The Onco-cardiologist Dilemma: to Implant, to Defer, or to Avoid Transcatheter Aortic Valve Replacement in Cancer Patients with Aortic Stenosis?

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Abstract

Purpose of Review Aging is associated with an increased prevalence of both cancer and heart disease. The progression of aortic valve calcification to aortic stenosis may be accelerated by both cardiovascular risk factors and cancer treatments, such as radiotherapy with mediastinal involvement. Symptomatic aortic stenosis is occasionally diagnosed in cancer patients undergoing cardiovascular evaluation; likewise, cancer is often recognized during assessment preceding aortic valve interventions. In these complex cases, physicians face difficult treatment decisions. Due to a myriad of clinical presentations of cancer and valve disease, specific guidelines for this patient population are not currently in place. Management is currently based on clinical judgment, on an individual basis.

Recent Findings Patients with cancer in remission or with a favorable prognosis should be treated according to current cardiovascular guidelines. In these patients, aortic valve replacement can be performed either by surgery or transcatheter. Significant challenges arise in patients with active cancer, especially those receiving anti-cancer treatment. Recent data suggests that these patients can be offered aortic valve replacement, with a trend of favoring the transcatheter route in order to minimize perioperative

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risk and complications associated with major surgery. Patients with advanced cancer and severe aortic stenosis should be offered palliative care and can benefit from aortic balloon valvuloplasty if indicated. Modern cancer treatments associated with improved long-term prognosis may allow the appropriate cure of aortic stenosis.

Summary We discuss the protocol, outcomes, and evolving recommendations of aortic valve replacement in cancer patients with aortic stenosis.

Introduction

The prevalence of heart valve calcifications increases with age [1] and their presence is associated with a poor prognosis [2]. Calcific aortic stenosis (AS) is a common condition of the elderly [3], caused by progressive atherosclerosis and structural valve degeneration due to inflammation, fibrosis, and calcification related to traditional cardiovascular risk factors [4]. The latter is the main driver of atherosclerotic cardiovascular disease in elderly populations [5]. Cancer also occurs more frequently with advancing age [6] and has a major impact on mortality. In the Atherosclerosis Risk in Communities (ARIC) Trial, the presence of ideal cardiovascular health markers in midlife (smoking, body mass index, total cholesterol, blood pressure, physical activity, and blood glucose) was associated with a lower incidence of both AS and cancer after 75 years of age [4, 7]. These results highlight not only the age-dependency, but also common predisposing factors for cancer and cardiovascular disease.

The elderly are at risk for both cardiovascular disease, either ischemic or valvular, and cancer. The simultaneous diagnosis of both these conditions in the same patient, which is a frequent occurrence [8], raises difficult treatment decisions. The treatment of the underlying cardiovascular disease process may lead to cancer-associated risks (such as bleeding) [9], while cancer therapies may lead to cardiac complications and worsen cardiovascular outcomes [10, 11].

Of all cardiovascular comorbidities in cancer patients, AS is one of the most important comorbidities. Surprisingly, no large-scale epidemiological studies currently report the exact prevalence of AS in cancer patients. The standard treatment is still surgical aortic valve replacement (SAVR), although the cancer patient is often a high-risk candidate for major cardiac surgery. Transcatheter aortic valve replacement (TAVR) was introduced in clinical practice to potentially benefit such patients, which are considered too high risk for SAVR [12]. Today, it is commercially available for patients with symptomatic AS at high and intermediate risk for traditional surgery. Very recently, the PARTNER 3 trial identified a survival benefit of TAVR over SAVR at 1-year in low-risk patients [13]. This conclusion is supported by the EVOLUT trial in low-risk patients, suggesting that TAVR was non-inferior to SAVR at 24 months [14]. Current research trials are investigating TAVR for asymptomatic patients as well. The current review considers the available data on the association between AS, cancer, and therapeutic options (Table 1) in this increasingly identified patient population, with emphasis on endovascular procedures.

Aortic Stenosis Prevalence and Prognosis in Cancer Patients

In the General Cancer Population

The prevalence of cancer in patients with severe AS varies between 5.4 and 26% [24, 28]. There are very few reports regarding the prognosis of patients with valvular disease and cancer, and even less are available in patients with AS. In a 10-year single-center retrospective study, cancer patients with severe AS and a mean aortic valve area 1.0 ± 0.3 cm^2 had a 5-year mortality of 48% [29]. Most deaths (59%) were due to cancer progression, but 31% were due to heart failure and stroke. Interestingly, the prevalence of AS was relatively low (111 cases from 26,325 cancer patients, 0.42%), despite a mean age of 79.8 years of the whole studied population. Older age and symptomatic AS (syncope or heart failure) were among the main independent predictors of mortality. Mortality due to heart failure was more frequently encountered in patients with AS than in cancer patients without aortic valve disease.

A Japanese retrospective study of 3815 patients in a multicenter AS registry found that outcomes are worse not only in patients with active cancer but also in those with a history of malignancy [25•]. Mortality was mainly cancer-related, with comparable aortic valve–related deaths between cancer and no-cancer patients.

In Patients with Previous Chest Radiotherapy

Chest irradiation used to treat thoracic cancers, such as lymphomas, is responsible for chronic pericarditis, coronary artery disease, myocardial fibrosis, and restrictive physiology, but also for valve disease including AS [30–32]. The prevalence of AS reaches 16% at 20 years after radiation therapy [33]. This is due to the osteogenic transformation of aortic valve interstitial cells, presumably involved in the

Table 1 Available non-interventional studies enrolling cancer patients with short- and/or long-term reported outcomes after aortic valve replacement

Study, year	No. of cancer/total patients (%)	Cancer types	No. of SAVR (STS, EuroSCORE II)	No. of TAVR (STS, EuroSCORE II)	30-Day mortality (%)	Long-term mortality (%)	Mortality HR (95% CI)	Median follow-up
Carrascal, 2008 [15]	89/2146 (4%)	Various	89 (NA, 7%)	NA	NA	12/89 (13%)	Active cancer 4.5 (1.2–16.8)	22–30 months
Yusuf, 2011 [16••]	48/48 (100%)	Various	13 (NA)	NA	NA	4/13 (31%)	SAVR: 0.22 (NA)	84 months
Wu, 2013 [17]	173/478 (36%)	Thoracic malignancy	40 (NA, 8%)	NA	7/173 (4%)	95/173 (55%)	Rx heart disease 2.5 (1.8–3.4) EuroSCORE 1.2 (1.2–1.3) Beta-blockers 0.7 (0.5–0.9)	7.6 years
Dijos, 2015 [18]	19/198 (10%)	Various	NA	19 (NA, 3%)	0/19 (0%)	0/19 (0%)	NA	6 months
Paven, 2015 [19]	32/37 (46%)	Hodgkin	16 (NA, 3%)	17 (NA, 3%)	SAVR 4/16 (25%) TAVR 1/17 (6%)	SAVR 25% TAVR 18%	NA	12 months
Sari, 2015 [20]	5/133 (4%)	Hematologic	NA	5 (6%, 17%)	0/5 (0%)	0/5 (0%)	NA	12 months
Watanabe, 2016 [21]	47/749 (6%)	Various	NA	47 (5%, 3%)	2/47 (4%)	5/47 (11%)	Metastasis 4.7 (1.1–20.0)	272 days
Berkovitch, 2018 [22],	91/477 (19%)	Various	NA	91 (5%, 5%)	1/91 (1%)	13/91 (14%)	Cancer treatment within 1 year prior to TAVR 4 (1–17)	851 days
Donnellan, 2018 [23]	81/243 (33%)	Thoracic malignancy	*123 (NA)	*23 (NA)	1/81 (1%)	*49/243 (20%)	Chest Rx 4 (2.1–7.8) AVR 0.5 (0.2–0.9)	35 months
Mangner, 2018 [24]	350/1821 (19%)	Various	NA	350 (6%, **14%)	Active cancer 6% History of cancer 4%	Active cancer 37% History of cancer 16%	Active cancer 2 (1.4–3.1)	3 years
Minamino-Muta, 2018 [25]	513/3815 (13%)	Various	Active cancer 16 AVR (4%, NA) History of cancer 114 AVR (4%, NA)	NA	NA	Active cancer 65% History of cancer 39%	Active cancer 2.5 (1.9–3.1) History of cancer 1.2 (1.0–1.5)	1176 days
Schechter, 2018 [26]	65/65 (100%)	Various	7 (NA)	30 (NA)	NA	31/65 (48%)	AVR 0.4 (0.2–0.8) TAVR 0.4 (0.2–0.8) SAVR 0.4 (0.1–1.5)	34 months
Landes, 2019 [27••]	222/2744 (8%)	Various	NA	222 (5%, 4%)	4/222 (2%)	33/222 (15%)	Cancer stages III–IV 3.2 (2.4–4.4)	330 days

AVR, aortic valve replacement; CI, confidence interval; HR, hazard ratio; NA, non-applicable; Rx, radiation; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgery score; TAVR, transcatheter aortic valve replacement

*Information on the whole group, without precise numbers within the cancer subgroup

**Logistic EuroSCORE I value

pathogenesis of calcific AS [34]. The rate of moderate AS progression in patients with previous mediastinal irradiation is the same as that of matched control patients: 60% of both groups progress to symptomatic severe AS at a mean of 3.6 ± 2 years of follow-up [23]. Symptoms attributable to AS occur earlier in patients with a history of chest radiation therapy, which increase referral for AVR. In the PARTNER trial, approximately 5% of the enrolled patients had a history of therapeutic thoracic irradiation [35]. Chest radiation therapy may induce mediastinal fibrosis and "porcelain aorta" that makes SAVR very difficult ("hostile thorax"). In patients who have achieved remission, TAVR is an appropriate therapy [19, 33, 36]. The risk of valvular disease with cancer therapy depends on radiation dose, concomitant chemotherapy, and duration from first exposure [37, 38]. Among all chemotherapeutic agents, anthracyclines accelerate valve fibrosis, mainly of the left heart [30, 39]. Literature data regarding specific cancers and aortic valve disease is missing.

Cancer as an Incidental Finding During TAVR Assessment

Cancer is sometimes found during the cardiovascular assessment preceding planned TAVR. In a single-center report on 394 patients assessed for TAVR, multi-slice computed tomography (CT) identified malignant findings in 4.2% of patients [40]. Similar results were reported in 131 TAVR candidates with a mean age of 81.6 years. Thoraco-abdominal CT angiography, which is performed for vascular anatomy imaging for procedural preplanning, identified masses highly suspicious for malignancy in 3.8% of the studied group [41]. In another single-center trial on 484 consecutive patients evaluated for TAVR, solitary pulmonary nodules larger than 5 mm were found by CT angiography in 87 patients (18%) [42]; at a median follow-up of 455 days, cancer was confirmed in just 2 patients. The incidental discovery of non-definite cancer lung nodules should prompt an expedited lung nodule workup. The decision for TAVR versus open heart surgery is based on the definite diagnosis of cancer, location and size of nodule, need for surgery, and overall prognosis. This is not the case for patients with a definite diagnosis of thoracic malignancy, where a multidisciplinary Tumor Board evaluation should establish future diagnostic work-up and treatment.

Aortic valve calcification can also be incidentally detected when low-dose CT is used to screen for cancer, identifying AS when the aortic valve calcium score is higher than 138.37 [43].

SAVR in Cancer Patients

Patients with severe AS are poor candidates for surgery mainly because of comorbidities that increase the estimated periprocedural morbidity and mortality. However, patients with cancer in early stages with symptomatic AS or an aortic valve area under 0.75 cm^2 should be considered for AVR [29]. Occasional reports describe SAVR being performed prior to cancer surgery, yielding various results [43].

An important issue related to SAVR in cancer patients is that valve surgery requires extracorporeal circulation. Among various other systemic effects, cardio-pulmonary bypass may induce immunosuppression, increase inflammation (as demonstrated by a significant increase in TNF-alpha, Il-10, Il-6, Il-1, and TGF-beta) [44], and worsen cancer outcomes [45]. Because of the immunosuppressive effects, patients with hematological cancers may have worse outcomes than those with solid tumors and better functioning immune system.

Old reports on small patient cohorts found an increased risk of metastasis in the early stages of lung cancer (I and II) [46], possibly related to the significant immunosuppression induced by the dampening of T cell–mediated response by TGF-beta [44]. Some small trials that investigated the outcome of major cardio-thoracic surgery excluded stage IV subjects and did not confirm the worsening of cancer prognosis, but reported higher periprocedural mortality [46]. No major influence on cancer-related outcome was observed in patients having a mean survival of 4.3 years if their AS was not surgically repaired and 5.8 years if it was surgically repaired [46]. In another small retrospective trial, SAVR provided a survival benefit in patients with severe AS irrespective of cancer status or the presence of metastatic disease [16••].

All these small trials suggest that cardio-pulmonary bypass needed for valve surgery may be used in cancer patients in early stages of the disease, prior to specific cancer treatment and irrespective of cancer type, including hematological neoplasms [47–49].

In patients with coronary artery disease, off-pump coronary artery bypass grafting (CABG) provides the same outcome as on-pump procedures in oncologic patients [47]. However, a large retrospective study performed on 43,347 patients treated by CABG with or without cardio-pulmonary bypass demonstrated a 12% increase in cancer mortality [50]. Among 11 different types of cancer, melanoma and lung cancer were associated with higher surgical risk when cardio-pulmonary bypass was performed (66% and 36% respectively versus off-pump surgery). Cardio-pulmonary bypass was indicated mainly for CABG, with very few patients undergoing surgery for valvular heart disease and AS in all the reported studies above.

In a trial performed on 89 cancer patients from different locations, the patients were operated under extracorporeal circulation; 45% had active cancer and were treated by SAVR [15]. Although perioperative morbidity and mortality were not different in cancer versus non-cancer patients, long-term survival was reduced in the active cancer subgroup because of cancer complications.

It is reasonable to assume that TAVR may provide better outcomes than SAVR in cancer patients with severe AS by avoiding cardio-pulmonary bypass. This hypothesis, however, has not yet been tested in a prospective randomized trial.

TAVR in Cancer Patients

The major therapeutic conundrum in cancer patients with AS is that they are often ineligible for valve replacement because of cancer and cannot undergo cancer surgery because of severe valve disease. If one includes active cancer as a major comorbidity that makes surgical risk prohibitive, then TAVR would be indicated. TAVR may be an acceptable-risk intervention for the treatment of AS and may allow patients to undergo cancer treatment as indicated [9]. In the original PARTNER trial report, 1-year mortality in patients with severe symptomatic AS randomized to optimal medical therapy reached 50.7% [12]. In the PARTNER trial, risk factors for death included the history of cancer (HR 2.4; 68% CI 1.7–3.2) along with a smaller body frame, lower albumin levels, and prosthesis mismatch [51]. Cancer was diagnosed in 14% (47 out of 310) of the patients enrolled in this trial.

Patients with AS are considered high-risk for SAVR because of surgical challenges (i.e., porcelain aorta) or major comorbidities, including cancer. Technical difficulties for surgery may be overcome by TAVR [36], but major comorbidities may influence post-TAVR prognosis just as with SAVR [51]. To qualify for TAVR, patients should have a prognosis of 1 year or greater [22]. However, accurately estimating prognosis is often difficult in this patient population, especially given the rapidly expanding therapies for cancer. In addition, it should be taken into consideration that cancer patients with AS may need a valve intervention in different stages of their neoplastic disease. Patients with already-treated cancers who are in remission are often eligible for TAVR [52]. In these cases, remission should be evaluated and confirmed by the oncology team before referring the patient to the catheterization lab.

The management of valvular heart disease is most difficult to decide in patients with a concomitant diagnosis of severe AS and cancer. Patients with a cancer diagnosis in early stages who can safely receive oncologic treatment could be easily considered for TAVR as soon as remission is confirmed. In other cases, performing TAVR first allows for radical oncologic surgical treatment shortly after valve intervention [53–55]. Patients with AS and a localized cancer complication (e.g., bleeding from colon adenocarcinoma) can be stabilized and TAVR can be considered after exclusion of metastatic disease. A small study of 65 cancer patients with severe AS found that AVR improves survival, regardless of the type of cancer or anti-cancer therapy, with TAVR being the most beneficial [26].

The difference in outcomes for patients with cancer and active disease versus those in remission was demonstrated recently in a registry that included 1821 subjects treated by TAVR [24]. Ninety-nine patients (5.4%) had different types of active cancer, while 251 patients had a history of treated cancers, currently in remission. One-year mortality was highest in patients treated by TAVR who also had active cancers versus those with cancers in remission (37.4% versus 16.4% respectively). Thirty-day mortality was the same between the subgroups, irrespective of cancer stage, cancer history, or cancer absence. The best 3-year outcome was observed in known, slowly progressing cancers, such as prostate neoplasia or chronic lymphocytic leukemia. It should be noted that the worst prognosis was observed in cancer patients undergoing TAVR before having their cancer treated by specific oncologic therapy. TAVR patients that needed a specific cancer treatment in the first 12 months after the valvular intervention had a higher mortality than patients in true remission [22].

Patients with advanced, stage IV, metastatic disease, with severe anemia, symptomatic heart failure, and a very short estimated survival could be offered balloon valvuloplasty as a "bridge-to-destination" intervention [56]. In these final disease stages, a more conservative approach toward improving quality of life during palliative treatment for the oncologic disease is preferred. In this type of scenario, there is a limited evidence base, as data are mainly derived from case reports and case series. The futility of costly and potentially dangerous interventions like TAVR should be established by a multidisciplinary team consisting of both the oncologist, the cardiologist, and the palliative care team [57].

In the OCEAN-TAVI registry that included 749 patients treated by TAVR, 47 patients had an active neoplastic disease of various types [21]; the Society of Thoracic Surgery (STS) and EuroSCORE II risk scores were lower in the cancer subgroup. Periprocedural complications and 30-day survival were similar in patients with versus without cancer. Late mortality (> 30-day post-TAVR) was 7% and was predicted by the presence of metastatic disease at the time of intervention with a hazard ratio of 4.73 (95% CI 1.12–20.0; $p = 0.035$). Late mortality in the cancer TAVR subgroup was 10.6% versus 6.4% in the non-cancer subgroup.

Data from the TOP-AS registry were recently published [27••]. The study included 222 cancer patients, of which 40% had stage IV cancer at the time of TAVR, and 2522 non-cancer patients. As with the OCEAN-TAVI registry, 30-day mortality was comparable between the groups. One-year mortality was higher in the cancer group (15%, of which half were cancer-related, versus 9% in the non-cancer group). Stage I and stage II cancer patients had similar outcomes to non-cancer patients, whereas those with progressive or stage III and IV malignancies had significantly worse survival.

A recent issue of biological transcatheter and surgically implanted valves related to subclinical leaflet thrombosis with

increased transvalvular gradients [58] may also occur in oncologic patients due to coagulation anomalies. Until further data will become available specifically for cancer patients, systemic anticoagulation should be given as the only treatment proven to control or reduce valve thrombosis [59].

Patients with radiation-induced AS are younger and have lower STS scores and better prognoses after TAVR than patients with calcific AS [18]. When accepting cancer patients with a history of chest irradiation and calcified ascending aorta for TAVR, the risk of perforation or annular rupture should be considered [60]. A small series of non-randomized patients with previous Hodgkin disease with radiation-induced AS demonstrated similar results for TAVR compared to SAVR [19]. Long-term mortality in patients with previous chest radiation therapy was higher than expected after SAVR and can reach up to 55% at a mean follow-up of 7.6 years [17].

A recent expert consensus issued by the Society for Cardiovascular Angiography and Interventions recommends aortic balloon valvuloplasty or TAVR for cancer patients with AS either as palliation or cure for the valve disease, as indicated, to improve the quality of life or to facilitate appropriate cancer therapy [61]. Again, given the nature of this patient population, large trials are difficult to conduct, limiting the quality of the data supporting this approach.

Frailty, defined as the age-related diminished capability to recover from pathologic or iatrogenic stressors [62], is an essential parameter when deciding between TAVR and SAVR in the general population. This parameter becomes of great interest in cancer patients, who can be frail due to their cancer treatments, despite having a favorable oncologic prognosis [63, 64]. Although there are multiple instruments that can be used to measure frailty and this parameter has been related to increased post-AVR mortality [65, 66], there are no guideline

recommendations regarding frailty and TAVR or SAVR in cancer patients. General recommendations to assess physical performance, disability regarding activities of daily living, cognitive function, hemoglobin, and albumin as part of the evaluation of older adults with severe AS [66–68] can be considered in cancer patients as well. The FRAILTY-AVR study, one of the largest studies evaluating the impact of frailty indices in patients undergoing TAVR and SAVR, included 151 (15%) patients with cancer [67]. Although the study found increased 1-year mortality in frail patients, the result was not statistically significant in the cancer subgroup (adjusted OR of 1.31, CI 0.79–2.19). The Essential Frailty Toolset (EFT) evaluating 4 simple parameters (i.e., chair rises, cognitive impairment, hemoglobin, and serum albumin) was the measurement tool for frailty best associated with 1-year mortality. The authors recommend EFT use for identifying vulnerable patients before TAVR and SAVR in order to better target pre- or postprocedural interventions to improve outcomes [67].

TAVR and Cancer: What Do the Current Guidelines Say?

In the European guidelines released in 2017, aortic valve replacement is indicated in patients with symptomatic severe AS in the "absence of comorbidity or general condition that make benefit unlikely" [69]. In these cases, medical treatment is preferred. When the medical team agrees upon the benefit of the procedure, the patient may be treated by TAVR or SAVR, depending on the pre-procedural calculated risk [69]. The same decision is stated in the 2017 AHA/ACC Focused Update for the management of valvular heart disease: TAVR is recommended in severe symptomatic AS (stage D of

Fig. 1 Proposed algorithm for the management of severe symptomatic aortic stenosis in cancer patients. SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement
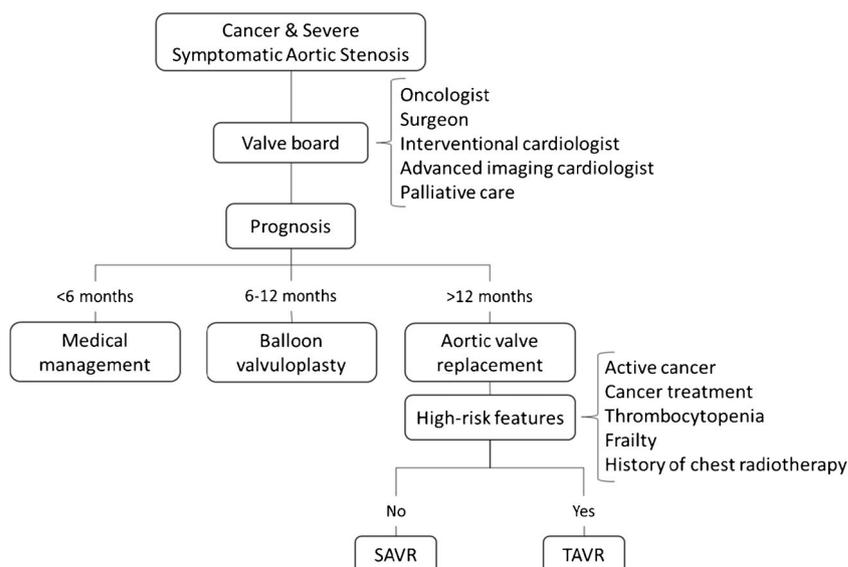
disease) when the patient has a prohibitive risk for SAVR and when anticipated survival is greater than 12 months [70].

Despite guideline recommendations, most cancer patients today have much better prognoses and survive for more than 12 months. Thus, most of the cancer patients excluded from randomized trials up-to-date could benefit from valve intervention to improve quality of life and likely even survival.

AS Treatment in Cancer Patients: Final Considerations

Randomized trials focused on the outcome are drastically needed in cancer patients with AS, depending on cancer type and stage of the neoplastic disease. Early-stage cancers may benefit from AS treatment just as non-cancer patients since the outcomes of most cancer types are significantly improved with modern therapy (i.e., surgical, chemo-, immuno-, and/ or radiotherapy).

The optimal treatment approach is not well established and should be decided on a case-by-case basis: valve disease or cancer, which should be treated first? We propose an algorithm for the management of aortic stenosis in cancer patients in Fig. 1. In terminal patients with cancer and severe AS, a "bridge-to-destination" treatment such as balloon valvuloplasty can be considered as part of the palliative care, in selected cases.

When caring for patients with gastrointestinal cancers that are not already cured or appropriately treated, the medical team should be alert and attempt to prevent bleeding complications of antithrombotic cardiac therapies.

Due to the minimally invasive nature of TAVR compared to SAVR, TAVR should be preferred in cancer patients as it offers similar 5-year outcomes. In patients with a remote history of cancer and radiation-induced AS, TAVR is by far the most useful intervention, especially in the presence of a "hostile thorax."

SAVR, TAVR, or balloon valvuloplasty in cancer patients with concomitant AS should be decided on a case-by-case basis depending on cancer stage and associated treatment, expected outcome, and frailty.

Compliance with Ethical Standards

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet. 2006;368(9540):1005–11.
2. Lindman B, Clavel M, Mathieu P, Lung P, Otto C, Pibarot P. Calcific aortic stenosis. Nat Rev. 2016;2:1–28.
3. Luise G, Lars A, George BBB, Philip M, Francesco M, Pepe Z, et al. Heart valve disease awareness survey 2017: what did we achieve since 2015? Clin Res Cardiol. 2018;108:61–7. https://doi.org/10.1007/s00392-018-1312-5.
4. Sengeløv M, Cheng S, Biering-Sørensen T, Matsushita K, Konety S, Solomon S, et al. Ideal cardiovascular health and the prevalence and severity of aortic stenosis in elderly patients. J Am Heart Assoc. 2018;7(3):e007234. https://doi.org/10.1161/JAHA.117.
5. Hemingway H, McCallum A, Shipley M, Manderbacka K, Martikainen P, Keskimaki I. Incidence and prognostic implications of stable angina pectoris among women and men. JAMA. 2006;295(12):1404–11.
6. Eyre H, Kahn R, Robertson R. ACS/ADA/AHA collaborative writing committee. Preventing cancer, cardiovascular disease, and diabetes: a common agenda for the American Cancer Society, the American Diabetes Association, and the American Heart Association. CA Cancer J Clin. 2004;54(4):190–207.
7. Rasmussen-Torvik L, Shay C, Abramson J, Friedrich C, Nettleton J, Prizment A, et al. Ideal cardiovascular health is inversely associated with incident cancer: the atherosclerosis risk in communities study. Circulation. 2013;127:1270–5.
8. Giza DE, Iliescu G, Hassan S, Marmagkiolis K, Iliescu C. Cancer as a risk factor for cardiovascular disease. Curr Oncol Rep. 2017;19(6):39.
9. Liu VY, Agha AM, Lopez-Mattei J, Palaskas N, Kim P, Thompson K, et al. Interventional cardio-oncology: adding a new dimension to the cardio-oncology field. Front Cardiovasc Med. 2018;5:48.
10. Guha A, Armanious M, Fradley MG. Update on cardio-oncology: novel cancer therapeutics and associated cardiotoxicities. Trends Cardiovasc Med. 2018.
11. Hassan SA, Palaskas N, Kim P, Iliescu C, Lopez-Mattei J, Mouhayar E, et al. Chemotherapeutic agents and the risk of ischemia and arterial thrombosis. Curr Atheroscler Rep. 2018;20(2):10.
12. Leon M, Smith C, Mack M, Miller G, Moses J, Svensson L, et al. Transcatheter aortic-valve implantation for aortic stenosis in patient who cannot undergo surgery. The New England journal of medicine, vol. 363; 2010. p. 1597–607.
13. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med. 2019.
14. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. N Engl J Med. 2019.
15. Carrascal Y, Gualis J, Arevalo A, Fulquet E, Florez S, Rey J, et al. Cardiac surgery with extracorporeal circulation in cancer patients: influence on surgical morbidity and mortality and on survival. Rev Esp Cardiol. 2008;61(4):369–75.
16.•• Yusuf SW, Sarfaraz A, Durand JB, Swafford J, Daher IN. Management and outcomes of severe aortic stenosis in cancer patients. Am Heart J. 2011;161(6):1125–32 **This study is one of the first to support aortic valve replacement and demonstrate improved outcomes in cancer patients with severe aortic stenosis.**

17. Wu W, Masri A, Popovic ZB, Smedira NG, Lytle BW, Marwick TH, et al. Long-term survival of patients with radiation heart disease undergoing cardiac surgery: a cohort study. Circulation. 2013;127(14):1476–85.

18. Dijos M, Reynaud A, Leroux L, Reant P, Cornolle C, Roudaut R, et al. Efficacy and follow-up of transcatheter aortic valve implantation in patients with radiation-induced aortic stenosis. Open Heart. 2015;2(1):e000252.

19. Paven E, Cimadevilla C, Urena M, Dilly MP, Nataf P, Raffoul R, et al. Management of radiation-induced valvular heart disease due to Hodgkin's Lymphoma in the modern era. EuroIntervention. 2018;13(15):e1771–e3.

20. Sari C, Ayhan H, Bastug S, Kasapkara HA, Karaduman BD, Aslan AN, et al. Transcatheter aortic valve implantation in the presence of hematologic malignancies. Turk Kardiyol Dern Ars. 2015;43(6): 529–35.

21. Watanabe Y, Kozuma K, Hioki H, Kawashima H, Nara Y, Kataoka A, et al. Comparison of results of transcatheter aortic valve implantation in patients with versus without active cancer. Am J Cardiol. 2016;118(4):572–7.

22. Berkovitch A, Guetta V, Barbash IM, Fink N, Regev E, Maor E, et al. Favorable short-term and long-term outcomes among patients with prior history of malignancy undergoing transcatheter aortic valve implantation. J Invasive Cardiol. 2018;30(3):105–9.

23. Donnellan E, Griffin BP, Johnston DR, Popovic ZB, Alashi A, Kapadia SR, et al. Rate of progression of aortic stenosis and its impact on outcomes in patients with radiation-associated cardiac disease: a matched cohort study. JACC Cardiovasc Imaging. 2018. https://doi.org/10.1016/j.jcmg.2018.04.019.

24. Mangner N, Woitek FJ, Haussig S, Holzhey D, Stachel G, Schlotter F, et al. Impact of active cancer disease on the outcome of patients undergoing transcatheter aortic valve replacement. J Interv Cardiol. 2018;31(2):188–96.

25.• Minamino-Muta E, Kato T, Morimoto T, Taniguchi T, Nakatsuma K, Kimura Y, et al. Malignant disease as a comorbidity in patients with severe aortic stenosis: clinical presentation, outcomes, and management. Eur Heart J Qual Care Clin Outcomes. 2018;4(3): 180–8 **This paper presents one of the largest analyses of clinical data, outcomes, and management of severe aortic stenosis in cancer patients**.

26. Schechter M, Balanescu DV, Donisan T, Dayah TJ, Kar B, Gregoric I, et al. An update on the management and outcomes of cancer patients with severe aortic stenosis. Catheter Cardiovasc Interv. 2018.

27.•• Landes U, Iakobishvili Z, Vronsky D, Zusman O, Barsheshet A, Jaffe R, et al. Transcatheter aortic valve replacement in oncology patients with severe aortic stenosis. JACC Cardiovasc Interv. 2019;12(1):78–86 **This pivotal study presents data from a large TAVR registry and is one of the largest analyses of TAVR outcomes in cancer patients**.

28. Faggiano P, Frattini S, Zilioli V, Rossi A, Nistri S, Dini FL, et al. Prevalence of comorbidities and associated cardiac diseases in patients with valve aortic stenosis. Potential implications for the decision-making process. Int J Cardiol. 2012;159(2):94–9.

29. Okura Y, Ishigaki S, Sakakibara S, Yumoto C, Hashitate M, Sekine C, et al. Prognosis of cancer patients with aortic stenosis under optimal cancer therapies and conservative cardiac treatments. Int Heart J. 2018;6:750–8. https://doi.org/10.1536/ihj.17-320.

30. Ong DS, Aertker RA, Clark AN, Kiefer T, Hughes GC, Harrison JK, et al. Radiation-associated valvular heart disease. J Heart Valve Dis. 2013;22(6):883–92.

31. Marmagkiolis K, Finch W, Tsitlakidou D, Josephs T, Iliescu C, Best JF, et al. Radiation toxicity to the cardiovascular system. Curr Oncol Rep. 2016;18(3):15.

32. Yusuf SW, Howell RM, Gomez D, Pinnix CC, Iliescu CA, Banchs J. Radiation-related heart and vascular disease. Future Oncol. 2015;11(14):2067–76.

33. Chang HM, Okwuosa TM, Scarabelli T, Moudgil R, Yeh ETH. Cardiovascular complications of cancer therapy: best practices in diagnosis, prevention, and management: part 2. J Am Coll Cardiol. 2017;70(20):2552–65.

34. Nadlonek NA, Weyant MJ, Yu JA, Cleveland JC Jr, Reece TB, Meng X, et al. Radiation induces osteogenesis in human aortic valve interstitial cells. J Thorac Cardiovasc Surg. 2012;144(6): 1466–70.

35. Beohar N, Kirtane AJ, Blackstone E, Waksman R, Holmes D Jr, Minha S, et al. Trends in complications and outcomes of patients undergoing transfemoral transcatheter aortic valve replacement: Experience From the PARTNER Continued Access Registry. JACC Cardiovasc Interv. 2016;9(4):355–63.

36. Latib A, Montorfano M, Figini F, Maisano F, Chieffo A, Benussi S, et al. Percutaneous valve replacement in a young adult for radiation-induced aortic stenosis. J Cardiovasc Med (Hagerstown). 2012;13(6):397–8.

37. Gujral DM, Lloyd G, Bhattacharyya S. Radiation-induced valvular heart disease. Heart. 2016;102(4):269–76.

38. Taylor CW, Wang Z, Macaulay E, Jagsi R, Duane F, Darby SC. Exposure of the heart in breast cancer radiation therapy: a systematic review of heart doses published during 2003 to 2013. Int J Radiat Oncol Biol Phys. 2015;93(4):845–53.

39. Boekel NB, Jacobse JN, Schaapveld M, Hooning MJ, Gietema JA, Duane FK, et al. Cardiovascular disease incidence after internal mammary chain irradiation and anthracycline-based chemotherapy for breast cancer. Br J Cancer. 2018;119:408–18.

40. Ben-Dor I, Waksman R, Hann N, Raizon A, Satler L, Torguson R, et al. Utility of radiologic review for noncardiac findings on multi-slice computed tomography in patients with severe aortic stenosis evaluated for transcatheter aortic valve implantation. Am J Cardiol. 2010;105:1461–4.

41. Gufler H, Schulze C, Wagner S. Incidental findings in computed tomographic angiography for planning percutaneous aortic valve replacement: advanced age, increased cancer prevalence? Acta Radiol. 2014;55(4):420–6.

42. Schmidt LH, Vietmeier B, Kaleschke G, Schulke C, Gorlich D, Schliemann C, et al. Thoracic malignancies and pulmonary nodules in patients under evaluation for transcatheter aortic valve implantation (TAVI): incidence, follow up and possible impact on treatment decision. PLoS One. 2016;11(5):e0155398.

43. Lee HY, Kim SM, Lee KS, Park SW, Chung MJ, Cho H, et al. Quantification of aortic valve calcifications detected during lung cancer-screening CT helps stratify subjects necessitating echocardiography for aortic stenosis diagnosis. Medicine (Baltimore). 2016;95(19):e3710.

44. Sablotzki A, Welters I, Lehmann N, Menges T, Gorlach G, et al. Plasma levels of immunoinhibitory cytokine interleukin-10 and transforming growth factor-β in patients undergoing coronary artery bypass grafting. Eur J Cardio Thorac Surg. 1997;11(4):763–8.

45. Akbas H, Erdal A, Demiralp E, Alp M. Effects of coronary artery bypass grafting on cellular immunity with or without cardiopulmonary bypass. Cardiovasc Surg. 2002;10:586–9.

46. Voets A, Joesoef K, van Teeffelen M. The influence of open heart surgery on survival of patients with co-existent surgically amenable lung cancer (stage I and II). Eur J Cardiothorac Surg. 1997;12:898–902.

47. Suzuki S, Usui A, Yoshida K, Matsuura A, Ichihara T, Ueda Y. Effect of cardiopulmonary bypass on cancer prognosis. Asian Cardiovasc Thorac Ann. 2010;18:536–40.

48. Plumereau F, Pinaud F, Roch A, Baufreton C. Do patients with haematological malignancy who need cardiopulmonary bypass

have a short-term higher mortality or a higher chance of disease progression? Interact Cardiovasc Thorac Surg. 2014;19(3):474–8.

49. Nguyen HG, Tilki D, Dall'Era MA, Durbin-Johnson B, Carballido JA, Chandrasekar T, et al. Cardiopulmonary bypass has no significant impact on survival in patients undergoing nephrectomy and level III-IV inferior vena cava thrombectomy: multi-institutional analysis. J Urol. 2015;194(2):304–8.

50. Pinto CA, Marcella S, August DA, Holland B, Kostis JB, Demissie K. Cardiopulmonary bypass has a modest association with cancer progression: a retrospective cohort study. BMC Cancer. 2013;13: 519.

51. Szeto WY, Svensson LG, Rajeswaran J, Ehrlinger J, Suri RM, Smith CR, et al. Appropriate patient selection or health care rationing? Lessons from surgical aortic valve replacement in the placement of aortic transcatheter valves I trial. J Thorac Cardiovasc Surg. 2015;150(3):557–68.e11.

52. Mrak M, Ambrozic J, Music S, Terseglav S, Kontestabile B, Lakic N, et al. Transcatheter aortic valve implantation in a cancer patient denied for surgical aortic valve replacement-a case report. Wien Klin Wochenschr. 2016;128(13–14):516–20.

53. Komatsu H, Izumi N, Tsukioka T, Chung K, Toda M, Hara K, et al. Pulmonary resection for lung cancer following transcatheter aortic valve implantation for severe aortic valve stenosis: a case report. Ann Thorac Cardiovasc Surg. 2018. https://doi.org/10.5761/atcs.cr.18-00028.

54. Drevet G, Maury JM, Farhat F, Tronc F. Transcatheter aortic valve implantation: a safe and efficient procedure to treat an aortic valve stenosis before lung cancer resection. Gen Thorac Cardiovasc Surg. 2018.

55. Sakai T, Yahagi K, Miura S, Hoshino T, Yokota T, Tanabe K, et al. Transcatheter aortic valve implantation for patients with lung cancer and aortic valve stenosis. J Thorac Dis. 2018;10(5):E387–e90.

56. Kogoj P, Devjak R, Bunc M. Balloon aortic valvuloplasty (BAV) as a bridge to aortic valve replacement in cancer patients who require urgent non-cardiac surgery. Radiol Oncol. 2014;48(1):62–6.

57. Puri R, Iung B, Cohen DJ, Rodes-Cabau J. TAVI or No TAVI: identifying patients unlikely to benefit from transcatheter aortic valve implantation. Eur Heart J. 2016;37(28):2217–25.

58. Chakravarty T, Sondergaard L, Friedman J, De Backer O, Berman D, Kofoed KF, et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. Lancet. 2017;389(10087):2383–92.

59. Hansson NC, Grove EL, Andersen HR, Leipsic J, Mathiassen ON, Jensen JM, et al. Transcatheter aortic valve thrombosis: incidence, predisposing factors, and clinical implications. J Am Coll Cardiol. 2016;68(19):2059–69.

60. Leroux L, Dijos M, Peltan J, Casassus F, Seguy B, Natsumeda M, et al. Lethal aorto-right ventricular defect after transcatheter aortic valve implantation in a patient with radiation-induced porcelain aorta: notes of caution. Can J Cardiol. 2016;32(1):135.e9–e11.

61. Iliescu CA, Grines CL, Herrmann J, Yang EH, Cilingiroglu M, Charitakis K, et al. SCAI expert consensus statement: evaluation, management, and special considerations of cardio-oncology patients in the cardiac catheterization laboratory (endorsed by the cardiological society of India, and sociedad Latino Americana de Cardiologia intervencionista). Catheter Cardiovasc Interv. 2016;87(5):E202–23.

62. Rodriguez-Manas L, Feart C, Mann G, Vina J, Chatterji S, Chodzko-Zajko W, et al. Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. J Gerontol A Biol Sci Med Sci. 2013;68(1):62–7.

63. Handforth C, Clegg A, Young C, Simpkins S, Seymour MT, Selby PJ, et al. The prevalence and outcomes of frailty in older cancer patients: a systematic review. Ann Oncol. 2015;26(6):1091–101.

64. Ness KK, Armstrong GT, Kundu M, Wilson CL, Tchkonia T, Kirkland JL. Frailty in childhood cancer survivors. Cancer. 2015;121(10):1540–7.

65. Kim DH, Kim CA, Placide S, Lipsitz LA, Marcantonio ER. Preoperative frailty assessment and outcomes at 6 months or later in older adults undergoing cardiac surgical procedures: a systematic review. Ann Intern Med. 2016;165(9):650–60.

66. Talbot-Hamon C, Afilalo J. Transcatheter aortic valve replacement in the care of older persons with aortic stenosis. J Am Geriatr Soc. 2017;65(4):693–8.

67. Afilalo J, Lauck S, Kim DH, Lefevre T, Piazza N, Lachapelle K, et al. Frailty in older adults undergoing aortic valve replacement: the FRAILTY-AVR study. J Am Coll Cardiol. 2017;70(6):689–700.

68. Hebeler KR, Baumgarten H, Squiers JJ, Wooley J, Pollock BD, Mahoney C, et al. Albumin is predictive of 1-year mortality after transcatheter aortic valve replacement. Ann Thorac Surg. 2018;106: 1302–7.

69. Baumgartner H, Volkmar Falk V, Bax J, De Bonis M, Hamm C, Johan P, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J. 2017;38:2739–91.

70. Nishimura R, Otto C, Bonow R, Carabello B, Erwin J, Fleisher L, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease. J Am Coll Cardiol. 2017;70:252–89.