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ORIGINAL RESEARCH ARTICLE

One thousand patients with symptomatic aortic valve disease and malignancy: Can they withstand aortic valve replacement?

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Abstract: Aortic valve disease is the third most common cardiovascular disease among the elderly. Once it becomes symptomatic, the short-term prognosis is poor. These patients often have comorbid conditions such as malignancies. The main question is to identify if such patients can undergo aortic valve replacement (AVR) which is the only way to improve prognosis. One thousand patients underwent valve replacement in a 7-year time span. A retrospective file study was performed to evaluate the presence of malignancies, other pre-operative comorbid conditions, severity of heart diseases, operative data and post-operative complications. Statistical analyses were performed using chi-square and Mann-Whitney U-test. Malignancies were found in 137 patients. With respect to comorbid conditions, there were no significant differences between cancer and non-cancer patients, except for a higher mean transvalvular gradient (P = 0.027) and less obesity (P = 0.033) or hyperlipidemia (P = 0.052). Post-operative results showed a trend of delirium cases in cancer patients (P = 0.071), and there was a borderline shorter length of hospital stay (P = 0.087). There were no significant differences in other post-operative complications or mortality, which was 5.8% for cancer patients and 4.5% for non-cancer patients (P = 0.704). Elderly patients with a history of malignancies can withstand major cardiac surgeries such as AVR. They did not exhibit comorbid conditions or major post-operative complications. Mortality was also comparable. If such patients have an acceptable cancer prognosis, they should not be denied the life-saving AVR. However, the decision to offer AVR should be made by a multidisciplinary team involving cardiologists, cardiac surgeons and oncologists. Once such decision is made, it should not be delayed.

Keywords*:* Aortic valve replacement; malignancy; 30-day mortality; 30-day complication rate.

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Introduction

Degenerative aortic valve stenosis is the most common valvular lesion among elderly patients. It is the third most common cardiovascular disease, after arterial hypertension and coronary artery atheromatosis[1]. Its prevalence is age-dependent and varies from 0.3%–0.7% in patients younger than 45 years old and 11.7%–13.3% in patients older than 75 years old[2]. Bach et al. also reported comparable figures[3]. Once symptoms such as dyspnea, angina or syncope develop, the short-term prognosis for this condition is poor[4]. Mortality rate is about 2% per month, with a median survival of 1.8 years and a high admission rate[5,6]. Symptoms and survival rate can only be improved by aortic valve replacement (AVR). However, because of their advanced age, concomitant diseases are often present in patients referred for AVR. Cancer is an important comorbid condition, owing to common risk factors shared by cancer and heart diseases, which include age, obesity and tobacco use.

Prior studies revealed that patients who underwent mainly coronary artery bypass graft (CABG) had a mean age of 69 years, while those who underwent a series of AVR with or without CABG had a mean age of 73 years[7,8]. In both cases, the presence of cancer before a heart surgery had an important mid-term outcome. Moreover, the time interval between cancer and heart surgery was a main determinant of survival[7]. In patients considered for a transcatheter aortic valve implantation, who are almost by definition –very old and frail patients, potential incidental malignant lesions found at pre-procedural imaging reached 18.7%[9]. Since age plays a role in the prevalence of malignancies, a prior malignancy might be more common in elderly heart patients. It might be that a history of treated malignancies increases fragility. Therefore, it is necessary to find out if patients with prior malignancies have more comorbid conditions, and if they can withstand AVR to the same degree as patients without prior malignancies. The pre-operative characteristics as well as the 30-day post-operative outcome of AVR were studied in a cohort of 1,000 consecutive patients.

Patients and methods

In a general teaching hospital, 1,000 consecutive patients with symptomatic aortic valve disease were operated between October 2006 and October 2014. These patients were subdivided according to the presence or absence of prior or current malignancies. Their mean age was 76.2 ± 6.5 years and a total of 709 patients needed additional procedures, with 616 patients requiring CABG. About 30 pre-operative and operative parameters, as well as 30-day post-operative outcomes, were studied. The findings are tabulated in *Tables 2*–*4*.

For this study, chronic obstructive pulmonary disease (COPD) was considered as present when the forced expiratory volume at one second (FEV1) was lower than 70% of the expected theoretical value. Chronic kidney disease (CKD) was present when plasma creatinine was over 1.30 mg % (or mg per 100 mL) or when the estimated glomerular filtration rate was under 60 mL/min. Previous cerebrovascular accident (CVA) was defined as a sudden neurological deficit, which did not resolve in 24 h. This was usually confirmed on computed tomographic (CT) scans. Hypertension was defined as blood pressure that repeatedly exceeded 140/90 mmHg when measured at rest. Carotid artery disease was defined as stenosis of over 50% on duplex-Doppler or with the presence of severe calcification. A left ventricular ejection fraction (LVEF) of less than 50% was considered abnormal. An alternative classification was the description of the left ventricular function as normal (N), mildly decreased (L), moderately decreased (M) or severely decreased (S). The latter three were grouped as subnormal. Atrial fibrillation, if present, was recorded as either paroxysmal or chronic. The severity of aortic stenosis (mean and peak transvalvular gradient), aortic valve area (AVA) or regurgitation (graded between 1 and 4) was estimated by echo-Doppler. Coronary artery disease (CAD) was documented by angiography.

Valve replacement was performed via median sternotomy and the installation of extracorporeal circulation was performed with topical cooling. Upon the opening of aorta, valve leaflets were excised and biological prosthesis valves were implanted. If necessary, additional procedures such as CABG and mitral valve repair were performed. Emergent surgeries were defined as the need to perform AVR within the same day to save the patients' life.

Patients were transferred to the intensive care unit (ICU) post-surgery. A stay of more than one day was defined as prolonged. If a return to the ICU was necessary, the durations of both stays were added together. The parameters of interest are given in *Table 4* and these included an increase in the need for transfusion plasma (over 4 units of packed cells) or its derivatives, concentrated thrombocytes, duration of mechanical ventilation (over 8 h) and a longer stay in the ICU (more than one day). Hospital complications that occurred within 30 days after surgery were also recorded. The complications included endocarditis (fever, positive culture, vegetation on echocardiography), thromboembolism (sudden neurological deficit or peripheral thrombi), bleeding, ventricular arrhythmia, new or recurrent atrial fibrillation, new or progressing conduction defect on ECG, congestive heart failure or low cardiac output syndrome (LCOS), pulmonary complication (prolonged hypoxia, clinical and radiological signs of atelectasis or pneumonia), pleural complications (pleural effusion needing evacuation, prolonged drainage), acute renal function impairment (a rise in creatinine to 0.30 mg %), low platelet (more than once

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below 100,000 per mm³), episodes of delirium, need for re-intervention (bleeding, tamponade) and mortality.

All data were collected retrospectively by studying patient files. Since the number of patients with active malignancies that are under control or newly diagnosed tumors is low, stratification is not useful. Statistical analyses performed included a chi-square and Fisher exact test to analyze the relationship between the presence of malignancies and other factors. A Mann-Whitney U-test was used to compare continuous variables between patients with and without cancer. The differences were considered as statistically significant if $P < 0.05$.

Results

Malignancies were found in 137 patients. *Table 1* shows the prevalence of each malignancy type. Malignancies were treated with curative intent in a majority of the cases. Malignancies such as chronic lymphatic leukemia, multiple myeloma and advanced cases of polycythemia vera (PV) or myelodysplasia (MDS) were under control. Only 2 malignancies were detected during the cardiac work-up and considered as curable. *Tables 2–4* described the differences between

Table 1 Types of malignancies

Type	Number
Prostate	40
Breast	32
Colon	27
Larynx	6
Renal cell carcinoma	4
Myelodysplastic	4
Pulmonary	3
Multiple myeloma	3
Bladder	3
Chronic lymphatic leukemia	3
Non-Hodgkin lymphoma	2
Colon + breast	2
Gastric	1
Esophagus	1
Hodgkin's disease	1
Mouth	1
Advanced polycythemia	1
Spinocellular cancer	1
Malignant thymoma	1

Table 2 Distribution of pre-operative factors between cancer and non-cancer patients

Pre-operative factor	With cancer (%)	Without cancer (%)	*P*
Demographic			
Male	88/137 (64.2)	480/841(57.1)	0.069
Over 80 years old	42/137 (30.7)	268/841 (31.9)	0.431
Mean age (years)	76.1 ± 6.6	76.3 ± 6.0	0.996
Non-cardiac comorbidity			
Obesity	46/137 (33.6)	355/840 (42.3)	0.033
Dyslipidemia	75/137 (54.7)	525/840 (62.5)	0.052
FEV1 (%)	87.0 ± 27.2	91.9 ± 23.1	0.180
Carotid artery disease	25/136 (18.4)	183/838 (21.8)	0.183
Hypertension	97/137 (70.8)	624/835 (74.7)	0.192
Pulmonary arterial hypertension	24/137 (17.5)	130/839 (15.5)	0.311
COPD	45/135 (33.3)	257/832 (30.9)	0.317
Peripheral artery disease	35/136 (25.7)	229/839 (27.3)	0.377
Diabetes	40/137 (29.2)	201/841 (23.9)	0.382
CKD	11/64 (17.2)	89/378 (23.5)	0.568
CVA	16/136 (11.8)	111/838 (13.2)	0.634
Ventricular factors			
Decreased LV function	43/127 (33.9)	198/761 (26.0)	0.066
Left ventricular hypertrophy	103/119 (86.6)	634/708 (89.5)	0.206
Congestive heart failure	35/136(27.5)	214/841(25.4)	0.509
Need for urgent surgery	11/137(8.0)	48/841(5.7)	0.696
LVEF (%)	61.2 ± 17.1	60.4 ± 16.1	0.828
Valvular factors			
Mean gradient (mmHg)	49.7 ± 17.8	45.1 ± 15.5	0.012
Peak gradient (mmHg)	71.4 ± 25.4	73.1 ± 24.9	0.904
Conduction defect and arrhythmias			
Ventricular arrhythmias	12/136 (8.8)	124/835 (2.9)	0.166
Conduction defect	49/135 (36.3)	258/830 (31.1)	0.391
Need for digitalis	5/132 (3.8)	25/830 (3.0)	0.395
Atrial fibrillation	33/135 (24.4)	212/835 (25.4)	0.454
Coronary related factors			
Prior CABG	68/839 (8.1)	15/137 (10.9)	0.172
Prior PCI	18/137 (13.1)	125/839 (14.9)	0.348
Myocardial infarction	23/137 (16.8)	136/838 (16.2)	0.476
Coronary artery disease	88/137 (64.2)	542/841 (64.4)	0.972

CABG: coronary artery bypass graft; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; FEV1: forced expiratory volume at 1 second; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention

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Table 3 Distribution of operative factors between cancer and non-cancer patients

Operative factor	With cancer (%)	Without cancer (%)	*P*
Carotid artery surgery	1/135 (0.7)	21/829 (2.5)	0.163
CC-time valve (min)	55.2 ± 15.3	57.4 ± 18.0	0.214
Mitral valve repair	5/134 (3.7)	47/828 (5.7)	0.243
CC-time all (min)	65.4 ± 19.1	67.3 ± 20.3	0.514
Concomitant CABG	82/137 (59.9)	520/841(61.8)	0.528
Aortoplasty	11/135 (8.1)	66/829 (8.9)	0.912

Table 4 Distribution of post-operative factors between cancer and non-cancer patients

Post-operative factor	With cancer (%)	Without cancer (%)	*P*
Delirium	18/135 (13.3)	74/837 (8.8)	0.071
Increased LOS	34/131 (26.0)	261/808(32.3)	0.087
Thromboembolism	7/135 (5.2)	23/837 (2.7)	0.109
Atrial fibrillation	46/134 (34.2)	331/837(39.5)	0.146
Pulmonary complication	16/135 (11.9)	127/835 (3.3)	0.188
Ventricular arrhythmia	7/135 (5.2)	28/837 (3.3)	0.202
Need for plasma	43/134 (32.1)	43/134 (32.1)	0.294
Pleura complication	19/135 (14.1)	137/836(16.4)	0.295
Low platelet count	12/135 (8.9)	61/835 (7.3)	0.309
Renal function decrease	30/133 (22.6)	186/825(22.5)	0.317
Congestive heart failure	11/135 (8.1)	57/835 (6.8)	0.341
Arterial oxygen (mmHg)	86.5 ± 23.3	89.3 ± 24.9	0.362
Post-operative stay (days)	9.7 ± 9.3	9.9 ± 8.1	0.402
Prolonged ICU stay	39/136 (28.7)	247/833(29.7)	0.452
Left atrial pressure (mmHg)	17.7 ± 4.5	18.0 ± 5.0	0.467
Need for thrombocytes	14/134 (10.4)	90/816 (11.0)	0.491
Bleeding	9/136 (6.6)	54/837 (6.5)	0.530
Endocarditis	0/135 (0.0)	8/836 (0.4)	0.638
Total stay (days)	12.3 ± 9.5	12.7 ± 9.5	0.666
Transfusion > 4 units	36/134 (26.9)	192/815(23.6)	0.690
Transfusion	101/134(75.4)	602/816(73.8)	0.696
Mortality	8/137 (5.8)	38/838 (4.5)	0.704
Conduction defect	26/137 (19.0)	158/841(18.8)	0.764
Ventilation time (h)	15.4 ± 48.7	16.6 ± 56.2	0.845
Glycaemia (mg %)	164.6 ± 39.9	165.0 ± 44.2	0.879
Myocardial infarction	1/135 (0.7)	8/836 (1.0)	0.916
Stay in ICU (days)	3.38 ± 8.2	2.78 ± 5.7	0.943

ICU: intensive care unit; LOS: length of stay

cancer and non-cancer patients. Categorical variables were presented as ratios and continuous variables as mean values with standard deviations. The results for each factor were computed and ranked according to their respective *P* values. The mean transvalvular gradients were significantly higher in patients with prior malignancies. These patients were also significantly less obese and had less dyslipidemia. There was also a trend of male patients being more diabetic and experiencing left ventricular (LV) dysfunctions. Other pre-operative factors as well as operative factors did not differ significantly between patients with and without prior malignancies. In cancer patients, post-operative delirium was more prominent but, remarkably, they also showed a shorter post-operative stay. There were no significant differences in factors related to the ICU admission. A longer hospital stay (more than one day) was observed in 28.5% of the cancer patients and 29.7% for non-cancer patients. However, the mean duration of stay was almost 4 days for cancer patients and just under 2 days for non-cancer patients. Arterial partial oxygen pressure, left atrial pressure and plasma glycaemia were very similar for both groups. The requirements for blood transfusion and its derivatives were also very comparable.

Discussion

Previous studies investigating the effects of prior cancer on patient outcomes after cardiac surgery were small and restricted to one type of tumor. Often, heart diseases were found during the work-up of cancer patients or vice versa. In the latter case, lung cancer is usually involved. In some studies, long-term effects of chest radiotherapy on the heart was examined[10,11]. There are only 3 other large studies, which compared the post-operative results between cancer patients with heart surgeries and non-cancer patients[7,12,13]. However, the design of experiment for each study differed, making comparisons difficult. Nevertheless, some general conclusions can be drawn. The first study focused entirely on the long-term outcome[7]. The long-term survival of 205 patients with malignancies depended not only on the presence of cancer but also on the time interval between the treatment of cancer and heart surgery. This time interval can be considered as a substitute for a chance of cure. In contrast, the

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current study focuses entirely on the short-term outcome. Interestingly, in the second study, the cancer group was subdivided into patients with cancer in remission and patients with active cancer[13]. No major differences in comorbidity were found between these groups and non-cancer patients. The number of patients, however, was considerably smaller and this could be why a significant level was not reached. The third study also focused solely on the short-term outcomes[12]. In all studies, breast and prostate cancers were very common but hematological malignancies were also prominent in the third study. The cancer incidence reported in previously was lower than that currently observed, 1.8% to 4.2%. The incidence in the current group is 13.7% and this could be attributed to an older patient age. Nevertheless, the presence of comorbidities such as diabetes, hypertension, CKD and COPD were comparable to the current study. The need for urgent surgery was remarkably high in one study[12]. However, as for most other comorbid conditions, definitions of comorbid conditions or post-operative events were absent, which made these studies difficult to compare.

As per our previous study, most cancer patients had received curative cancer treatments and subsequently survived for several years[7]. Therefore, these cancer survivors belong to a select group that is potentially responsible for a lesser degree of obesity and hyperlipidemia. A pre-operative assessment of patients' condition is usually performed using the Society of Thoracic Surgeons (STS) or European System for Cardiac Operative Risk Evaluation (EUROScore) scoring system. STS scoring includes a patient's height and weight while EUROScore does not. Moreover, lipid levels were not considered in these scoring systems. A body mass index (BMI) lower than 20 or higher than 30 (and even 35) was not identified as predictors of short-term outcomes, but being underweight was a risk factor for long-term mortality[14]. This indicates that it is unnecessary to include BMI in these scoring systems. A higher mean transvalvular gradient points to a more severe valve disease, which could delay a patient's referral for AVR. The absence of important differences in the pre-operative factors of our study was reflected by the absence of differences in the operative data as there were no significant differences in the cross-clamp times. This indicated that cancer patients did not experience more technical difficulties or undergo additional procedures compared to other patients. In the older studies, there were also no significant differences in the types of surgery undergone by cancer and non-cancer patients[7,12,13]. One has to take into account that the aortic valve disease is the prime indication for surgery for almost all of the patients reported in the current study, while CABG was the most frequently performed procedure in the other studies.

The absence of differences in pre-operative factors was also reflected in the post-operative results. There was an increase in post-operative delirium in patients with prior malignancies, *i.e.* 13.3% compared to 8.8% in other patients. This, however, is inconsistent. In one review paper, cancer is not identified as a predictor for post-operative delirium, nor is it included in the analysis[15,16]. Moreover, it only considered delirium with agitation, which is more easily detected than hypoactive delirium. Hence, the latter condition might be missed. However, post-operative delirium may be a marker of poor outcome for patients admitted into the ICU[15]. Furthermore, an extracorporeal circulation, along with its known effects on post-operative mental states, needed to be installed in all cases where AVR was performed.

Other 30-day complications were not significantly present in cancer patients. In the current study, there was no increased need for blood or other blood products. However, in an older study, the need for transfusion, re-intubation and arrhythmias was significantly increased in patients with cancer[12]. One could assume that the large proportion of hematological malignancies could be held responsible for the tendency of post-operative bleeding or infection. However, the same observation was made even after excluding hematological malignancies. Other studies also reported higher post-operative complications and mortality rates in patients with chronic lymphatic leukemia[17,18]. This observation, however, is not universal[19]. A possible reason for the increased need for transfusion could be the frequency of redo surgeries, which is in the range of 15% to 19% in the older studies, compared to 8% to 9% in the current report[12].

The mortality rate between current cancer and non-cancer patients was comparable (4.5% vs. 5.8%) and in line with older results. The post-operative mortality in the cancer group could not be attributed to malignancies nor to any other factors[12,13]. Together,

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these facts suggested that cancer patients are not more fragile than other patients.

These data showed the importance of AVR as the operation alleviates an immediate life-threatening heart condition. Even in patients with active cancer and severe aortic valve disease, it is worthwhile to replace the defective valve. In contrast to other medical treatments, AVR significantly prolongs a patient's survival rate. This is reflected in the cause of death as most deaths in the medically treated group were of cardiac origin. In the operated group, mortality at 3–4 years was much lower and was more commonly attributed to cancer. The survival rate in advanced cancer patients who had undergone AVR was acceptable, although the size of the group was small[20].

Another concern is the prior irradiation of the chest, usually for mediastinal lymphomas, breast cancers and pulmonary cancers. There was a dose response relation for cardiopulmonary damage with a safe upper limit of 25 Gray to the left atrium, or 30 Gray to the left ventricle[11]. This damage develops slowly and can remain asymptomatic for a long time, involving all parts of the heart including the coronary arteries and valves[11,21]. Valve stenosis is a late onset complication, which usually becomes clinically relevant after 20 years or more[21]. However, one must take into account the heterogeneity of cancer survivors, who received varying doses of radiation that was delivered to the heart and lungs. A high dose resulted in higher perioperative complications and mortality, even after adjusting for age and other factors. Radiation-induced pulmonary disease seemed to be the precipitating factor, but in the current population, there was no significant difference in the number of patients needing prolonged ventilation[10]. Moreover, radiation-induced heart or lung diseases can be largely prevented by modern protocols. Hence, the prior irradiation of the chest did not play a major role in the current outcome.

This study demonstrated some limitations as its design is retrospective; however, the collection of 1,000 consecutive patients represented a "real life" situation. Registration was incomplete, especially with malignancies that were usually diagnosed and treated in other centers. A randomized controlled trial could be performed to confirm or disprove the current results. However, denying the AVR treatment as the only means of prolonging life in patients with a double disease is unethical since the survival rate of most malignancies, if properly treated, is much longer than that of a symptomatic aortic valve disease. Moreover, current results suggested that there was no need to include malignancies in scoring systems, which evaluated the short-term risk of aortic valve surgeries. Comparisons with other studies can be difficult because pre-operative factors and post-operative complications are not always defined.

Conclusion

In spite of senescence and considerable pre-operative comorbidity, patients with prior or even current malignancies can withstand surgical AVR. These patients did not show more comorbid conditions compared to non-cancer patients, and their 30-day mortality and complication rates were also comparable. Therefore, if such patients have an acceptable mid- or long-term cancer prognosis, they should not be denied the benefits of AVR, which is considered as life prolonging and symptom-reducing. AVR seems to be able to restore the chances of survival for dual condition patients to that which is comparable to a cancer population free from valve stenosis. However, the decision to offer AVR should be made by a multidisciplinary team involving cardiologists, cardiac surgeons and oncologists, and once a decision is made, its implementation should not be delayed.

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