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Transcatheter and surgical aortic valve replacement impact on outcomes and cancer treatment schedule

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ABSTRACT

Background.
Recent data suggest that transcatheter aortic valve replacement (TAVR) for the treatment of severe aortic stenosis (AS) is viable in cancer patients. TAVR may be preferred in cancer patients due to its minimally invasive nature and smaller impact on oncologic therapies compared to SAVR.
Objectives
We sought to determine if TAVR is an acceptable alternative to SAVR in cancer patients and whether TAVR allows for earlier initiation or resumption of anti-cancer therapies.
Methods.
Cancer patients in a tertiary cancer center diagnosed with severe AS were retrospectively included. Patients accepted by the heart team underwent either TAVR or SAVR, while remaining patients received medical therapy alone. Time intervals to initiation of cancer treatment and the impact of cancer treatment on the replaced valves were recorded. Logistic regression was performed to determine the impact of treatment strategy on overall survival (OS) in all 3 subgroups.
Results.
One hundred and eighty-seven cancer patients diagnosed with severe AS were identified. AVR was associated with better OS compared to medical therapy alone ($p < 0.0001$). TAVR was associated with better OS at 72 months (HR = 0.468, $p < 0.001$) compared to medical therapy alone, with no difference in OS observed between SAVR and TAVR. Time intervals to initiation of cancer treatments were shorter in the TAVR group, with no valve deterioration or infection observed in all groups.
Conclusion.
Cancer patients with severe AS benefit from AVR. TAVR is a viable alternative to SAVR in high-risk cancer patients to prolong survival and allow for earlier administration or resumption of anti-neoplastic therapies.

1. Introduction

The most common heart valve disease in developed countries is degenerative calcific aortic stenosis (AS), the prevalence of which increases with age [1,2]. Symptomatic severe calcific AS carries a poor prognosis without intervention; the 2- and 5-year mortality rates of patients who do no undergo aortic valve replacement (AVR) are 50% and 80%, respectively [3,4]. Among cancer patients especially the elderly, severe AS is becoming more prevalent owing to improved survival rates as well as some treatments that increase this risk further (e.g. mediastinal radiation therapy) [5] resulting in an increasing complexity of these patients' care. As the number of cancer patients with concomitant

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cardiovascular diseases increases, cardiologists are becoming more involved in these patients' care to improve their overall survivorship and quality of life.

The principal treatment for most patients with symptomatic severe AS and acceptable surgical risk is surgical AVR (SAVR) [6,7], although recent landmark transcatheter aortic valve replacement (TAVR) trials for low risk patients may result in an increased number of patients who will be eligible for TAVR [8,9]. SAVR is seldom considered for cancer patients, who often have comorbidities that greatly increase their surgical risk. Most of these patients receive medical treatment only, which can delay their cancer therapy indefinitely putting these patients at greater risk of disease progression and cancer-related death. One option that has been used with increasing frequency for patients with symptomatic severe AS and intermediate to prohibitive surgical risk is transcatheter AVR (TAVR), which has a similar risk of perioperative mortality and lower risk of major bleeding compared with SAVR [8,10–12]. TAVR may enable cancer patients to resume or begin cancer therapy more quickly than SAVR.

Scarce data exist about the effect of TAVR on the survival of cancer patients, many of which would not be considered for SAVR given disease- and treatment-related comorbidities. This study sought to determine whether TAVR could be considered for patients with symptomatic severe AS who are scheduled to receive cancer treatment and to assess the extent to which TAVR affects the time to cancer treatment and the resilience of the bioprosthetic valve during cancer treatment.

2. Methods

2.1. Patients

The Institutional Review Board of The University of Texas MD Anderson Cancer Center approved this retrospective study, and written informed consent was waived since treatments for AS were administered as part of routine care. Using our institution's cardiac valve abnormalities database, which documents cases of severe structural or functional valvular abnormalities, diagnosed by echocardiography and/or cardiac catheterization, we identified patients with hematological or solid cancers who underwent AVR (SAVR or TAVR) or received medical treatment only for severe AS between January 2004 and August 2018. Those individuals who underwent balloon aortic valvuloplasty only, AVR with unknown prosthesis type, or those who were lost to follow-up were excluded from the study. Patients' demographic, clinico-pathological, and treatment data were obtained by reviewing the patients' medical records and performing extensive medical, family, procedural, and social histories as described previously [13]. We used anthropometric measurements, including height, weight, and waist circumference, to calculate patients' body mass indexes (BMIs) and body surface areas [14,15].

At the time of diagnosis of severe symptomatic AS, we recorded patients' creatinine levels, electrolytes, liver function panels, fasting lipid panel results, complete blood counts, coagulation parameters, glycated hemoglobin, and fasting plasma glucose levels. Hypertension, dyslipidemia, diabetes mellitus, and coronary artery disease were defined using a self-reported history and/or guidelines set forth by respective associations [16,17].

Patients were also classified into early or advanced staged cancer. Advanced cancer was defined as the presence of metastasis, stage III or higher in solid tumors or a history of stem cell transplant in hematological malignancies, or relapsed and/or refractory disease. Any cancer treatment not intended to be curative in nature was considered palliative with patients being referred to hospice by the oncology specialists when all treatment options were exhausted and no further antineoplastic treatment was provided.

2.2. Aortic stenosis diagnosis and treatment

Severe AS was diagnosed by transthoracic echocardiography, according to American Society of Echocardiography guidelines; patients believed to have low-flow AS because of a reduced ejection fraction underwent dobutamine-stress echocardiography [18]. Patient-reported symptoms of severe AS, such as angina pectoris, syncope, and dyspnea during exertion or at rest were recorded at the time of echocardiography. Only those patients with self-reported symptoms and severe AS as defined above were given a diagnosis of symptomatic severe AS and thus eligible to be considered for AVR.

Overall prognosis and expected future survival, independent of AVR, was determined by a patient's oncologist taking into account among many things the patient's cancer staging, co-morbidities, laboratory data, and anthropometric characteristics. As demonstrated in Fig. 1, only those patients who opted against palliative/hospice care and were in agreement to undergo AVR evaluation were considered for AVR. In addition, prior to referral to an AVR facility, a patient had to have an acceptable survivorship of at least 50% at 12 months prior to the initiation of anti-neoplastic therapy. Such patients were then referred to an AVR facility in Houston, Texas for evaluation for SAVR or TAVR by that facility's "heart team." After evaluation, patients who were deemed to have a low surgical risk by the Society for Thoracic Surgery (STS) risk score and/or patients who required concomitant aorto-coronary bypass surgery or ascending aortic graft repair at the time of AVR were further evaluated for SAVR, with acceptance for surgery determined by each institution. Patients deemed to have an intermediate to prohibitive surgical risk were further evaluated for TAVR with concomitant percutaneous coronary intervention, if necessary, with acceptance for the procedure(s) determined by each institution. The physician who performed the SAVR or TAVR, taking into account any co-existing arrhythmias, coronary artery disease, hematologic disturbances, etc. decided whether to give the patient anticoagulants after the procedure. Patients not eligible for AVR or those patients who refused to undergo AVR received optimal medical treatment at The University of Texas MD Anderson Cancer Center. Patients who underwent SAVR or TAVR underwent repeat transthoracic echocardiography 1 month and 6 months after AVR to obtain aortic valve measurements to assess the success of the AVR.

2.3. Statistical analysis

Patients' demographic characteristics were summarized using means (with standard deviations) and median (with ranges) for continuous variables and patient counts (with percentages) for categorical variables. Overall survival (OS) was defined as the time from the date of AVR to the date of last follow-up or death while OS for those who underwent medical treatment only was defined as the time from diagnosis of symptomatic severe aortic stenosis to the date of last follow-up or death. Patient deaths were established through a review of the electronic medical records or scheduled surveillance telephone contact with patients' families and external providers. The Kaplan–Meier method and log-rank test were used to estimate and compare OS among patients who received medical treatment only, patients who underwent SAVR, and patients who underwent TAVR. Univariate Cox proportional hazards regression analyses were conducted to identify variables associated with OS to obtain Kaplan–Meier curves. Follow-up times (calculated from the date of AVR to the date of last follow-up of death) and times from the date of AVR to the date of the initiation or resumption of cancer therapy were compared between TAVR and SAVR patients using the log-rank test. Aortic valve measurements taken 1 and 6 months after AVR were compared between the TAVR and SAVR patients using a 2-sample t-test or Wilcoxon rank-sum test. p-Values <0.05 indicated statistical significance. SAS 9.4 (SAS Institute INC, Cary, NC) was used for data analysis.

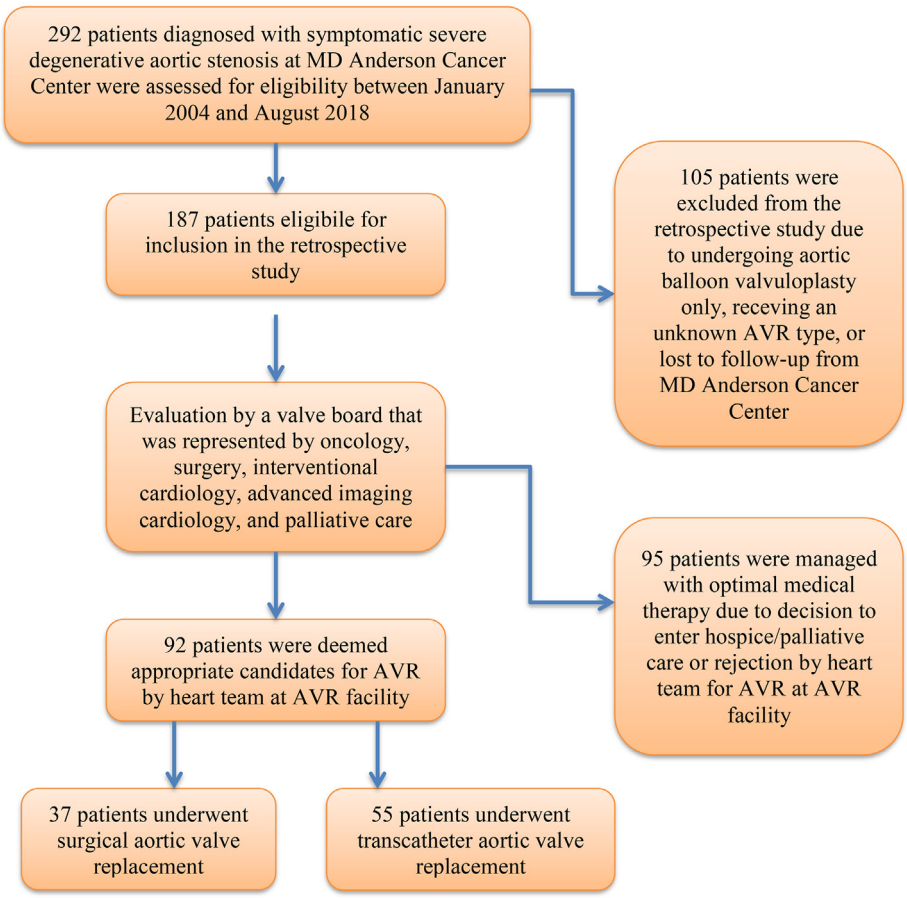

Fig. 1. Algorithm of cancer patients with severe symptomatic aortic stenosis. Cancer patients with severe symptomatic aortic stenosis underwent extensive evaluation prior to referral to aortic valve replacement (AVR) facility. Cancer patients referred to an AVR facility then underwent facility-specific pre-surgical evaluation prior to determination of transcatheter versus surgical aortic valve replacement or referral back to cancer facility for medical management if patient was deemed to be a poor candidate for AVR.

3. Results

3.1. Patient characteristics

The demographic characteristics and clinico-pathological characteristics of the 187 patients (110 men [58.8%] and 77 women [41.2%]) that were included are summarized in Table 1 with no patients lost to follow-up. The median and maximum follow-up times were 38 months and 96 months, respectively. The median follow-up time for those patients who underwent medical treatment only was 7 months. The patients' mean age was 72.84 years (SEM 9.62 years) with over 75% older than 65 years of age. A vast majority of the patients were white and classified as overweight or obese. Known risk factors for cardiovascular disease such as diabetes mellitus, hypertension, and dyslipidemia were prevalent in this population with almost half of the cohort diagnosed with coronary artery disease.

3.2. Patient characteristics by intervention type

All patients were New York Heart Association class III or IV at the time of diagnosis of symptomatic severe aortic stenosis. Of the 187 patients, 95 (50.8%) received medical treatment only. Thirty-seven (19.8%) underwent SAVR, and 55 (29.4%) underwent TAVR as demonstrated in Fig. 1. Initial transthoracic echocardiography diagnosing severe AS showed that the patients who went on to receive medical treatment only had a mean aortic valve gradient of 42.78 mm Hg (SEM 10.84 mm Hg), a mean aortic valve area of 0.83 cm^2 (SEM 0.15 cm^2), and a mean aortic valve peak velocity of 4.21 m/s (SEM 0.62 m/s); their mean left ventricular ejection fraction was 55.79% (SEM 10.15%). Among patients who went on to undergo SAVR or TAVR, the pre-procedural mean aortic valve gradients and mean aortic valve peak velocities were higher than those of the medical treatment only group. Compared to those of the medical treatment only group, the patients who underwent AVR had lower pre-procedural mean aortic valve areas with no difference noted in the mean left ventricular ejection fractions. Following AVR, the mean aortic valve gradients was reduced by approximately three-fourths and the mean aortic valve peak velocities reduced by over 50%; meanwhile, there was an over 200% increase in the mean aortic valve areas with no significant change noted in the mean left ventricular ejection fractions.

Compared with patients who received medical treatment only, those who underwent AVR (SAVR or TAVR) had a significantly higher mean BMI, higher mean serum creatinine level, and lower mean platelet count; they were also significantly more likely to have coronary artery disease.

3.3. Statistical analysis by intervention type

Univariate analysis revealed that compared with medical therapy alone, AVR (SAVR or TAVR) was associated with better OS compared to medical treatment only. Upon analysis of the OS between the patients who underwent SAVR versus TAVR, there was no difference in mortality benefit between the 2 subgroups censored at 12 months and in patients who completed cancer treatment (Fig. 2a–d). For patients who underwent AVR, worse OS was associated with older age, especially in those patients with an age greater than 65 years (Table 2). Improved

Table 1
Descriptive characteristics by valvular intervention.

Variables	Number (%) or Mean ± SD			p-Value
	No AVR (N = 95)	SAVR (N = 37)	TAVR (N = 55)	
Gender				**0.0186**
Male	50(52.6%)	19(51.4%)	41(74.5%)	
Female	45(47.4%)	18(48.6%)	14(25.5%)	
Age (years)	73.83 ± 10.46	69.49 ± 8.42	73.38 ± 8.45	0.0633
< 65 years of age	19(20%)	12(32.4%)	9(16.4%)	0.1638
≥ 65 years of age	76(80%)	25(67.6%)	46(83.6%)	
Race				0.6960
White	76(80%)	30(81.1%)	45(81.8%)	
Hispanic	12(12.6%)	2(5.4%)	5(9.1%)	
African American	6(6.3%)	4(10.8%)	5(9.1%)	
Indian	1(1.1%)	1(2.7%)	0(0%)	
Body Mass Index (kg/m^2)	27.69 ± 6.62	31.07 ± 6.53	30.31 ± 8.32	**0.0063**
Hypertension	83(87.4%)	32(86.5%)	48(87.3%)	0.9904
Dyslipidemia	69(72.6%)	34(91.9%)	37(67.3%)	**0.0220**
Coronary Artery Disease	30(31.6%)	21(56.8%)	25(45.5%)	**0.0208**
Diabetes Mellitus	30(31.6%)	8(21.6%)	15(27.3%)	0.5107
Cancer Type				
Hematologic	29(30.5%)	12(32.4%)	26(47.3%)	0.1064
Solid	72(75.8%)	30(81.1%)	36(65.5%)	0.2029
Laboratory Data				
Platelet Count (K/mL)	186.26 ± 109.01	176.81 ± 76.72	142.67 ± 80.53	**0.0468**
Prothrombin Time (s)	14.92 ± 2.48	14.94 ± 2.63	16.49 ± 5.12	0.0886
International Normalized Ratio	1.26 ± 0.56	1.16 ± 0.27	1.3 ± 0.54	0.2885
Creatinine (mg/dL)	1.09 ± 0.67	1.23 ± 1.08	1.31 ± 0.81	**0.0023**
Hemoglobin (g/dL)	10.46 ± 1.76	11.49 ± 2.49	10.68 ± 2.06	0.1005
Treatment				
Aspirin Only	41(51.9%)	20(62.5%)	15(30.6%)	**0.0105**
Aspirin and Clopidogrel	9(11.4%)	7(21.9%)	14(28.6%)	**0.0470**
Aspirin, Clopidogrel, and Oral Anticoagulant	5(6.3%)	4(12.5%)	10(20.4%)	0.0566
Echocardiographic Parameters				
Before Intervention				
Peak Velocity (m/s)	4.21 ± 0.62	4.47 ± 0.59	4.39 ± 0.69	**0.0124**
Aortic Valve Area (cm^2)	0.83 ± 0.15	0.76 ± 0.21	0.79 ± 0.25	**0.0303**
Mean Gradient (mm Hg)	42.78 ± 10.84	49.03 ± 13.31	47.47 ± 13.92	**0.0052**
Stroke Volume Index (mL/m^2)	41.22 ± 6.53	40.54 ± 9.97	40.08 ± 10.35	0.3242
Left Ventricular Ejection Fraction (%)	55.79 ± 10.15	54.27 ± 12.12	55.27 ± 11.06	0.9689
1 Month After Intervention				
Peak Velocity (m/s)	–	2.14 ± 0.4	2.23 ± 0.44	0.1353
Aortic Valve Area (cm^2)	–	2.06 ± 0.42	2.02 ± 0.55	0.4956
Mean Gradient (mm Hg)	–	10.98 ± 4.48	10.51 ± 3.48	1.0000
Stroke Volume Index (mL/m^2)	–	46.32 ± 9.81	41.45 ± 10.53	0.0763
Left Ventricular Ejection Fraction (%)	–	58.72 ± 9.76	58.46 ± 10.12	0.8697
6 Months After Intervention				
Peak Velocity (m/s)	–	2.2 ± 0.39	2.31 ± 0.46	0.0960
Aortic Valve Area (cm^2)	–	2.06 ± 0.44	1.99 ± 0.52	0.3163
Mean Gradient (mm Hg)	–	11.73 ± 4.41	11.87 ± 3.65	0.4277
Stroke Volume Index (mL/m^2)	–	47 ± 9.42	42.43 ± 10.14	0.0824
Left Ventricular Ejection Fraction (%)	–	59.4 ± 8.17	59.85 ± 7.65	0.8650
Survival				
Alive	22(23.2%)	19(51.4%)	30(54.5%)	**0.0001**
Death type				
Cancer Related	47(64.4%)	10(55.6%)	21(84%)	0.1129
Cardiovascular Related	2(2.7%)	3(16.7%)	1(4%)	
Other	2(2.7%)	0(0%)	0(0%)	
Unknown	22(30.1%)	5(27.8%)	3(12%)	

SD: standard deviation; AVR: aortic valve replacement; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement. Bold: statistical significance.

OS was associated with a higher hemoglobin level and higher platelet count. For patients who underwent AVR, the use of aspirin only was associated with an improved OS, the use of dual-antiplatelet therapy with aspirin and a P2Y12 inhibitor or the use of aspirin with a systemic oral anticoagulant did not. Gender, race, cancer type, BMI, prothrombin time, international normalized ratio, and a diagnosis of hypertension, dyslipidemia, diabetes mellitus, or coronary artery disease did not affect the OS of patients who underwent AVR compared to those who received medical therapy alone. A majority of patients enrolled in this study had advanced cancer (66% in the SAVR group, 81% in the TAVR group, and 81% in the medical management group). 84% of the patients in the SAVR group and 81% of patients in the TAVR group completed cancer treatment.

3.4. Statistical analysis for time to cancer therapy

Patients who underwent SAVR were less likely to resume or start cancer treatment than those who underwent TAVR (Table 3). Compared with SAVR patients, TAVR patients had a significantly shorter median time to initiation or resumption of cancer therapy (0.8 months versus 2.4 months, $p < 0.0001$). However, the median follow-up time for SAVR patients was significantly longer compared than that for TAVR

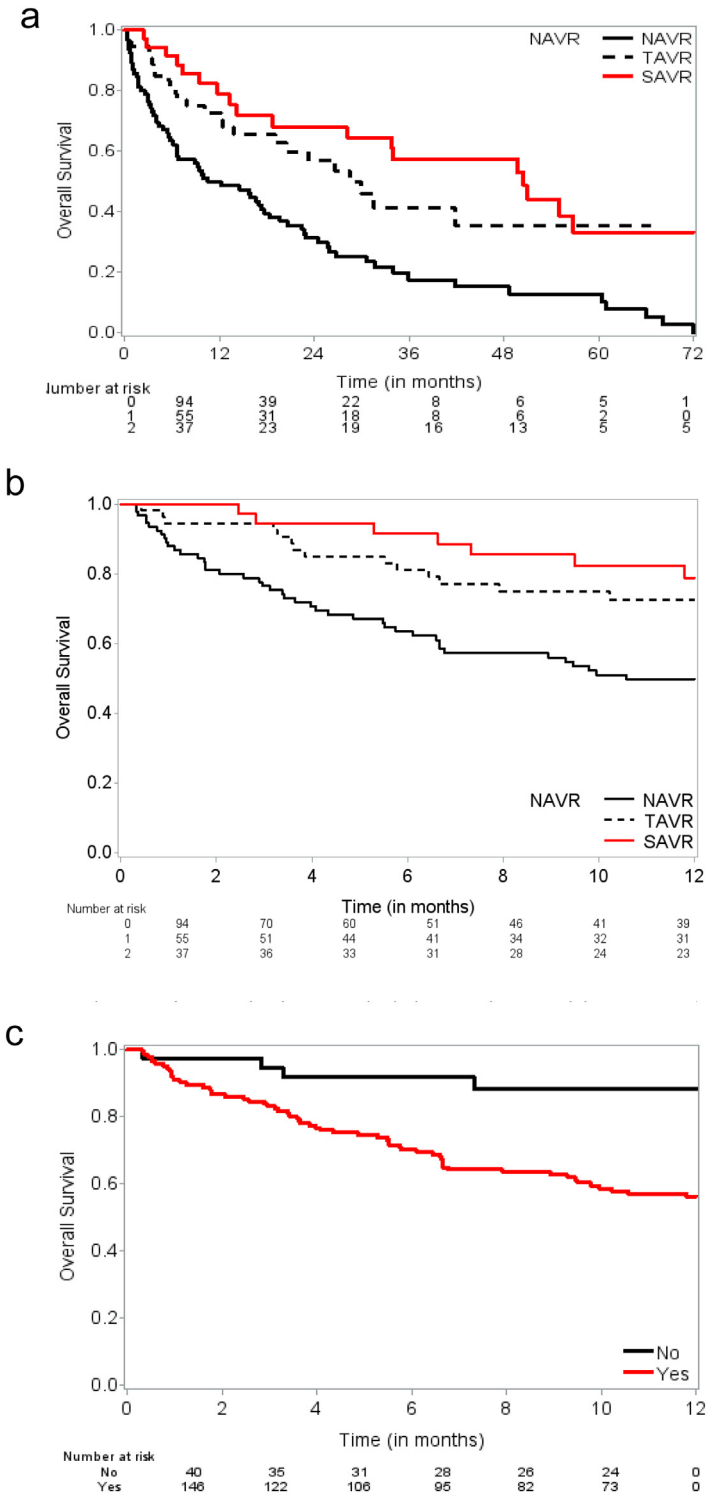

Fig. 2. (a) Overall survival by aortic valve intervention subtype. Kaplan–Meier analysis revealed that patients with NAVR (no aortic valve replacement) have significantly lower survival than patients with TAVR (transcatheter aortic vavle replacement) or SAVR (surgical aortic valve replacement) (p-value <0.0001); patients with TAVR and SAVR appear to have similar long-term survival (p-value = 0.3072). (b) Overall Survival by Aortic Valve Intervention Subtype, survival time censored at 12 months. Kaplan–Meier analysis revealed that patients with NAVR (no aortic valve replacement) have significantly lower survival than patients with TAVR (transcatheter aortic vavle replacement) or SAVR (surgical aortic valve replacement) (p = 0.0010); patients with TAVR and SAVR appear to have similar long-term survival (p = 0.4088). (c) Overall Survival by advanced cancer status, survival time censored at 12 months. Kaplan–Meier analysis revealed that patients with advanced staged cancer had a lower survivorship at 12 months compared to patients who had early staged cancer (p = 0.0018). (d) Overall Survival by NAVR and cancer treatment completion (Yes/No), survival time censored at 12 months.

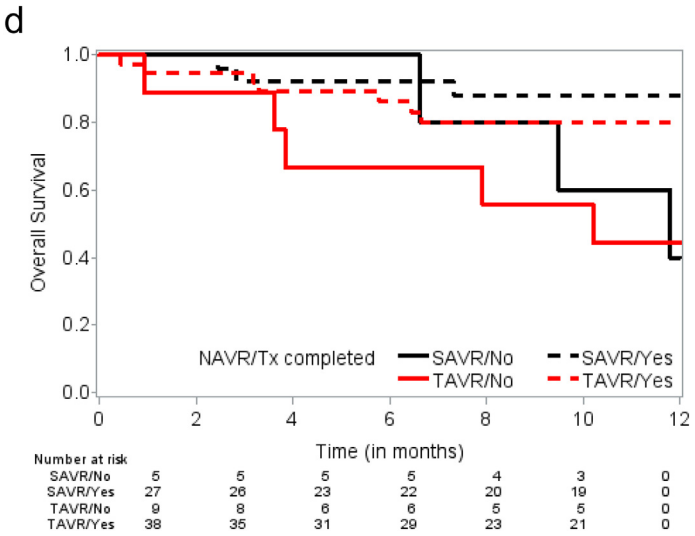

Fig. 2 (*continued*).

Table 2
Overall survival in patients who underwent aortic valve replacement.

Covariate	Hazard ratio	(95% CI)	p-Value
Women	0.859	(0.591-1.249)	0.4262
Age	1.039	(1.019-1.060)	**0.0002**
≥65 years of age	1.762	(1.082-2.869)	**0.0228**
Weight	0.991	(0.982-1.000)	**0.0454**
Height	0.986	(0.968-1.004)	0.1153
Body Mass Index	0.981	(0.954-1.009)	0.1794
Underweight	0.751	(0.264-2.132)	0.5903
Normal	1.000	-	-
Overweight	0.590	(0.369-0.941)	**0.0267**
Obese	0.671	(0.428-1.052)	0.0821
Hypertension	1.062	(0.596-1.894)	0.8376
Dyslipidemia	0.954	(0.610-1.492)	0.8358
Coronary Artery Disease	0.977	(0.674-1.417)	0.9030
Diabetes Mellitus	0.970	(0.646-1.454)	0.8810
Cancer Type			
Hematologic	1.102	(0.747-1.626)	0.6253
Solid	1.059	(0.684-1.640)	0.7977
Laboratory Data			
Platelet Count	0.997	(0.995-0.999)	**0.0130**
Prothrombin Time	1.019	(0.965-1.077)	0.4962
INR	1.221	(0.844-1.767)	0.2900
Creatinine	1.098	(0.920-1.311)	0.2993
Hemoglobin	0.809	(0.732-0.893)	**<0.0001**
Treatment			
Aspirin Only	0.587	(0.388-0.887)	**0.0114**
Aspirin and Clopidogrel	0.870	(0.508-1.491)	0.6125
Aspirin, Clopidogrel, and Oral Anticoagulant	0.884	(0.458-1.708)	0.7141
TAVR	0.468	(0.297-0.739)	**0.0011**
SAVR	0.324	(0.191-0.550)	**<0.0001**
Echocardiographic parameters			
Before Intervention			
Peak Velocity (m/s)	0.924	(0.674-1.267)	0.6241
Aortic Valve Area (cm^2)	1.069	(0.411-2.779)	0.8915
Mean Gradient (mm Hg)	0.990	(0.975-1.006)	0.2363
Stroke Volume Index (mL/m^2)	1.007	(0.986-1.028)	0.5079
Left Ventricular Ejection Fraction (%)	1.009	(0.990-1.029)	0.3324
After Intervention			
Peak Velocity (m/s)	0.879	(0.445-1.736)	0.7112
Aortic Valve Area (cm^2)	0.967	(0.949-1.042)	0.6917
Mean Gradient (mm Hg)	0.988	(0.924-1.057)	0.7335
Stroke Volume Index (mL/m^2)	0.993	(0.961-1.026)	0.6781
Left Ventricular Ejection Fraction (%)	0.993	(0.959-1.029)	0.7060

CI: confidence interval; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement. Bold: statistical significance.

patients (91 months versus 30 months, $p < 0.0001$). Analysis of transthoracic echocardiography performed 1 and 6 months after AVR showed that SAVR and TAVR patients had no significant differences in mean aortic valve measurements (aortic valve gradient, aortic valve area, and peak aortic valve velocity), stroke volume index, or left ventricular ejection fraction following the resumption or initiation of cancer therapy. Patients with transcatheter aortic valve replacement (TAVR) resumed surgery and conventional chemotherapy significantly faster than patients who underwent surgical aortic valve replacement (SAVR).

Of the 116 registered deaths that occurred during the study period, 78 (67.2%) were cancer-related and 6 (5.2%) were attributed to cardiovascular disease. There were 79 deaths in the medical treatment-only group, 22 in the TAVR group, and 15 in the SAVR group. Of the 6 cardiovascular disease related deaths, the 4 deaths seen in the AVR group were attributed to worsening left ventricular dysfunction from chemotherapy resulting in cessation of chemotherapy and the initiation of palliative care for the patients; meanwhile the 2 deaths in the no AVR group were attributed to myocardial infarctions. The median OS for all patients was 21 months.

4. Discussion

Given its poor prognosis, symptomatic severe AS, by itself, is considered a malignant disease. As each cancer patient is unique, the goal of cardiovascular care is to annul the cardiac morbidity and mortality to improve a patient's resiliency to cancer therapeutics thus making cancer the only driver of mortality. No difference in survival has previously been observed in cancer patients who underwent AVR and matched cancer controls [19]. Cancer patients often have a myriad of comorbidities, including bleeding diatheses, multi-organ dysfunction, and frailty that increase their perioperative surgical risk making them ineligible for SAVR. Our findings demonstrate that for cancer patients with symptomatic severe AS who are ineligible for SAVR, TAVR may allow these patients to start or resume oncologic therapies in a timely manner in an attempt to improve cancer mortality.

Our study is the first to demonstrate that the time to initiation or resumption of cancer therapy following AVR is significantly shorter for patients who undergo TAVR than for those who undergo SAVR. Because many of our patients present to our tertiary facility in an advanced clinical stage ultimately requiring the administration of novel/experimental cancer therapeutics, the earlier time difference in patients receiving cancer therapeutics following TAVR versus SAVR (~1.6 months) could

Table 3
Time to cancer treatment resumption after aortic valve replacement.

Cancer treatment	Number (%) or Mean ± SD (Min-Max)		p-Value
	TAVR (N = 48)	SAVR (N = 32)	
Surgery	8 (16.7%)	7 (21.9%)	
Time to treatment	22.6 ± 2.7 (19-26)	79.0 ± 18.3 (50-110)	<0.0001
Conventional chemotherapy	35 (72.9%)	16 (50%)	
Time to treatment	22.7 ± 3.8 (15-29)	72.5 ± 18.1 (40-117)	<0.0001
Immunotherapy	1 (2.1%)	1 (3.1%)	
Time to treatment	27 (NA)	110 (NA)	NA
Radiation therapy	1 (2.1%)	0 (0%)	
Time to treatment	41 (NA)	NA	NA
No therapy	3 (6.3%)	8 (25%)	

SD: standard deviation; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement

mean the administration of additional cycles of chemotherapy or earlier cancer removal surgery, increasing the likelihood of slowing or stopping the cancer progression and possibly improving patient survival. While the researchers were concerned about prosthetic valvular dysfunction in the anti-neoplastic group, none of the cancer therapeutics used [anthracyclines (N = 6), 5-fluorouracil (N = 14), cyclophosphamide (N = 2), cisplatin (N = 6), tyrosine kinase inhibitors (N = 3), and immunotherapies (N = 10)] were associated with prosthetic valvular dysfunction, as defined in a previous study [19], seen on the 1 or 6 month post-operative transthoracic echocardiogram. We also found the follow-up time for SAVR patients was significantly longer than for TAVR patients, but this finding is not uncommon. Since patients who undergo SAVR tend to be healthier compared to those who undergo TAVR, TAVR patients have a higher chance of dying from comorbidities that often do not afflict SAVR patients. Although more cardiovascular deaths were observed in the TAVR group, as the TAVR technology evolved and indications expanded, cardiovascular deaths in TAVR patients began to decrease over time (Fig. 3).

Hematologic disturbances such as thrombocytopenia are common in cancer patients, most often as a result of anti-neoplastic therapies and/or the natural progression of the malignancy. Thus, cancer patients often have clinically significant bleeding events, especially following open heart surgery such as SAVR [20]. Bleeding complications stemming from SAVR are often attributed to the invasive nature of the surgery and/or coagulopathy resulting from cardiopulmonary bypass [21]. Compared with SAVR, TAVR is less invasive and has a lower risk of clinically significant bleeding complications and might be a better option for cancer patients who have a high bleeding risk due to thrombocytopenia, anemia, and hypocoagulability [22,23]. An interesting finding of our study was that individuals who underwent AVR and were able to tolerate ASA afterwards had an improved survival compared to those individuals who were unable to tolerate ASA. The likely mechanism behind this finding is that individuals who were able to tolerate ASA had higher platelet counts and were less likely to experience major bleeding events resulting in an improved overall survival.

End-organ dysfunction, especially acute or chronic renal disease, occurs in up to 50% of patients with AS [24]. Renal dysfunction, a known consequence of many anti-neoplastic therapies, increases the risk of coronary and valvular calcification by inducing metabolic derangements that include increased parathyroid hormone levels, calcium-phosphate products, and vitamin D levels [25]. In addition, severe AS can cause systolic and/or diastolic heart failure, which decreases renal perfusion resulting in renal dysfunction. High surgical risk coupled with poor long-term outcomes after SAVR are common reasons why such patients with renal disease usually receive medical treatment only for AS. Beohar et al. demonstrated that for patients with compromised renal function who are considered ineligible for SAVR because of high or prohibitive risk, TAVR offered an improvement (42%) or no change (34%) in renal function [26]. Patients with chronic renal disease who undergo SAVR have a lower survival rate than those who undergo

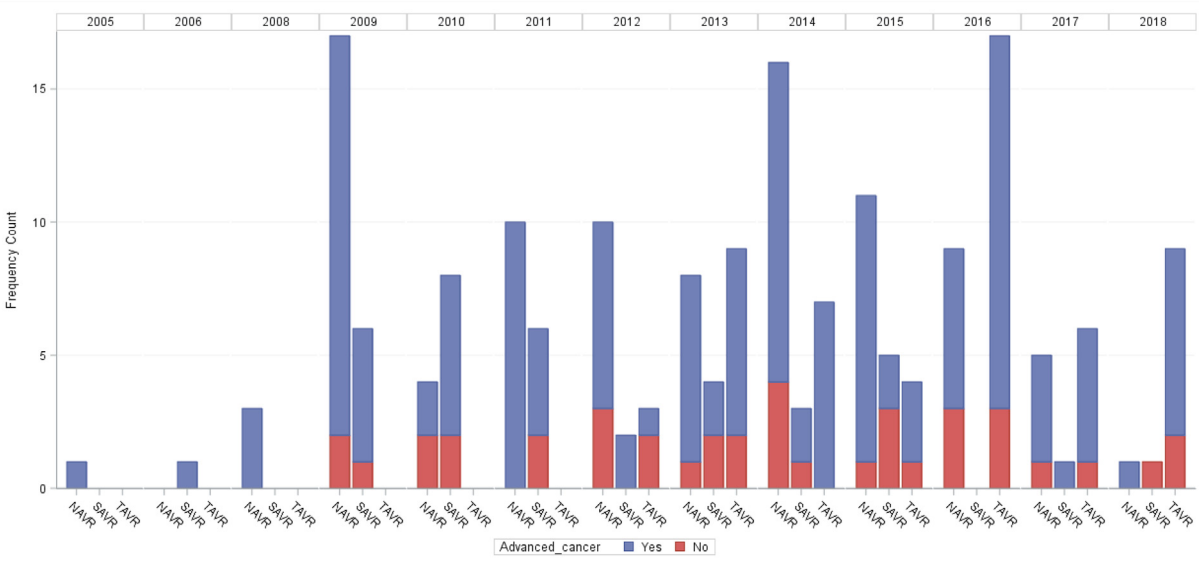

Fig. 3. Number of advanced cancer vs. no advanced cancer by year and no AVR vs. AVR.

TAVR [27]; therefore, for cancer patients with symptomatic severe AS and concomitant renal dysfunction, TAVR may be a better option to reduce the perioperative risk of morbidity and allow such patients to receive timely cancer therapy.

Most cancer patients have some degree of malnutrition due to their disease and/or its treatments; some patients even have cancer-related weight loss and cancer cachexia. As described in a previous study [28], we found that patients who underwent AVR for symptomatic severe AS had a higher mean BMI than their counterparts who received medical treatment only. In cancer patients, higher BMI has been associated with prolonged survival, possibly because patients with higher BMIs have adequate nutrient reserves to counterbalance the malnourishment caused by the side effects of cancer and its treatments [29,30]. This finding underscores the influence of frailty in the perioperative risk assessment of cancer patients with symptomatic severe AS. Increased frailty is common among cancer patients with disease-related weight loss from multiple etiologies [30], and patients with high BMIs are potentially more likely than patients with low BMIs due to cancer-related weight loss to tolerate invasive procedures such as AVR. SAVR is an invasive operation with a prolonged recovery time [31] that increases the risk of worsening malnutrition and cachexia, especially with the development of perioperative complications that prolong recovery. Thus, owing to its shorter recovery time, TAVR could be a more viable option than SAVR for cancer patients with increased frailty, especially in those with cancer cachexia [30].

We did not observe any significant difference in the OS of patients with hematologic versus solid cancer in those who underwent SAVR versus TAVR, which is consistent with previous studies showing that cancer patients who underwent AVR for symptomatic severe AS had a survival benefit regardless of the type or stage of the disease [32,33]. In addition, cardiovascular co-morbidities such as dyslipidemia, hypertension, and diabetes mellitus did not result in a significant difference in OS between patients who underwent SAVR versus TAVR.

5. Limitations

Like the previous study involving this population [28], our study has several limitations. Our study had a small sample size, and its retrospective nature of this study precluded the randomization of patients to TAVR, SAVR, or medical therapy alone. Differences in electronic medical records amongst the AVR facilities, lack of researcher access to each AVR facility's electronic medical record, and non-standardization of the documentation of AVR evaluation amongst AVR facilities made it difficult to obtain patient characteristics such as the presence of concomitant lung disease, frailty scores, etc. and unfortunately had to be omitted from the study. Because our institution is a tertiary center, many of its patients present in severe clinical states requiring advanced cancer management, which can result in unpredictable clinical courses, which could explain why many of our patients who did undergo AVR did ultimately succumb to cancer despite the administration of cancer therapeutics. Such unpredictability can be especially problematic for an institution's "heart team" who try to limit AVR to patients with predicted survival duration of at least 1 year. However, many of these cancer-related deaths were likely delayed by the administration of cancer therapeutics that the patient likely would not have received without prompt resolution of symptomatic severe aortic stenosis. Furthermore, we calculated OS duration from the date of the initial echocardiography at our institution that demonstrated symptomatic severe AS. Also, longer follow-up studies are needed to fully assess prosthetic valve patency during treatment. The use of univariate analysis when determining overall survival following AVR does not allow us to take into account the multitude of factors that impact the overall survival of cancer patients with symptomatic severe AS. Finally, there may have been physician selection bias for AVR versus medical therapy alone, as extremely ill patients were more likely to be referred to hospice care by their oncology specialist than be considered for AVR.

6. Conclusion

This study is the first to demonstrate that in cancer patients with symptomatic severe AS, the time to the initiation or resumption of cancer therapeutics following AVR was significantly shorter for individuals who underwent TAVR compared to those who underwent SAVR. However, longitudinal studies adjusting for other comorbidities are required to assess the impact of earlier initiation or resumption of anti-cancer treatment post-AVR on oncologic outcomes.

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Declaration of competing interest

No conflict of interest is reported with any of the authors

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