery for malignancy before or without AVR/TAVI had very severe AS. STS scores were comparable. There were no procedure complications within 30 days in both groups. One patient died within 30 days of the surgery for malignancy before or without AVR/TAVI group, and the death was malignancy-related death.

Discussion

The main findings of this study are as follows: 1) Malignancy had a marked effect on all-cause mortality and malignancy-related mortality and was associated with a lower rate of AVR/TAVI. 2) Past history of malignancy had a smaller but significant effect on these mortalities but no substantial effect on the rate of AVR/TAVI. 3) In patients with malignancy, the main reasons behind selecting AVR/TAVI strategy were HF symptoms and severity of AS, whereas the common reasons for the choice of conservative treatment strategy were high operative risk and limited life expectancy. 4) The rates of perioperative complications and mortality for malignancy surgery were low both in patients before or without AVR/TAVI and in patients who had underwent AVR/TAVI prior to malignancy surgery.

Multiple models have been developed to predict accurately operative and early mortality following aortic valve(17) and heart surgery(18-21), but none of these models has considered the additional complexity related to a malignancy diagnosis. Moreover, no differences in STS scores were found among the three groups classified according to the presence of malignancy. Patients with AS and malignancy were less likely to have symptoms of AS. One reason for this might be that the malignancy status may mask the symptoms of AS through decreased physical activity, which is common in patients with malignancy. Another reason might be related to the screening of cardiovascular disease in patients with

malignancy, leading to diagnosis of severe AS without symptoms. Despite the lack of malignancy in the operative risk models, our data may support that clinically relevant choices had been made for the surgical AVR or conservative management in patients with malignancy, considering the relatively low rate of malignancy-related mortality in the AVR cohort. Another consideration is that terminally ill patients may not have undergone echocardiography initially and may not have been identified to be included in this study. There might be patients with malignancy and severe AS who had not undergone echocardiography as it had not been recognized by their oncologists or who felt that further investigation was not required due to the prognosis from their malignant disease, as this was an observational study based on the hospital database for transthoracic echocardiography.

The malignancy group also showed high mortality due to malignancy. In clinical practice, the presence of malignancy in patients with severe AS is often considered a contraindication to surgical aortic valve replacement (22). The recent progress in TAVI has allowed extending the overall life expectancy of patients with malignancy to more than 1 year (7). However, it is difficult to determine the length of life expectancy permitting TAVI. We also considered decreased daily life activities, which are due to malignancy or AS, as well as other surgical risk when accounting for TAVI indication. The past history of malignancy had a small but a significant effect on mortality. It was mainly due to the increase of malignancy-related death. Various studies reported that anti-cancer drug had cardiotoxicity and increase

the risk of heart failure (23, 24). In our study, there were no differences in cardiac function or pressure gradient among the three groups. Based on the competing risk model, the risk of aortic valve-related death was lower in the past history group. Close attention to the potential recurrence of malignancy or newly developed malignancy might decrease aortic valve-related death through frequent contact with health care providers in the past history group.

There is a paucity of data on the safety of the surgery for malignancy in the presence of severe AS. Malignant disease might cause serious perioperative complications such as bleeding (25) due to vulnerable tissue and infection (26) due to cachexia if AVR was performed in the presence of malignancy. In addition, invasive AVR might cause the delay of the treatment of malignancy. In this study, we evaluated the perioperative complications in patients who underwent malignancy surgery in the presence of severe AS (“malignancy first” strategy) and in those who underwent malignancy surgery after AVR (“AVR first” strategy) in the registry data. We could not draw solid conclusions due to the small number of patients, although there were no significant differences in the rate of perioperative complications. A prospective study by Watanabe et al. (7) in Japan reported that patients with malignancy with severe AS who underwent TAVI had similar 1-year mortality as patients without malignancy. By contrast, another prospective study by Mangner et al. (27) reported that malignancy in patients undergoing TAVI more adversely affected 1-year mortality compared with that in those with a history of malignancy and controls without known malignant disease. This

discrepancy might be due to variances in malignancy type distribution and racial disparities (28). Further studies, which are retrospective or prospective, are needed to answer questions about what malignancy type, malignancy stage, and level of surgical invasiveness would allow each strategy.

The process of decision-making for the treatment strategy is complicated in patients whom malignant disease and cardiac disease coexist because the prognosis and cardiovascular complications of malignancy therapy vary depending on the malignancy type, stage, and therapy. As some patients with long-term thoracic radiation therapy have radiation-related pericardial fibrosis (29), TAVI might be an indication for such patients (30, 31). It is necessary to decide treatment strategy considering various factors based on perspectives from cardiovascular physicians, cardiac surgeons, oncologist, and radiologist. There is a report that incidental findings of tumor in a computer tomography before undergoing TAVI did not have a significant effect on the outcomes for elderly patients with severe AS based on the decision of the interdisciplinary heart team (6). A heart team approach with oncologists and radiologist can make clinically relevant decision-making easier and reduce the perioperative complications. Thus, it is important to investigate contemporary data when we consider the choice of “TAVI first” strategy, “surgical AVR first” strategy, or “malignancy first” strategy in patients with AS and malignancy for optimizing treatment through the heart team approach.

Limitations

First, the precise staging and lines of prior chemotherapy were not collected; therefore, we could not analyze the data according to malignancy staging or therapy. Second, the exact expected life expectancy of each patient in the malignancy group was unclear. However, a substantial portion of patients was estimated to have a limited life expectancy in the malignancy group. Third, categorization of the circumstances surrounding each death, particularly the mechanism of death, was related to the process of adjudication and may be incomplete. It is unclear whether sudden death or endocarditis is due to pulmonary embolism or endocarditis related malignancy. Fourth, we did not collect the data about a heart team approach nor the referral for oncologists. Fifth, there remain unmeasured confounders affecting the mortality, although we conducted extensive statistical adjustment for the measured confounders. Sixth, the number of patients in the malignancy group according to the initial treatment strategy and number of patients who underwent surgery for the active malignancy with severe AS were very small. However, in conjunction with other reports, our data shed light on the practice for the complicated conditions of patients with malignancy and severe AS. Seventh, the number of patients undergoing TAVI in our study was too small to analyze the difference between patients undergoing TAVI and AVR. Finally, although this study was based on a registry in Japan, the prevalence of malignancy might be different depending on the countries and race. The external validity should be confirmed to further

investigate this issue, and a study in another country or race is required.

Conclusion

Active malignancy had a marked effect on all-cause death and malignancy-related death in patients with severe AS. History of malignancy also had a smaller but significant effect on mortality.

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Figure legend

Figure 1. Study patient flow.

AVR=aortic valve replacement

Figure 2. Kaplan-Meier curves for the cumulative 3-year incidence of clinical events

(A) surgical AVR or TAVI during follow-up, (B) the primary outcome measure (all-cause death), (C) malignancy-related death, and (D) aortic valve-related death.

AVR=aortic valve replacement, and TAVI=transcatheter aortic valve implantation.

Table 1. Baseline clinical and echocardiographic characteristics in the malignancy group, past history group, and no history group

Variable	Malignancy group (N=124)	Past history group (N=389)	No malignancy group (N=3302)	P value
Clinical characteristics				
Age, years*	78.8±7.1	78.7±8.3	77.6±10.0	0.045
Age ≥80 years	53 (43)	196 (50)	1480 (45)	0.14
Male*	65 (52)	191 (49)	1187 (36)	<0.001
BMI	21.1±3.5	21.7±3.7	21.8±3.9	0.16
BMI <22 * ‖	88 (71)	222 (57)	2016 (61)	0.02
BSA, m^2	1.45±0.18	1.48±0.18	1.46±0.19	0.14
Initial AVR group	16 (13)	114 (29)	1067 (32)	<0.001
Recurrence of malignancy	45 (36)	11 (3)	0	<0.001
Hypertension*	75 (60)	265 (68)	2327 (70)	0.042
Current smoking*	6 (5)	17 (4)	173 (5)	0.75
History of smoking	34 (27)	108 (28)	688 (21)	0.002
Diabetes mellitus	35 (28)	92 (24)	770 (23)	0.45
On insulin therapy*	13 (10)	20 (5)	155 (5)	0.01

Coronary artery disease*	40 (32)	123 (32)	981 (30)	0.63
Prior myocardial infarction*	10 (8)	36 (9)	277 (8)	0.83
Prior symptomatic stroke*	22 (17)	50 (13)	431 (13)	0.31
Atrial fibrillation or flutter*	17 (14)	83 (21)	728 (22)	0.09
Aortic/peripheral vascular disease*	2 (2)	36 (9)	244 (7)	0.02
Serum creatinine, mg/dL*	0.9 (0.7-1.3)	0.9 (0.7-1.4)	0.9 (0.7-1.2)	0.25
Dialysis*	12 (10)	47 (12)	346 (10)	0.59
Anemia* §	93 (75)	234 (60)	1790 (54)	<0.001
Chest wall irradiation	10 (8)	10 (3)	5 (0.2)	<0.001
Immunosuppressive therapy	7 (6)	11 (3)	113 (3)	0.32
Chronic lung disease ≥moderate*	4 (3)	14 (4)	94 (3)	0.69
Liver cirrhosis*	7 (6)	12 (3)	19 (1)	<0.001
STS score (PROM), %	3.6 (2.3-5.9)	4.0 (2.5-7.0)	3.8 (2.2-6.6)	0.17
Symptoms at index echocardiography	44 (35)	194 (50)	1767 (54)	<0.001
Chest pain	14 (11)	46 (12)	438 (13)	0.35
Syncope	3 (2)	26 (7)	169 (5)	0.12
Chronic exertional dyspnea	33 (27)	148 (38)	1422 (43)	<0.001

Admission for heart failure at index echocardiography*	18 (15)	75 (19)	697 (21)	0.16
Echocardiographic variables				
Vmax, m/s	4.0±0.9	4.1±0.8	4.1±0.9	0.16
Vmax >4m/s*	67 (54)	224 (56)	1894 (57)	0.76
Peak aortic PG, mmHg	68±30	70±28	72±32	0.11
Mean aortic PG, mmHg	39±18	39±17	41±20	0.08
AVA (equation of continuity), cm^2	0.75±0.16	0.72±0.18	0.72±0.19	0.21
LV end-diastolic diameter, mm	45±6	46±7	46±7	0.61
LV end-systolic diameter, mm	30±7	31±8	30±8	0.56
LVEF, %	64.0±11.7	62.3±13.8	63±13.5	0.47
LVEF <68%*	72 (58)	231 (59)	1939 (59)	0.96
IVST (mm)	11±2	11±2	11±2	0.40
LVPW (mm)	10±2	11±2	11±2	0.02
Any combined valvular disease (moderate or severe)*	50 (40)	160 (41)	1348 (41)	0.99
TR pressure gradient ≥40 mmHg*	21 (17)	60 (15)	525 (16)	0.92

Values are number (%), mean ± SD, or median (interquartile range).

P values were calculated from a chi-square test or Fisher's exact test for categorical variables, and the one-way

analysis of variance or Kruskal-Wallis test for continuous variables.

|| Body mass index was calculated as weight in kilograms divided by height in meters squared.

§ Anemia was defined by the World Health Organization criteria (hemoglobin <12.0 g/dL in women and <13.0 g/dL in men).

* Potential risk-adjusting variables selected for Cox proportional hazard models.

AS=aortic stenosis, AVA=aortic valve area, AVR=aortic valve replacement, BMI=body mass index, BSA=body surface area, Cre=creatinine, LV=left ventricular, LVEF=left ventricular ejection fraction, LVPW= left ventricular posterior wall, IVST= interventricular septum thickness, PG=pressure gradient, PROM=predicted risk of mortality, SD=standard deviation, STS=Society of Thoracic Surgeons, TR=tricuspid regurgitation, and Vmax=peak aortic jet velocity

Table 2. Reason why treatment strategy was chosen for AS in the malignancy group

Reasons	**N of patients (N=124)**	**Detailed reasons***	**N**
Conservative management cohort	**(N=108)**		
No indication for AVR	51	Asymptomatic	46
		Improved symptoms by medical treatment	3
		Symptoms by coronary artery disease	2
High risk for AVR/TAVI	51	Limited life expectancy due to diseases unrelated to AS	36
		Aged	15
		Liver cirrhosis	5
		Renal failure	5
		Cognitive dysfunction	4
		Prior open surgery	2

		Low respiratory function	2
		Very high-risk operative procedure	1
		Malnutrition	1
Patients refusal of AVR/TAVI	6		
Initial AVR cohort	**(N=16)**		
Symptomatic AS	11	Heart failure	8
		Chest pain	4
		Syncope	1
Asymptomatic AS	5	AVR was required before non-cardiac surgery	3
		Very severe AS	3

*Detailed reasons allowed for overlaps.

TAVI=transcatheter aortic valve implantation

Other abbreviations are same as in Table 1.

Table 3. Characteristics and perioperative complications in patients undergoing surgery for malignancy

	Surgery for malignancy without AVR or before AVR group (N=30)	Surgery for malignancy after AVR group (N=5)	P value
Age (years)	77.1±6.9	71.7±5.5	0.07
LVEF<50%	1 (3)	0 (0)	0.62
Vmax>5m/s	1 (3)	3 (43)	0.002
Symptom at index echocardiography	6 (20)	2 (29)	0.62
Admission for heart failure at Index UCG	3 (10)	2 (29)	0.20
STS (PROM) score, %	2.7 (2.1-3.8)	3.9 (1.7-3.9)	0.59
Involved organs	Lung, Stomach, Breast, Gall bladder, Prostate	Stomach, Esophagus, Kidney and urethra, Larynx	
Anesthesia procedures			
General anesthesia	25 (80%)	4 (80%)	0.85
Lumbar anesthesia	4	0	
Intravenous anesthesia	1	1	

Procedure complication (within 30 days)			
Worsening heart failure	0	0	
Stroke	0	0	
Death (within 30 days)	1	0	0.68
Death due to malignancy	1	0	

Values are number (%), mean ± SD, or median (interquartile range).

Abbreviations are same as in Table 1.

Figure 1.

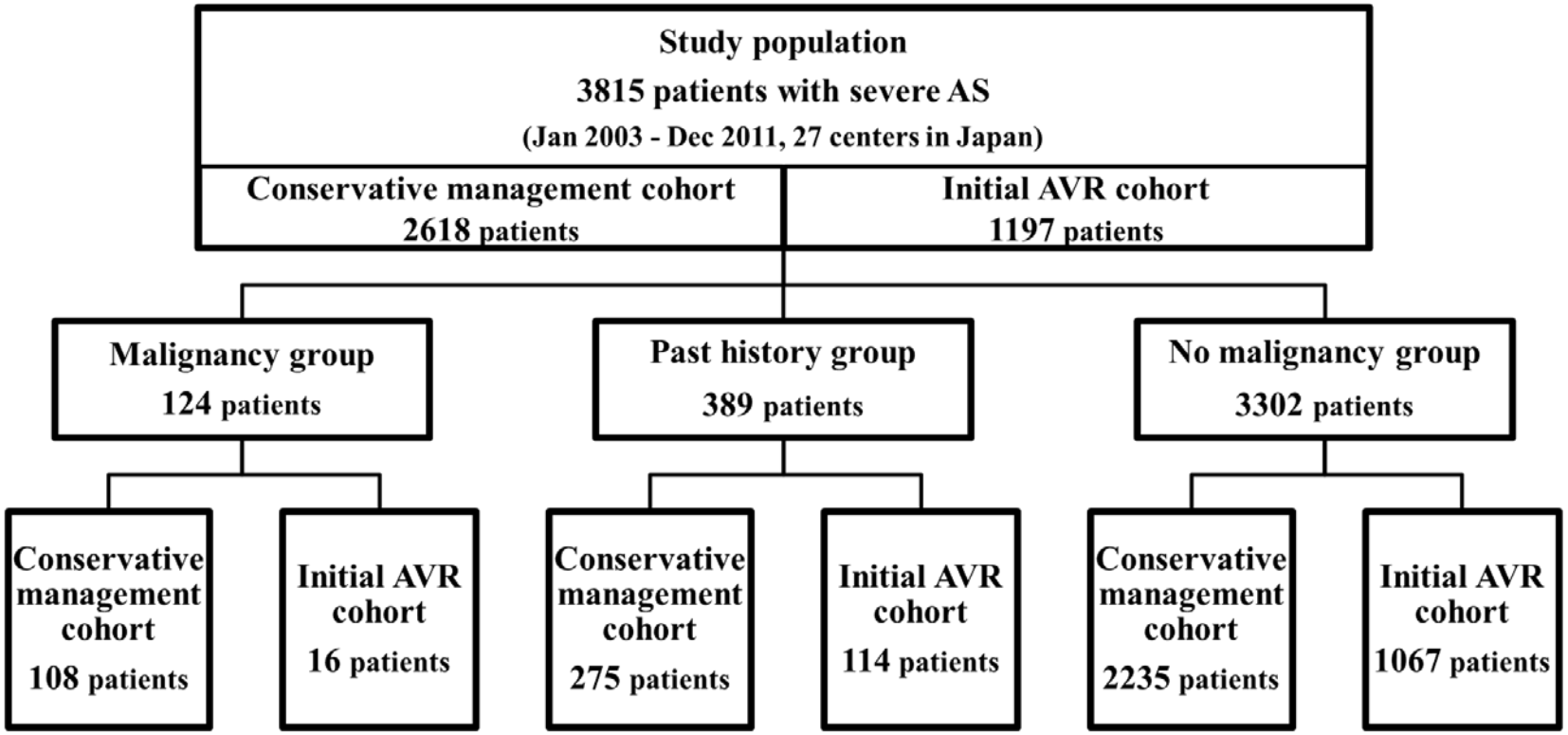
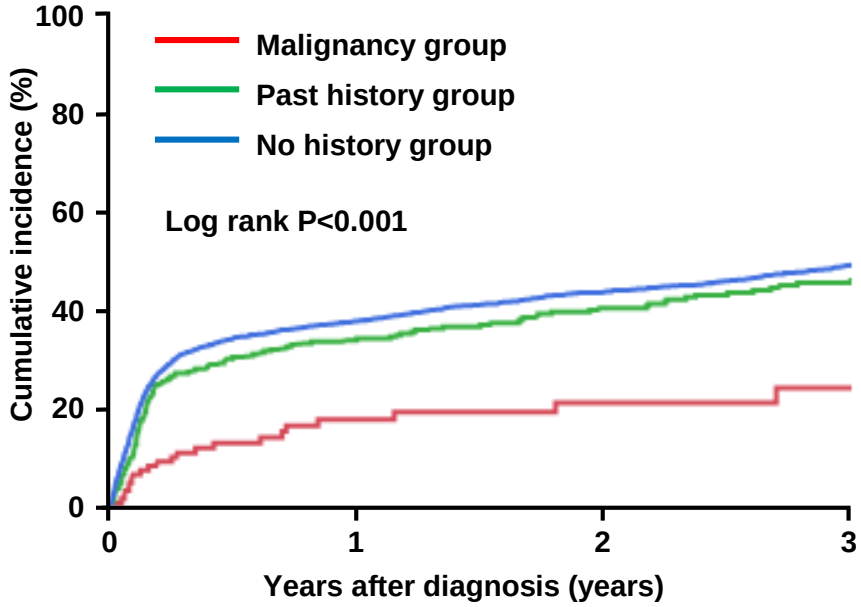
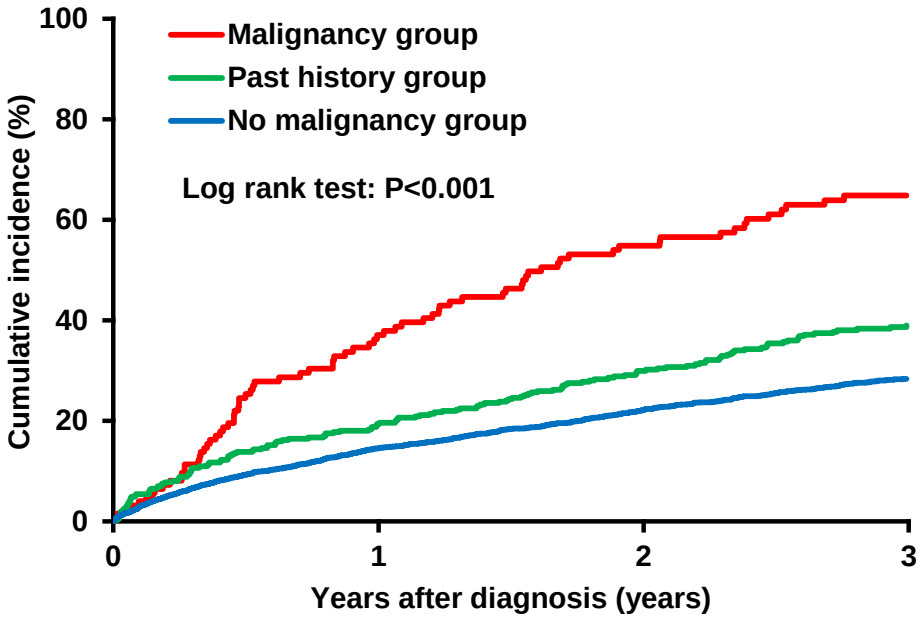

Study population
3815 patients with severe AS
(Jan 2003 - Dec 2011, 27 centers in Japan)
Conservative management cohort
2618 patients
Initial AVR cohort
1197 patients
Malignancy group
124 patients
Past history group
389 patients
No malignancy group
3302 patients
Conservative management cohort
108 patients
Initial AVR cohort
16 patients
Conservative management cohort
275 patients
Initial AVR cohort
114 patients
Conservative management cohort
2235 patients
Initial AVR cohort
1067 patients

Figure 2(A)



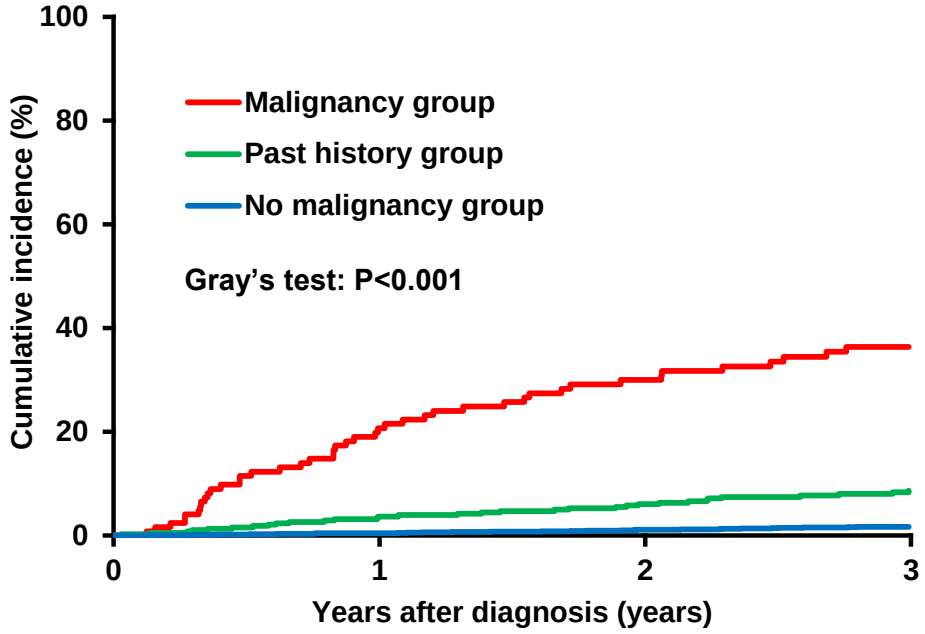
	Interval (years)	0	1	2	3
Malignancy group	N of patients with at least 1 event		19	21	22
	N of patients at risk	124	60	38	21
	Cumulative incidence		17.9%	21.3%	24.4%
Past history group	N of patients with at least 1 event		123	140	152
	N of patients at risk	389	197	144	94
	Cumulative incidence		34.4%	40.7%	46.3%
No malignancy group	N of patients with at least 1 event		1178	1324	1431
	N of patients at risk	3302	1625	1241	826
	Cumulative incidence		38.0%	44.0%	49.5%

Figure 2(B)



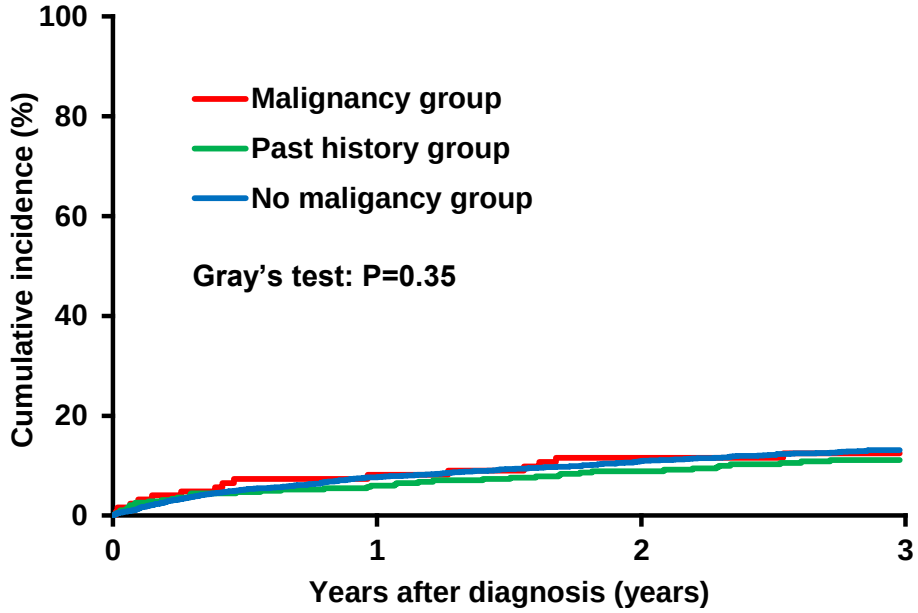
	Interval (years)	0	1	2	3
Malignancy group	N of patients with at least 1 event		45	66	77
	N of patients at risk	124	75	52	32
	Cumulative incidence		37.1%	54.9%	64.9%
Past history group	N of patients with at least 1 event		74	114	146
	N of patients at risk	389	307	262	189
	Cumulative incidence		19.4%	29.9%	39.0%
No malignancy group	N of patients with at least 1 event		465	701	874
	N of patients at risk	3302	2672	2345	1747
	Cumulative incidence		14.6%	22.2%	28.4%

Figure 2(C)



	Interval (years)	0	1	2	3
Malignancy group	N of patients with at least 1 event		25	36	43
	N of patients at risk	124	75	52	32
	Cumulative incidence		20.7%	30.0%	36.4%
Past history group	N of patients with at least 1 event		14	23	32
	N of patients at risk	389	307	262	189
	Cumulative incidence		3.7%	6.1%	8.6%
No malignancy group	N of patients with at least 1 event		14	34	51
	N of patients at risk	3302	2672	2345	1747
	Cumulative incidence		0.44%	1.1%	1.7%

Figure 2(D)



	Interval (years)	0	1	2	3
Malignancy group	N of patients with at least 1 event		10	14	15
	N of patients at risk	124	75	52	32
	Cumulative incidence		8.2%	11.6%	12.5%
Past history group	N of patients with at least 1 event		23	34	42
	N of patients at risk	389	307	262	189
	Cumulative incidence		6.0%	8.9%	11.2%
No malignancy group	N of patients with at least 1 event		245	345	408
	N of patients at risk	3302	2672	2345	1747
	Cumulative incidence		7.7%	10.9%	13.1%

Supplementary material

Malignant Disease as a Comorbidity in Patients with Severe Aortic Stenosis: Clinical Presentation, Outcomes, and Management

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Supplementary material content

Supplementary Figures **Page 3-14**

Supplementary Tables **Page 15-30**

List of investigators

Supplementary figure legend

Supplementary Figure 1. Kaplan-Meier curves for the cumulative 3-year incidence of clinical events in the conservative management cohort

(A) surgical AVR or TAVI during follow-up, (B) the primary outcome measure (all-cause death), (C) malignancy-related death, (D) aortic valve-related death.

AVR=aortic valve replacement, and TAVI=transcatheter aortic valve implantation.

Supplementary Figure 2. Kaplan-Meier curves for the cumulative 3-year incidence of clinical events in the initial AVR cohort

(A) surgical AVR or TAVI during follow-up, (B) the primary outcome measure (all-cause death), (C) malignancy-related death, (D) aortic valve-related death.

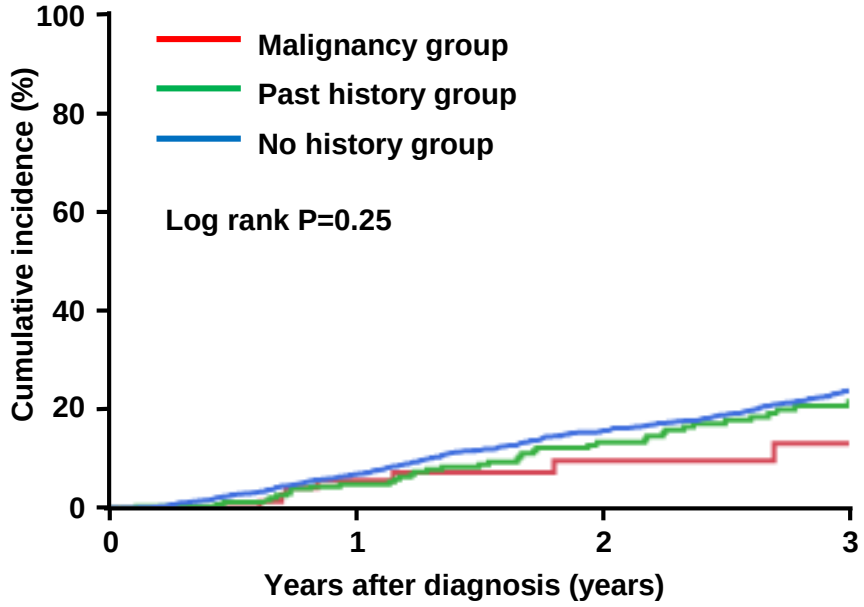
AVR=aortic valve replacement, and TAVI=transcatheter aortic valve implantation.

Supplementary Figure 3. Kaplan-Meier curves for the cumulative incidence of clinical events according to the malignancy status in the malignancy group; metastatic versus non metastatic

(A) surgical AVR or TAVI during follow-up, (B) the primary outcome measure (all-cause death), (C) malignancy-related death

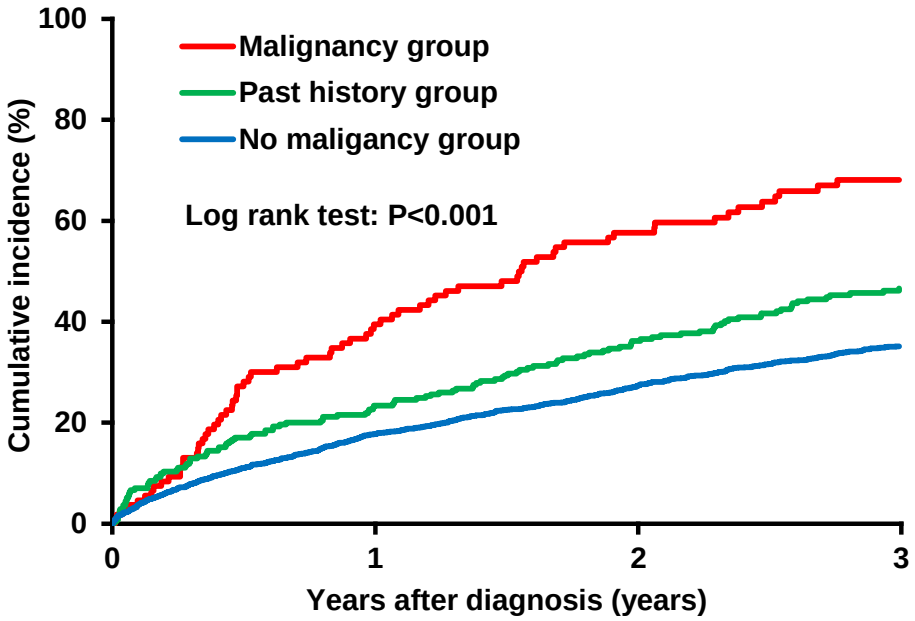
AVR=aortic valve replacement, and TAVI=transcatheter aortic valve implantation.

Supplementary Figure 1 (A)



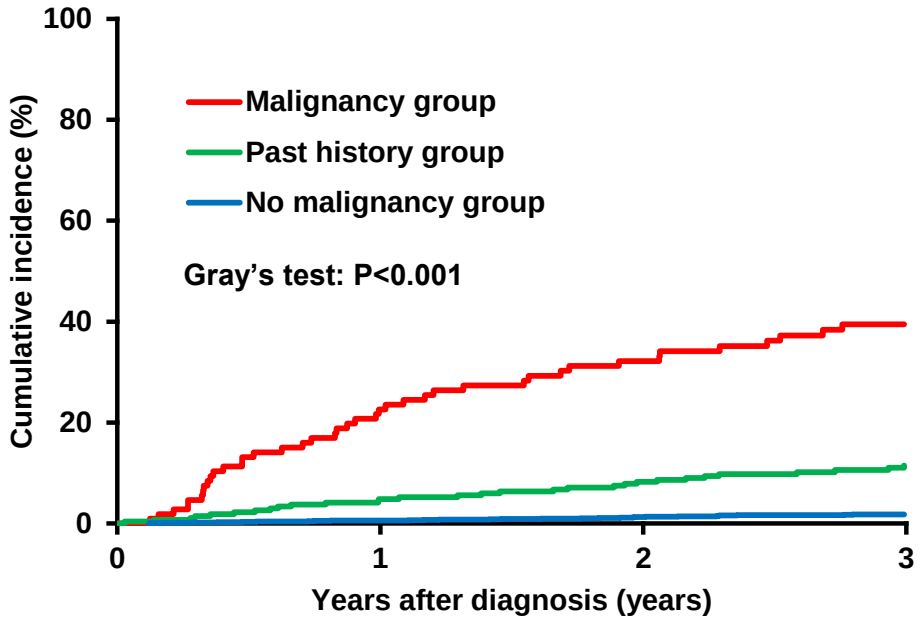
	Interval (years)	0	1	2	3
Malignancy group	N of patients with at least 1 event		4	6	7
	N of patients at risk	108	60	37	21
	Cumulative incidence		5.6%	9.8%	13.0%
Past history group	N of patients with at least 1 event		11	27	39
	N of patients at risk	275	195	143	94
	Cumulative incidence		5.0%	13.6%	21.9%
No malignancy group	N of patients with at least 1 event		133	278	385
	N of patients at risk	2235	1620	1238	823
	Cumulative incidence		7.0%	15.9%	24.3%

Supplementary Figure 1 (B)



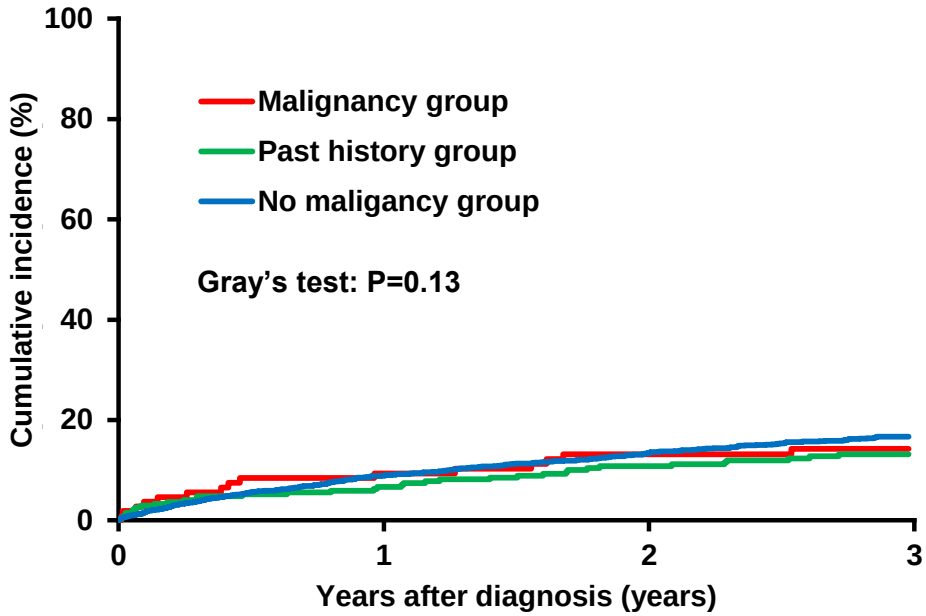
	Interval (years)	0	1	2	3
Malignancy group	N of patients with at least 1 event		42	61	71
	N of patients at risk	108	64	43	24
	Cumulative incidence		39.5%	57.7%	68.1%
Past history group	N of patients with at least 1 event		63	97	123
	N of patients at risk	275	205	167	120
	Cumulative incidence		23.4%	36.2%	46.6%
No malignancy group	N of patients with at least 1 event		383	583	734
	N of patients at risk	2235	1740	1481	1106
	Cumulative incidence		17.8%	27.4%	35.1%

Supplementary Figure 1 (C)



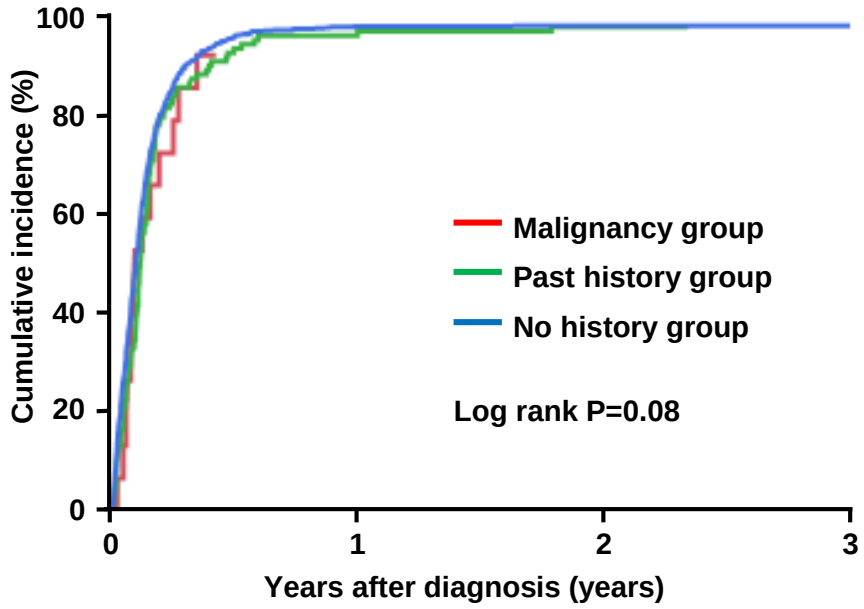
	Interval (years)	0	1	2	3
Malignancy group	N of patients with at least 1 event		24	34	41
	N of patients at risk	108	64	43	24
	Cumulative incidence		22.6%	32.2%	39.5%
Past history group	N of patients with at least 1 event		13	22	30
	N of patients at risk	275	205	167	120
	Cumulative incidence		4.8%	8.2%	11.5%
No malignancy group	N of patients with at least 1 event		12	27	37
	N of patients at risk	2235	1740	1481	1106
	Cumulative incidence		0.56%	1.3%	1.8%

Supplementary Figure 1(D)



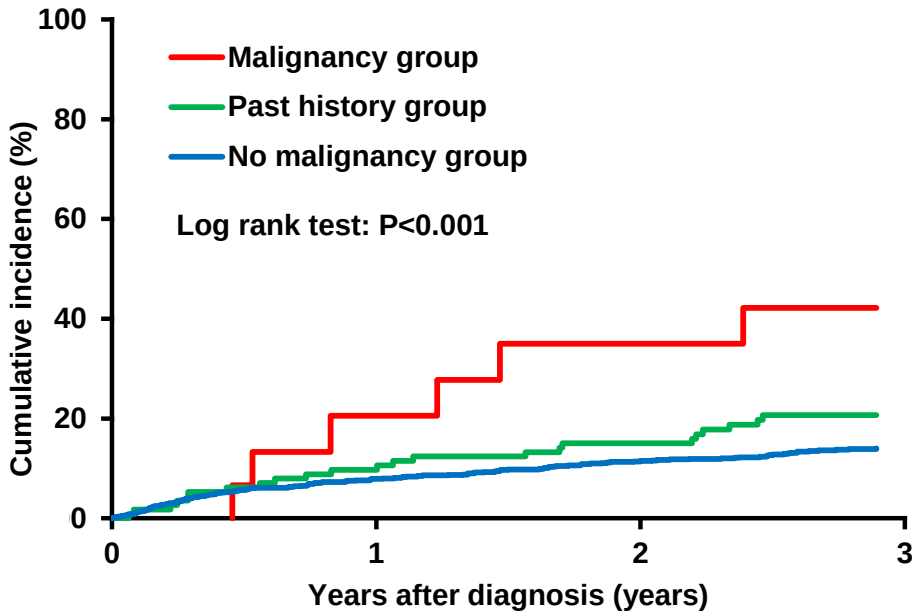
	Interval (years)	0	1	2	3
Malignancy group	N of patients with at least 1 event		10	14	15
	N of patients at risk	108	64	43	24
	Cumulative incidence		9.4%	13.2%	14.3%
Past history group	N of patients with at least 1 event		18	29	35
	N of patients at risk	275	205	167	120
	Cumulative incidence		6.7%	10.8%	13.2%
No malignancy group	N of patients with at least 1 event		192	287	350
	N of patients at risk	2235	1740	1481	1106
	Cumulative incidence		8.9%	13.5%	16.7%

Supplementary Figure 2 (A)



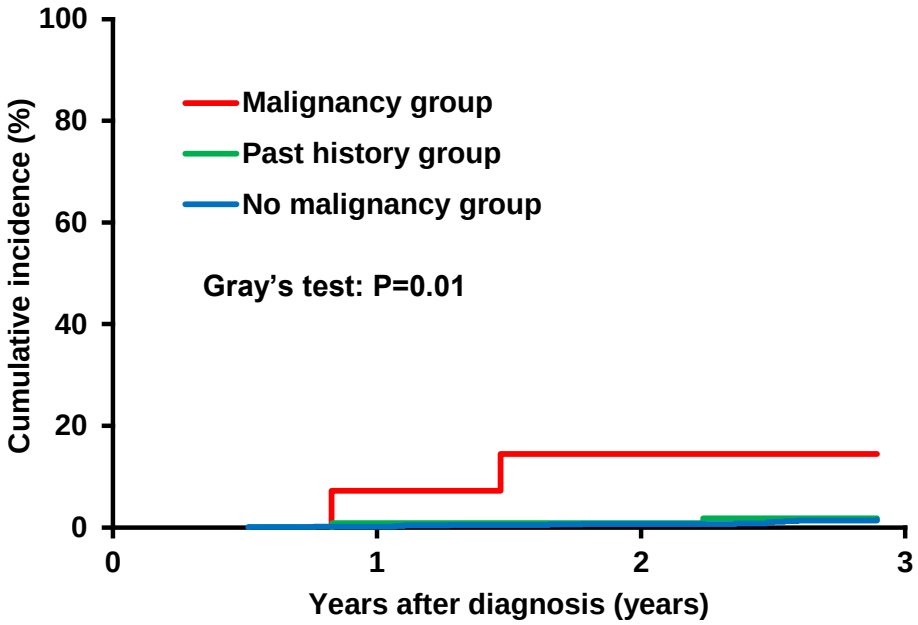
	Interval (years)	0	1	2	3
Malignancy group	N of patients with at least 1 event		15	15	15
	N of patients at risk	16	0	0	0
	Cumulative incidence		93.8%	93.8%	93.8%
Past history group	N of patients with at least 1 event		112	113	113
	N of patients at risk	114	2	1	0
	Cumulative incidence		98.3%	99.1%	99.1%
No malignancy group	N of patients with at least 1 event		1045	1046	1046
	N of patients at risk	1067	5	3	3
	Cumulative incidence		99.3%	99.5%	99.5%

Supplementary Figure 2 (B)



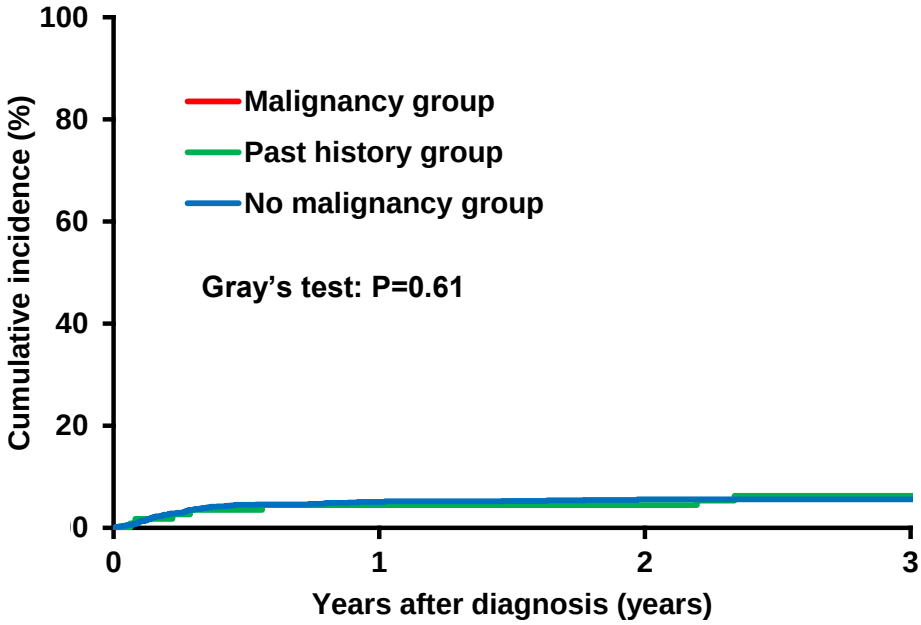
	Interval (years)	0	1	2	3
Malignancy group	N of patients with at least 1 event		3	5	6
	N of patients at risk	16	11	9	8
	Cumulative incidence		20.6%	35.0%	42.2%
Past history group	N of patients with at least 1 event		11	17	23
	N of patients at risk	114	101	95	69
	Cumulative incidence		9.7%	15.0%	20.7%
No malignancy group	N of patients with at least 1 event		82	118	140
	N of patients at risk	1067	932	864	641
	Cumulative incidence		7.9%	11.5%	14.0%

Supplementary Figure 2 (C)



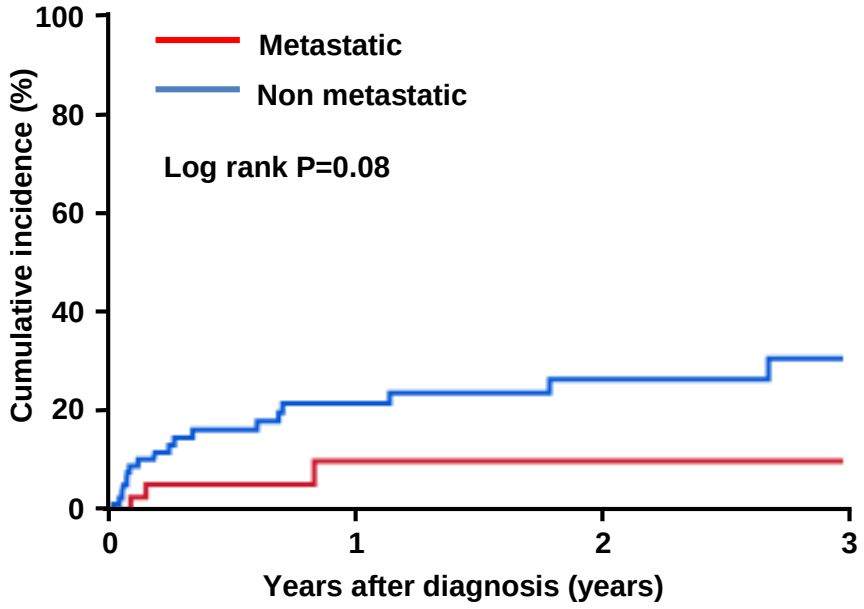
	Interval (years)	0	1	2	3
Malignancy group	N of patients with at least 1 event		1	2	2
	N of patients at risk	16	11	9	8
	Cumulative incidence		7.2%	14.4%	14.4%
Past history group	N of patients with at least 1 event		1	1	2
	N of patients at risk	114	102	95	69
	Cumulative incidence		0.89%	0.89%	1.8%
No malignancy group	N of patients with at least 1 event		2	7	14
	N of patients at risk	1067	932	864	641
	Cumulative incidence		0.20%	0.69%	1.5%

Supplementary Figure 2 (D)



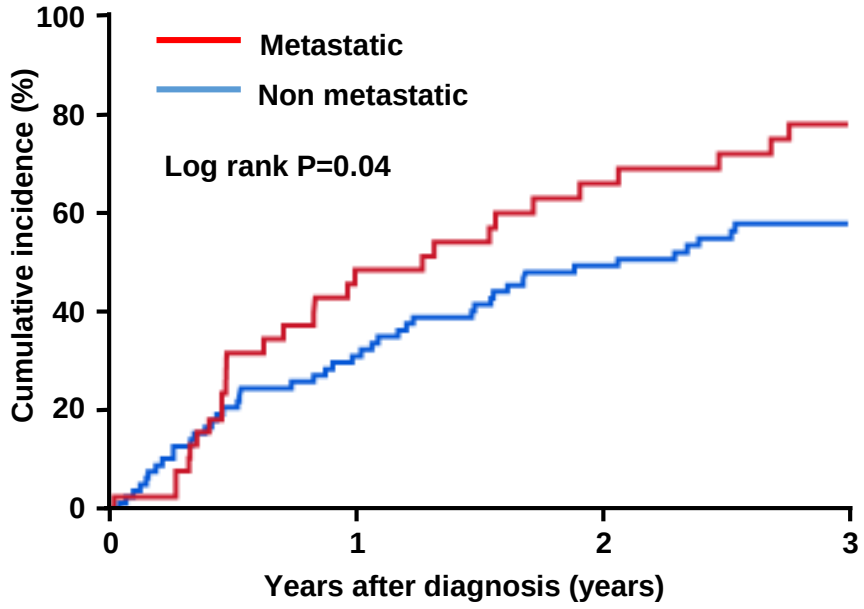
	Interval (years)	0	1	2	3
Malignancy group	N of patients with at least 1 event		0	0	0
	N of patients at risk	16	11	9	8
	Cumulative incidence		0%	0%	0%
Past history group	N of patients with at least 1 event		5	5	7
	N of patients at risk	114	102	95	69
	Cumulative incidence		4.4%	4.4%	6.3%
No malignancy group	N of patients with at least 1 event		53	58	58
	N of patients at risk	1067	932	864	644
	Cumulative incidence		5.1%	5.6%	5.6%

Supplementary Figure 3 (A)



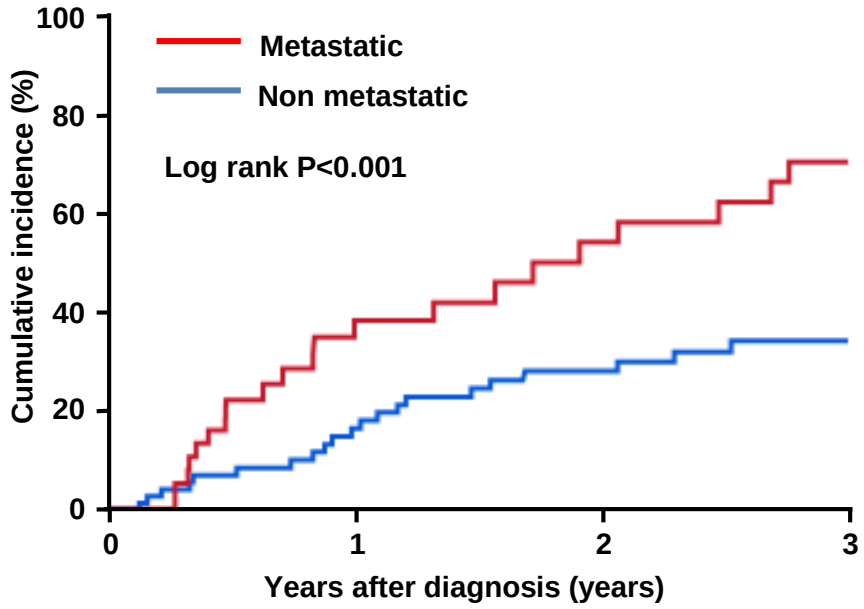
	Interval (years)	0	1	2	3
Metastatic	N of patients with at least 1 event		3	3	3
	N of patients at risk	38	17	10	5
	Cumulative incidence		10.1%	10.1%	10.1%
Non metastatic	N of patients with at least 1 event		15	17	18
	N of patients at risk	78	39	25	14
	Cumulative incidence		22.0%	27.0%	31.3%

Supplementary Figure 3 (B)



	Interval (years)	0	1	2	3
Metastatic	N of patients with at least 1 event		18	24	28
	N of patients at risk	38	18	11	5
	Cumulative incidence		49.0%	66.8%	78.9%
Non metastatic	N of patients with at least 1 event		24	38	44
	N of patients at risk	78	52	37	24
	Cumulative incidence		31.4%	49.9%	58.5%

Supplementary Figure 3 (C)



	Interval (years)	0	1	2	3
Metastatic	N of patients with at least 1 event		13	17	21
	N of patients at risk	38	18	11	5
	Cumulative incidence		38.8%	54.7%	71.2%
Non metastatic	N of patients with at least 1 event		11	18	21
	N of patients at risk	78	52	38	24
	Cumulative incidence		16.6%	28.3%	34.5%

Supplementary Tables

Supplementary Table 1. Clinical outcomes according to the malignancy status

Supplementary Table 2. Baseline clinical and echocardiographic characteristics in the malignancy group, past history group, and no malignancy group in the conservative management cohort

Supplementary Table 3. Clinical outcomes according to the malignancy status in the conservative management cohort

Supplementary Table 4. Baseline clinical and echocardiographic characteristics in the malignancy group, past history group, and no history group in the Initial AVR cohort

Supplementary Table 5. Clinical outcomes according to the malignancy status in the AVR cohort

Supplementary Table 6. The number of patients who underwent TAVI according to the malignancy status in the conservative management and initial AVR cohorts

Supplementary Table 7. Types of malignancy in the malignancy group (N=124)

Supplementary Table 1. Clinical outcomes according to the malignancy status

		N of patients with event/N of patients at risk (Cumulative 3-year incidence)	P value	Adjusted risk		
				HR	95% CI	P value
All-cause death	No malignancy group	1189/3302 (28.4%)	<0.001	1 (reference)		
	Past history group	173/389 (39.0%)		1.23	1.04-1.46	0.01
	Malignancy group	87/124 (64.9%)		2.49	1.98-3.14	<0.001
Malignancy related death	No malignancy group	80/3302 (1.7%)	<0.001	1 (reference)		
	Past history group	35/389 (8.6%)		3.66	2.43-5.52	<0.001
	Malignancy group	46/124 (36.4%)		16.2	10.64-24.54	<0.001
Aortic valve related death	No malignancy group	538/3302 (13.1%)	0.35	1 (reference)		
	Past history group	53/389 (11.2%)		0.72	0.53-0.96	0.03

	Malignancy group	18/124 (12.5%)		0.79	0.48-1.29	0.35

CI=confidence interval, HR=hazard ratio

Supplementary Table 2. Baseline clinical and echocardiographic characteristics in the malignancy group, past history group, and no malignancy group in the conservative management cohort

Variable	Conservative management cohort (N=2618)			
	Malignancy group (N=108)	Past history group (N=275)	No malignancy group (N=2235)	P value
Clinical characteristics				
Age, years	79.6±6.8	80.0±8.4	79.7±9.7	0.91
Age ≥80 years	50 (46)	158 (57)	1222 (55)	0.14
Male	56 (52)	135 (49)	745 (33)	<0.001
BMI <22 ‖	78 (72)	169 (61)	1457 (65)	0.13
BSA, m^2	1.44±0.18	1.46±0.19	1.43±0.18	0.03
Recurrence of malignancy	44 (41)	10 (4)	0	<0.001
Hypertension	65 (60)	188 (68)	1607 (72)	0.02
Current smoking	5 (5)	14 (5)	94 (4)	0.78
History of smoking	29 (27)	71 (26)	416 (19)	0.003
Diabetes mellitus	31 (29)	64 (23)	526 (24)	0.46
On insulin therapy	11 (10)	12 (4)	107 (5)	0.04

Coronary artery disease	34 (31)	78 (28)	634 (28)	0.78
Prior symptomatic stroke	21 (19)	35 (13)	340 (15)	0.24
Atrial fibrillation or flutter	15 (14)	61 (22)	545 (24)	0.04
Serum creatinine, mg/dL	0.9 (0.7-1.1)	1.0 (0.7-1.6)	0.9 (0.7-1.3)	0.17
Cre>2mg/dl and Hemodialysis	14 (13)	52 (19)	340 (15)	0.21
Anemia§	82 (76)	172 (63)	1234 (55)	<0.001
Chest wall irradiation	8 (7)	7 (3)	3 (0.1)	<0.001
Immunosuppressive therapy	7 (6)	10 (4)	83 (4)	0.34
Chronic lung disease (moderate or severe)	3 (3)	11 (4)	79 (4)	0.84
STS score (PROM), %	3.8 (2.4-5.9)	4.2 (2.8-7.8)	4.3 (2.6-7.5)	0.16
Symptoms at index echocardiography	32 (30)	110 (40)	958 (43)	0.003
Chest pain	10 (9)	19 (7)	178 (8)	0.06
Syncope	2 (2)	11 (4)	75 (3)	0.047
Chronic exertional dyspnea	24 (22)	93 (34)	827 (37)	<0.001
Admission for heart failure at index echocardiography	11 (10)	52 (19)	457 (20)	0.03
Echocardiographic variables				

Vmax, m/s	3.9 (0.8)	3.9 (0.8)	3.9 (0.8)	0.99
Vmax >4m/s	52 (48)	129 (47)	1010 (45)	0.74
Peak aortic PG, mmHg	63 (27)	62 (25)	63 (28)	0.94
Mean aortic PG, mmHg	35 (15)	34 (16)	35 (17)	0.62
AVA (equation of continuity),cm^2	0.76 (0.16)	0.76 (0.17)	0.75 (0.18)	0.68
LV end-diastolic diameter, mm	45 (6)	46 (7)	45 (7)	0.04
LV end-systolic diameter, mm	29 (7)	31 (8)	30 (8)	0.10
LVEF, %	64.1±11.9	62.0±14.3	62.8±13.2	0.34
LVEF <68%	63 (58)	161 (59)	1350 (60)	0.78
IVST (mm)	11 (2)	11 (2)	11 (2)	0.50
LVPW (mm)	10 (2)	11 (2)	11 (2)	0.10
Any combined valvular disease (moderate or severe)	41 (38)	116 (42)	922 (41)	0.75
TR pressure gradient ≥40 mmHg	15 (14)	44 (16)	367 (16)	0.78

Values are number (%), mean ± SD, or median (interquartile range).

P values were calculated from a chi-square test or Fisher's exact test for categorical variables, and the one-way analysis of variance or Kruskal-Wallis test for continuous variables.

|| Body mass index was calculated as weight in kilograms divided by height in meters squared.

§ Anemia was defined by the World Health Organization criteria (hemoglobin <12.0 g/dL in women and <13.0

g/dL in men).

AS=aortic stenosis, AVA=aortic valve area, BMI=body mass index, BSA=body surface area, Cre=creatinine, LV=left ventricular, LVEF=left ventricular ejection fraction, PG=pressure gradient, PROM=predicted risk of mortality, SD=standard deviation, STS=Society of Thoracic Surgeons, TR=tricuspid regurgitation, and Vmax=peak aortic jet velocity

Supplementary Table 3. Clinical outcomes according to the malignancy status in the conservative management cohort

		N of patients with event/N of patients at risk (Cumulative 5-year incidence [%])	P value	Adjusted risk		
				HR	95% CI	P value
All-cause death	No malignancy group	991/2235 (49.9%)	<0.001	1 (reference)		
	Past history group	142/275 (55.9%)		1.25	1.04-1.51	0.02
	Malignancy group	28/108 (82.3%)		2.55	2.00-3.25	<0.001
Malignancy related death	No malignancy group	58/2235 (3.0%)	<0.001	1 (reference)		
	Past history group	33/275 (13.1%)		5.04	3.22-7.89	<0.001
	Malignancy group	44/108 (43.7%)		19.06	12.24-29.68	<0.001
Aortic valve related death	No malignancy group	477/2235 (24.2%)	0.13	1 (reference)		
	Past history group	46/275 (18.8%)		0.69	0.51-0.95	0.02
	Malignancy group	18/108 (18.0%)		0.83	0.49-1.38	0.47

CI=confidence interval, HR=hazard ratio

Supplementary Table 4. Baseline clinical and echocardiographic characteristics in the malignancy group, past history group, and no history group in the Initial AVR cohort

Variable	Initial AVR cohort (N=1197)			
	Malignancy group (N=16)	Past history group (N=114)	No malignancy group (N=1067)	P value
Clinical characteristics				
Age, years	73.7±6.7	75.7±7.2	73.1±9.1	0.01
Age ≥80 years	3 (19)	38 (33)	258 (24)	0.08
Male	9 (56)	56 (49)	442 (41)	0.15
BMI <22 ||	10 (63)	53 (46)	559 (52)	0.34
BSA, m^2	1.53±0.17	1.50±0.17	1.50±0.18	0.83
Recurrence of malignancy	1 (6)	1 (1)	0	<0.001
Hypertension	10 (63)	77 (68)	720 (67)	0.91
Current smoking	1 (6)	3 (3)	79 (7)	0.16
History of smoking	5 (31)	37 (32)	272 (25)	0.25
Diabetes mellitus	4 (25)	28 (25)	244 (23)	0.90
On insulin therapy	2 (13)	8 (7)	48 (5)	0.18
Coronary artery disease	6 (38)	45 (39)	347 (33)	0.31

Prior symptomatic stroke	1 (6)	15 (13)	91 (9)	0.24
Atrial fibrillation or flutter	2 (13)	22 (19)	183 (17)	0.74
Serum creatinine, mg/dL	0.9 (0.6-17)	0.8 (0.7-1.1)	0.8 (0.7-1.1)	0.97
Cre>2mg/dl and Hemodialysis	2 (13)	15 (13)	135 (13)	0.99
Anemia§	11 (69)	62 (54)	556 (52)	0.38
Chest wall irradiation	2 (13)	3 (3)	2 (0.2)	<0.001
Immunosuppressive therapy	0	1 (1)	30 (3)	0.38
Chronic lung disease (moderate or severe)	1 (6)	3 (3)	15 (1)	0.20
STS score (PROM), %	2.9 (1.9-5.7)	3.0 (1.9-5.3)	2.7 (1.7-4.7)	0.32
Symptoms at index echocardiography	12 (75)	84 (74)	809 (76)	0.98
Chest pain	4 (25)	27 (24)	260 (24)	0.10
Syncope	1 (6)	15 (13)	94 (9)	0.62
Chronic exertional dyspnea	9 (56)	55 (48)	595 (56)	0.64
Admission for heart failure at index echocardiography	7 (44)	23 (20)	240 (22)	0.11
Echocardiographic variables				
Vmax, m/s	4.9 (0.8)	4.6 (0.7)	4.7 (0.8)	0.23

Vmax >4m/s	15 (94)	95 (83)	884 (83)	0.52
Peak aortic PG, mmHg	100 (31)	87 (26)	91 (32)	0.19
Mean aortic PG, mmHg	60 (21)	51 (16)	54 (20)	0.18
AVA (equation of continuity),cm^2	0.64 (0.13)	0.64 (0.16)	0.65 (0.18)	0.79
LV end-diastolic diameter, mm	50 (5)	46 (6)	47 (7)	0.03
LV end-systolic diameter, mm	33 (6)	30 (6)	31 (9)	0.30
LVEF, %	63.3±10.9	63.1±12.8	62.7±14.2	0.95
LVEF <68%	9 (56)	70 (61)	589 (55)	0.45
IVST (mm)	12 (2)	12 (2)	12 (2)	0.76
LVPW (mm)	12 (2)	12 (2)	12 (2)	0.93
Any combined valvular disease (moderate or severe)	9 (56)	44 (39)	426 (40)	0.40
TR pressure gradient ≥40 mmHg	6 (38)	16 (14)	158 (15)	0.04

Values are number (%), mean ± SD, or median (interquartile range).

P values were calculated from a chi-square test or Fisher's exact test for categorical variables, and the one-way analysis of variance or Kruskal-Wallis test for continuous variables.

AVR=aortic valve replacement

Other abbreviations are same as in supplementary table 1.

Supplementary Table 5. Clinical outcomes according to the malignancy status in the AVR cohort

		N of patients with event/N of patients at risk (Cumulative 3-year incidence [%])	P value	Adjusted risk		
				HR	95% CI	P value
All-cause death	No malignancy group	198/1067 (21.8%)	0.001	1 (reference)		
	Past history group	31/114 (29.6%)		1.43	0.95-2.15	0.09
	Malignancy group	7/16 (56.7%)		1.79	0.77-4.15	0.17
Malignancy related death	No malignancy group	22/1067 (3.2%)	0.01	1 (reference)		
	Past history group	2/114 (1.8%)		0.82	0.16-4.18	0.81
	Malignancy group	2/16 (14.4%)		10.93	1.87-64.00	0.008
Aortic valve related death	No malignancy group	61/1067 (6.0%)	0.61	1 (reference)		
	Past history group	7/114 (6.3%)		1.29	0.58-2.86	0.53
	Malignancy group	0/16 (0.0%)		0.0	0.0	<0.001

Abbreviations are same as in supplementary table 2 and 3.

Supplementary Table 6. The number of patients who underwent TAVI according to the malignancy status in the conservative management and initial AVR cohorts

Initial treatment strategy	N of patients who underwent TAVI/N of patients who underwent surgical AVR or TAVI			P value
	Malignancy group	Past history group	No malignancy group	
Conservative management cohort	1/10	2/51	26/508	0.51
Initial AVR cohort	0/15	3/113	8/1046	0.20

TAVI=transcatheter aortic valve implantation

Other abbreviations are same as in supplementary table 4.

Supplementary Table 7. Types of malignancy in the malignancy group (N=124)

	Number (N=124)
Prostate cancer	24
Lung cancer	19
Gastric cancer	13
Hepatic cancer	8
Breast cancer	8
Kidney and ureter cancer	7
Malignant lymphoma	7
Colon cancer	6
Oral and pharyngeal cancer	5
Bladder cancer	4
Esophagus cancer	4
Gall bladder and bile duct cancer	3
Other cancers	16

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