Management of valvular heart disease in patients with cancer: Multidisciplinary team, cancer-therapy related cardiotoxicity, diagnosis, transcatheter intervention, and cardiac surgery. Expert opinion of the Association on Valvular Heart Disease, Association of Cardiovascular Interventions, and Working Group on Cardiac Surgery of the Polish Cardiac Society

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DOI: 10.33963/KP.a2023.0023

Received:
January 4, 2022

Accepted:
January 4, 2022

Early publication date:
January 15, 2022

ABSTRACT

The Association on Valvular Heart Disease, Association of Cardiovascular Interventions, and the Working Group on Cardiac Surgery of the Polish Cardiac Society have released a position statement on risk factors, diagnosis, and management of patients with cancer and valvular heart disease (VHD). VHD can occur in patients with cancer in several ways, for example, it can exist or be diagnosed before cancer treatment, after cancer treatment, be an incidental finding during imaging tests, endocarditis related to immunosuppression, prolonged intravenous catheter use, or combination treatment, and nonbacterial thrombotic endocarditis. It is recommended to employ close cardiac surveillance for patients at high risk of complications during and after cancer treatment and for cancer treatments that may be cardiotoxic to be discussed by a multidisciplinary team. Patients with cancer and pre-existing severe VHD should be managed according to the 2021 European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS) guidelines for VHD management, taking into consideration cancer prognosis and patient preferences.

Key words: cardiooncology, cancer, cancer therapy related cardiotoxicity, cardiovascular imaging, valvular heart disease

INTRODUCTION TO CARDIO-ONCOLOGY. CURRENT EUROPEAN SOCIETY OF CARDIOLOGY GUIDELINES

In the United States, the 5-year survival rate of cancer survivors reached 69% in 2022. Cardiovascular (CV) disease (CVD) is the most common cause of death in this population. The incidence of CVD and cancer increases with age. Moreover, the risk factors for CVD are the same as those for cancer. Therefore, with Europe and America facing the problem of population aging, it is increasingly common to see patients with both conditions.

The overarching goal of cardio-oncology is to assess CV toxicity risk during and after cancer treatment, including the risk of valvular heart disease (VHD). If cancer therapy-related CV toxicity occurs, the role of a cardiologist is to address all the CV needs of a cancer patient, so as not to interrupt specific anticancer treatment or to ensure that the interruption is as short as possible.

In patients with cancer, VHD can most often occur in the following clinical scenarios:

- VHD existing and/or diagnosed before cancer treatment or diagnosed as an incidental finding during imaging tests for cancer diagnosis
- endocarditis related to immunosuppression, catheter use, or combination treatment
- nonbacterial thrombotic endocarditis as the first possible symptom of cancer
- VHD caused by left ventricular (LV) dysfunction due to cancer treatment
- VHD caused by collagen accumulation as well as valvular fibrosis and calcification as late cardiotoxic effects of radiotherapy causing interstitial damage.

Irrespective of the underlying cause, the severity of VHD in patients with cancer is assessed using the same criteria as in patients without cancer.

In August 2022, the European Society of Cardiology (ESC) published its first guidelines on the management of CVD in patients with cancer [1]. The guidelines replaced or complemented the 2016 ESC position paper on cancer treatments and CV toxicity [2].

The main focus of the 2022 ESC guidelines is assessment of CV toxicity risk [1]. Pre-existing severe VHD is associated with high risk of cancer therapy-related CV toxicity in patients treated with anthracyclines, anti-human epidermal growth factor receptor 2 (HER-2) monoclonal antibody, and combination therapy with RAF and MEK inhibitors [1]. However, the reasons why pre-existing VHD is relevant in association with these cancer therapies remain unclear [1]. The presence of VHD itself may be associated with asymptomatic myocardial damage. This may be due to increased myocardial wall stress, which may lead to cardiac cell damage and subsequent cardiotoxicity. Moreover, severe VHD may cause an increase in baseline left ventricular ejection fraction (LVEF).

Therefore, close CV surveillance (cardiac imaging and biomarkers) is recommended in all patients at high risk of CV complications (including patients with VHD receiving the above cancer therapies) during and after cancer treatment, and cardiotoxic anticancer treatment should be discussed by a multidisciplinary team before starting treatment (class I, level C). Beta-blockers, angiotensin-converting enzyme inhibitors, and statins should be considered for primary prevention in patients at high CV toxicity risk, irrespective of VHD etiology (class IIa, level C) [1].

Echocardiography is recommended for assessment of cardiac function in all patients with cancer before treatment, with 3-dimensional echocardiography to assess LVEF and the measurement of global longitudinal strain if available (class I) [1].

Apart from the section on CV risk assessment (Table 1), the 2022 ESC guidelines [1] do not contain any specific recommendations for the management of patients with cancer and pre-existing VHD or new VHD during cancer treatment but refer to the 2021 ESC guidelines on the management of VHD [4].

Table 1. Adopted protocol for cardiovascular risk assessment in patients with cancer scheduled to receive cardiotoxic cancer therapies (e.g., anthracycline chemotherapy) based on reference [3]. Severe valvular heart disease — high risk

Medical history	Risk factor [Y/N]	Score	Level of evidence
Cardiovascular disease			
Heart failure or cardiomiopathy		Very high	B
Severe valvular heart disease		High	
Myocardial infarction or previous coronary revascularization		High	C
Stable angina		High	C
Baseline left ventricular ejection fraction <50%		High	B
Borderline left ventricular ejection fraction 50%–54%		Medium	C
Cardiac biomarkers			
Elevated troponin		Medium	C
Elevated NT-proBNP or BNP		Medium	C
Demographic or other risk factors			
≥80 years		High	B
65–79 years		Medium	B
Hypertension[a]		Medium	B
Diabetes mellitus[a]		Medium	C
Chronic kidney disease[a]		Medium	C
Current smoker or smoking history		Medium	C
Obesity (>30 kg/m^2)		Medium	C
Previous cardiotoxic cancer treatment			
Anthracycline exposure		High	B
Non-anthracycline chemotherapy		Medium	C
Left chest or mediastinum radiotherapy		High	C
SCORE: • low — no risk factors or 1 medium • medium — 2–4 medium risk factors • high — > medium risk factors or 1 high • very high — heart failure or cardiomiopathy			
[a]Blood pressure >140/90 mm Hg; HbAc1 >7.0% or > 53 mmol/mol or diabetes treatment; GFR < 60 ml/min/1.73 m^2			

Abbreviations: BMI, body mass index; BNP, B-type natriuretic peptide; GFR, glomerular filtration rate; HbA1C, glycated hemoglobin; NT-proBNP, N-terminal pro-B-type natriuretic peptide

Patients with cancer and pre-existing severe VHD should be managed according to the 2021 ESC/EACTS guidelines for the management of VHD, taking into consideration cancer prognosis and patient preferences (class I C).

Patients with cancer who develop new VHD during cancer treatment should be managed according to the 2021 ESC/EACTS guidelines for the management of VHD (class I C), taking into consideration cancer prognosis and comorbidities. However, the 2021 ESC/EACTS guidelines do not specifically address the management of patients with cancer [4]. Instead, they contain general recommendations that only indirectly refer to this complex population of patients. According to the guidelines, decision-making in patients considered for valve intervention should take into account estimated life expectancy and comorbidities, among other factors [4]. The guidelines recommend the Heart Team's discussion about benefits and risks of valvular surgery using popular risk scores. The Society of Thoracic Surgeons predicted risk of mortality score (STS-PROM) and the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) are recommended to discriminate between low- and high-risk surgical patients. However, only the STS-PROM incorporates previous mediastinal radiotherapy and a history of cancer.

In the 2022 ESC guidelines [1], specific recommendations for the cancer population with VHD are limited to patients with radiation-induced symptomatic severe valvular aortic stenosis (AS) at intermediate surgical risk. In these patients, transcatheter aortic valve implantation (TAVI) should be considered (class IIa, level B).

A multidisciplinary team (MDT) approach is recommended to discuss and determine the surgical risk in cancer survivors (class I, level C). MDT should include an oncologist, cardiologist with expertise in managing CVD in patients with cancer, invasive cardiologist, cardiac surgeon, anesthesiologist, and palliative medicine specialist.

Patients with cancer are usually poor candidates for classic cardiac surgery and should preferably be considered for minimally invasive procedures without extracorporeal circulation and transcatheter heart valve interventions [5, 6].

In 2021, more than 2000 TAVI procedures, 256 transcatheter mitral edge-to-edge repair (TEER) procedures, 29 percutaneous pulmonary valve implantation procedures, and 19 tricuspid valve interventions were performed in Poland. In 2021, 8294 heart valve surgeries were performed in Poland, including 7085 prosthetic valve implantations and 1744 valvular repair procedures. These numbers of procedures relate to all patients with VHD in Poland and include the population with cancer. All procedures, except tricuspid valve interventions, were reimbursed. The key aspect to consider in determining eligibility for the procedure is cancer prognosis (life expectancy >12 months).

Considering that the ESC guidelines on cardio-oncology put minimal emphasis on the specific population of patients with VHD receiving cancer treatment and contain only general recommendations, the present position statement seems to be particularly important.

Clinical assessment — summary

1. Each patient with cancer should be assessed for the presence of VHD.
2. Patients with known VHD should be assessed for previous cancer and cancer treatment.
3. Frequent CV surveillance is recommended in patients with VHD receiving cancer treatment (more frequent echocardiographic evaluation, measurement of biomarker levels [natriuretic peptides, cardiac troponins] than in patients without VHD).
4. The frequency of surveillance in patients at high and very high risk of CV toxicity is guided by the type of cancer treatment.
5. If significant VHD is diagnosed in patients with cancer, the treatment decision should follow a multidisciplinary team discussion.
6. A multidisciplinary team should include an oncologist, cardiologist with expertise in managing CVD in patients with cancer, invasive cardiologist, cardiac surgeon, anesthesiologist, and palliative medicine specialist.
7. The management strategy should take into consideration cancer prognosis and the patient's preferences and should be discussed with the patient.

DIAGNOSIS OF VALVULAR HEART DISEASE IN PATIENTS WITH CANCER

The use of imaging techniques for assessment of VHD in oncological patients largely follows the general recommendations for this disease entity developed by cardiology societies and expert groups. However, some specific circumstances should be considered in relation to the cancer process itself or side effects or complications of cancer treatment.

Echocardiography is the first-choice imaging technique for VHD diagnosis in all patients, including those with cancer [7]. Echocardiographic standards can be found in specific documents developed by the European Association of Cardiovascular Imaging and the American Society of Echocardiography [8, 9]. Although transthoracic echocardiography is often sufficient for assessing valvular lesions and related hemodynamic disturbances, transesophageal echocardiography (particularly 3D echocardiography) may offer a more detailed characterization of valvular pathology, providing a clear incremental value in infective endocarditis. It should be emphasized that transesophageal echocardiography can be performed only after the exclusion of esophageal cancer or related complications.

One should bear in mind that the quantitative assessment of valvular heart disease may be confounded by the cardiotoxic effect of anticancer drugs on left and right ventricular functions. Similarly, the interpretation of LVEF and global longitudinal strain (GLS) decision thresholds when assessing eligibility for valve intervention may be difficult in the presence of overlapping cardiotoxic effects of chemotherapy or radiotherapy. Due to the paucity of data on this subject in the available literature, a tailored imaging approach should be used in such cases.

Cardiac computed tomography (CT) and magnetic resonance imaging (CMR) are not routinely performed in assessment of valvular disease and are used as supportive tools. Cardiac CT is important in preprocedural planning of transcatheter and surgical valve replacement, including assessment of aortic root calcification, aortic valve calcium score, measurement of the valve annulus, coronary orifice height, and assessment of peripheral arteries for transcatheter interventions. CT can help identify complications of infective endocarditis, especially abscesses and pseudoaneurysms [10].

CMR can be used to quantify valvular VHD, especially regurgitation, when the quality of echocardiographic imaging is inadequate. This technique provides important prognostic information on the severity of myocardial fibrosis resulting from valvular disease and/or oncological therapies. CMR and CT can help investigate the etiology of masses on valvular structures, including differentiation of cancer tumors from thrombi [11].

Positron emission tomography (PET) can be used in the diagnosis of endocarditis on prosthetic valves [12].

Cardiac CT, CMR, and PET are important tools in diagnosis of carcinoid heart disease, providing information on the mechanisms of valve dysfunction (thrombosis vs. carcinoid deposits — CT and CMR) and identifying cardiac metastases (PET) [13].

Echocardiography is a safe technique, which is particularly important considering the need for serial testing as part of CV surveillance. CMR is also safe for patients, except for cases where metal elements are present in the body. A group of patients for whom this examination may be hazardous are women after the first stage of breast reconstruction with the use of tissue expanders due to the risk of dislodgement of the port [7]. Because of the exposure to ionizing radiation during CT and PET, the purposefulness of the use of these diagnostic techniques, despite a relatively low radiation dose from a single examination, should be carefully deliberated in oncological patients.

Diagnosis of valvular heart disease in patients with cancer — summary

1. Echocardiography is the first-line imaging test for the diagnosis of valvular heart disease. This also applies to the cancer population.
2. Echocardiographic evaluation should be performed in all patients before cancer treatment, if feasible, and novel techniques should be applied.
3. Cardiac CT is an important tool for planning transcatheter and surgical heart valve interventions. It may also

help identify infective-endocarditis-related complications, but radiation exposure should be considered.
4. CMR can be used to quantify VHD and the severity of myocardial fibrosis resulting from valvular disease and/or oncological therapies.
5. It should be noted that quantitative assessment of VHD may be confounded by the cardiotoxic effect of anticancer drugs on left and right ventricular functions.

PATIENTS DEVELOPING NEW VALVULAR HEART DISEASE AFTER CHEMOTHERAPY

In patients with active cancer or cancer survivors, new or worsening VHD may be related to chemotherapy, radiotherapy, or cancer-therapy-related CV events such as acute coronary syndrome, endocarditis, pulmonary hypertension, and mechanical prosthetic valve thrombosis.

Usually, two types of valvular dysfunction should be considered: (1) primary — structural dysfunction, which refers to alterations caused by damage to the components of the valve apparatus; and (2) secondary — functional dysfunction secondary to LV remodeling and enlargement as well as alterations in LV geometry. Another type of heart valve dysfunction occurs due to tumor invasion (most often myxoma), leading to functional narrowing of the valve orifice.

Cancer treatments can cause myocardial damage, LV remodeling, LV systolic dysfunction, and symptomatic heart failure (HF), which are described as cancer-therapy-related cardiac dysfunction (CTRCD). Cardiac dysfunction can be caused by various anticancer drugs acting via different mechanisms [14]. CTRCD thus encompasses a broad spectrum of clinical symptoms and morphological changes linked to the cardiotoxic effects of cancer therapies, including their impact on valve function. CTRCD with mitral and tricuspid valve dysfunction can be caused by classic cytostatic drugs, molecularly targeted cancer drugs, and immunomodulatory drugs. Secondary mitral and tricuspid regurgitation due to LV remodeling is a rare complication of radiotherapy, with structural alterations of the valve apparatus being more common.

The effect of chemotherapy on primary valve dysfunction is less well documented. Available literature data are conflicting, with some studies providing evidence for a link between valvular dysfunction and chemotherapy [14], and others reporting contradictory findings [15, 16]. The most likely complication of chemotherapy is secondary mitral and tricuspid regurgitation.

The management of patients with secondary mitral and tricuspid regurgitation associated with CTRCD is the same as that of patients with functional valve dysfunction of other etiologies. The mainstay of treatment is pharmacological management of HF (β-blockers, sodium-glucose cotransporter 2 inhibitors, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, sacubitril/valsartan, mineralocorticoid receptor antagonists, diuretics) [16]. Early initiation of medical therapy has a significant beneficial effect on survival, LV remodeling, and the severity of mitral regurgitation (MR) [17]. Also, cardiac resynchronization therapy was shown to reverse LV remodeling and reduce MR severity in patients fulfilling standard eligibility criteria [18]. Selected patients may be eligible for interventional treatment of severe MR.

Patients with new valvular heart disease after chemotherapy — summary

1. In patients with active cancer or cancer survivors, new or worsening VHD may be related to chemotherapy or cancer-therapy-related CV events such as acute coronary syndrome, endocarditis, pulmonary hypertension, and mechanical prosthetic valve thrombosis.
2. Treatment of CRTCD-related valve disease is the same as functional valve disease from other causes. The mainstay of treatment is pharmacological management of HF (beta-blockers, sodium-glucose cotransporter 2 inhibitors, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, sacubitril/valsartan, mineralocorticoid receptor antagonists, diuretics).

PATIENTS WITH NEW VALVULAR HEART DISEASE AFTER RADIOTHERAPY

The main risk factor for VHD in patients subjected to cancer treatments is radiotherapy which causes damage to valvular tissues in close proximity to the radiation field. This mostly refers to patients with Hodgkin lymphoma or left-sided breast cancer who were treated with radiotherapy between 1965 and 1995 before the era of modern radiotherapy planning [19].

Radiation affects not only valvular tissues but also other tissues exposed to the radiation field. Therefore, radiation-induced VHD is usually accompanied by endocarditis, coronary and peripheral artery disease (atherosclerotic plaque formation in the aorta, neck, subclavian, axillary, and internal thoracic arteries), LV diastolic dysfunction (following myocardial fibrosis), restrictive cardiomyopathy, and conduction system disease (fibrosis of the conducting tissue) [20].

The pathomechanism of radiation-induced VHD has not been fully elucidated. Most likely, injury to valvular endothelial cells and interstitial cells of the endocardium leads to the onset of progressive "subclinical" inflammation as well as the release of cytokines and bone morphogenetic proteins, resulting in collagen accumulation, fibrosis, and calcifications [21]. The chronic inflammation process associated with cancer itself may further enhance the progression of valvular lesions. Radiation-related structural valve dysfunction occurs mainly after radiotherapy to the anterior and left side of the chest with exposure of the heart.

In the population that previously received mediastinal irradiation, the risk of valvular disease was 34-fold higher than in the Framingham population, which had never been subjected to radiotherapy [22]. The incidence of

Table 2. Risk factors for radiation-induced cardiovascular disease

High dose of radiation fractions and high cumulative dose of radiation
Longer radiation exposure time
Left chest irradiation location, a tumor in close proximity to the heart (exposure of the heart)
Pre-existing cardiovascular disease
Concomitant chemotherapy (anthracyclines)
Hypertension, dyslipidemia, diabetes, obesity, smoking

VHD increases with a longer time from radiation exposure. Clinically significant VHD was reported in 1% of patients at 10 years after radiotherapy; in 5%, after 15 years; and in 6%, after 20 years [8]. The incidence of cardiac lesions increased significantly at 20 years from exposure [23], with mild aortic regurgitation (AR) reported in 45% of patients; moderate AR, in 15%; AS, in 16%; mild MR, in 48%; and mild pulmonary regurgitation, in 12%. Tricuspid regurgitation is more common among adult survivors of childhood cancer than in the general population, but the reasons for this association remain unclear [24]. However, most patients with cancer have mild or moderate VHD that does not require surgical treatment. Severe VHD necessitating surgical intervention is rare.

The risk factors for radiotherapy-related VHD are presented in Table 2 [25].

Radiation-induced morphological changes in the valve apparatus

Radiation effects include valve leaflet fibrosis, thickening, calcification, and shortening as well as fibrosis, calcification, distortion, and degeneration of the mitral and aortic annulus and the ascending aorta, especially at the base. Fibrosis and calcification can present as diffuse foci and can be randomly dispersed or combined into extensive conglomerates.

Lesions in the mitral valve leaflet are usually located in the basal and middle segments while the apical segments near the coaptation line and the commissures do not show advanced damage [26, 27] (Figure 1). Such a distribution of lesions helps differentiate radiation-induced valve disease from a rheumatic disease characterized by degenerative lesions in the entire leaflets as well as commissural fibrosis and fusion [1].

Radiation-induced lesions are more common with left-sided valves (mitral and aortic). This is linked to the higher pressure in the left heart, which enhances radiation-induced microdamage. Valvular regurgitation is more common than stenosis. Aortic stenosis is more common than stenosis of other heart valves [28–30].

An unusual pattern of lesions in the aortic valve, mitral valve, and the aortic-mitral curtain is considered to be typical of radiation-induced valve disease [26] (Figure 2).

A characteristic feature is porcelain aorta, a term used to describe fibrosis and calcification of the ascending thoracic aorta (Figure 3).

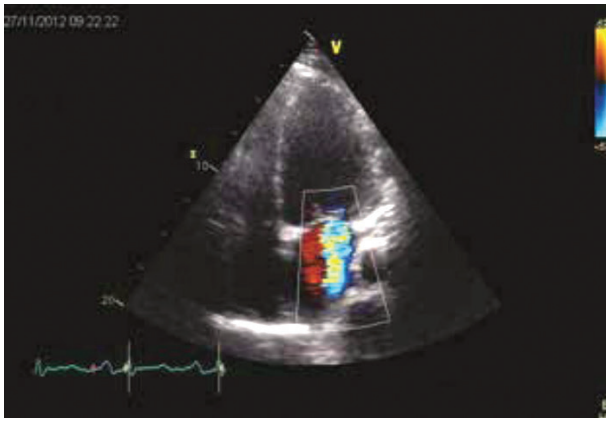

Figure 1. Mitral regurgitation after radiotherapy. Fibrosis found mainly in the mitral annulus and the basal segments of the mitral leaflets; minor lesions in the apical segments

The risk of clinically significant valvular disease is higher at radiation doses exceeding 30 Gy [31]. Notably, exposure to standard radiation doses of 20 to 30 Gy used in modern radiotherapy is associated with a low risk of VHD [32]. Some observations indicate that chemotherapy used before or during radiotherapy may increase the sensitivity of valvular tissue to radiation [1].

Echocardiography is the first-line modality for assessing radiation-induced valvular lesions. Typical echocardiographic features of radiation-induced VHD are presented in Table 3.

The recommendations for multimodality imaging evaluation of patients after radiotherapy were developed by the European Association of Cardiovascular Imaging and the American Society of Echocardiography in 2013 [25]. In all patients with prior exposure to anterior and left chest radiation, history-taking and physical examination should be performed annually to identify new heart and carotid murmurs, neurological signs and symptoms, symptoms of HF, and chest pain. Moreover, intensive measures should be taken to reduce CV risk factors. In asymptomatic low-risk patients, echocardiography 10 years after completion of cancer therapy and every 5 years thereafter is recommended. In high-risk patients (with prior exposure to anterior or left chest radiation and with at least one risk factor for cardiotoxicity), echocardiography should be performed no later than 5 years after radiotherapy, and noninvasive stress testing should be considered.

In patients with cancer, minimally invasive and transcatheter interventions are preferable due to increased bleeding risk, particularly in the setting of critical AS [5, 6]. In specific cases, TAVI for AR can also be considered [33].

Patients with cancer may present with mediastinal, pericardial, and pleural fibrosis as well as coronary artery disease following previous radiation exposure. Difficulties during surgery may also be related to frequent pericardial adhesions due to constrictive pericarditis, LV dysfunction, porcelain aorta, and pulmonary fibrosis [31, 34].

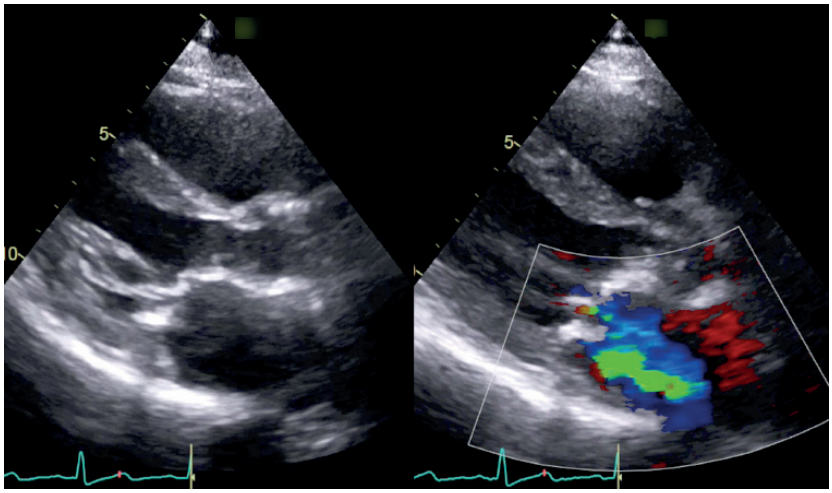

Figure 2. Radiation-induced valvular heart disease. Thickening of the aorto-mitral curtain. Moderate mitral regurgitation

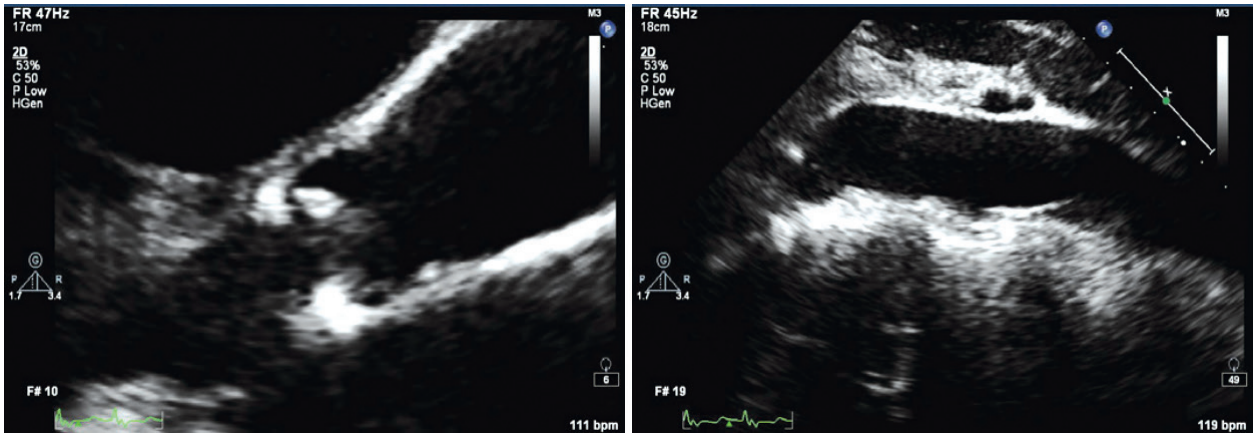

Figure 3. A. Aortic valve and ascending aortic calcification in an adult female patient 13 years after mediastinal radiotherapy for Hodgkin lymphoma. **B.** Similar calcification in the aortic arch (porcelain aorta)

Table 3. Echocardiographic features of radiation-induced valvular heart disease

Uniform valvular thickening due to fibrosis
Uniform distribution of lesions in the aorto-mitral curtain
Porcelain aorta
More severe lesions in left-sided valves (aortic, mitral) than in right-sided valves (tricuspid, pulmonary)
Regurgitation prior to stenosis
Fibrosis and calcification mostly of the base and mid portions of the valves; preservation of mitral commissural fissures

Patients with new valvular heart disease after radiotherapy — summary

1. In all patients with prior exposure to radiation, history-taking and physical examination should be performed annually to identify new heart and carotid murmurs, neurological signs and symptoms, symptoms of HF, and chest pain.
2. In patients after radiotherapy, intensive efforts should be made to reduce and treat CV risk factors.
3. In asymptomatic low-risk patients with prior radiation exposure, echocardiography 10 years after completion of cancer therapy and every 5 years thereafter is recommended.
4. In high-risk patients, echocardiography should be performed no later than 5 years after radiotherapy, and noninvasive stress testing should be considered.
5. High-risk patients are patients with previous exposure to anterior or left chest radiation and at least one risk factor (total radiation dose >30 Gy or 2 Gy/day; age <50 years; a tumor near the heart or an intracardiac tumor; concomitant chemotherapy with anthracyclines; presence of CV risk factors or known CVD).

TREATMENT OF VALVULAR HEART DISEASE IN PATIENTS WITH CANCER

Critical valve disease may be a contraindication to aggressive cancer treatment. This refers both to surgical treatment, with surgical risk increasing with the severity of VHD and to selected chemotherapy regimens. In such cases, priority is given to surgical valve repair, which should be done promptly, especially in patients with fast tumor growth and a relatively good prognosis. Considering the potential complications of chemotherapy (thrombocytopenia, coagulation disorders, immunosuppression, and susceptibility to infections), therapeutic strategies that do not require long-term anticoagulation or antiplatelet treatment should

be considered. Therefore, mechanical prosthetic valve implantation should be avoided, where justified, and bioprosthetic valve should be considered instead, especially since patients with cancer are usually at an older age and present with frailty and numerous comorbidities.

If the patient is at high surgical risk due to cancer or other biological causes, less invasive procedures should be considered, such as TAVI, balloon aortic valvuloplasty as palliative treatment, or — where justified — transcatheter mitral and tricuspid valve edge-to-edge repair. Minimally invasive procedures shorten recovery times, speed up urgent diagnostic workup, and reduce the waiting time for life-saving cancer treatment. Moreover, with minimally invasive procedures, extensive wounds can be avoided along with healing difficulties due to cancer itself and the use of chemotherapy and radiotherapy.

Palliative care patients with end-stage cancer and the quality of life determined by critical VHD constitute a specific population. The management of these patients is particularly challenging. They may require palliative treatment of VHD to improve the quality of life at the end of life. In the era of considerable advances in cancer treatment resulting in significantly longer survival, death in some cancer patients receiving palliative care may be caused by VHD rather than cancer. In these patients, valve replacement is not recommended because of poor outcomes and the high risk of classic cardiac surgery. Minimally invasive and percutaneous interventions such as palliative treatment are indicated. The risks and benefits of heart valve interventions should be carefully balanced, and medical futility should be avoided.

Effect of valvular heart disease on cancer treatment — summary

1. Significant VHDs, particularly stenosis, may be a contraindication to aggressive cancer treatment and may increase surgical risk. In such cases, priority is given to surgical valve repair, which should be done promptly, especially in patients with fast tumor growth and a relatively good prognosis.
2. In patients with VHD scheduled for chemotherapy (particularly with anthracyclines, HER-2, RAF/MEK), close and frequent monitoring (echocardiography, biomarkers) is indicated during and after treatment.
3. Considering potential chemotherapy-related complications (thrombocytopenia, coagulation disorders, immunosuppression, susceptibility to infection), therapeutic strategies that do not require long-term anticoagulation or antiplatelet treatment should be considered (mechanical prosthetic valve implantation should be avoided).
4. If the patient is at high surgical risk due to cancer or other biological causes, less invasive procedures should be considered, such as TAVI, balloon aortic valvuloplasty as palliative treatment, or – where justified – TEER.
5. TAVI should be considered in patients at intermediate surgical risk with symptomatic AS caused by radiotherapy.

TRANSCATHETER AORTIC VALVE INTERVENTION IN PATIENTS WITH CANCER

AS is the most common acquired heart disease in elderly patients, and older age is also associated with an increased incidence of cancer. Patients who underwent mediastinal radiotherapy at a younger age for the treatment of malignancy (e.g. breast cancer, lung cancer, lymphoma) are at risk of late cardiotoxicity manifesting as aortic and mitral valve fibrosis. The risk of VHD is significantly higher at radiation doses exceeding 25 Gy [25, 35] or 30 Gy [31]. Radiation-induced valvular calcifications are extensive and affect numerous surrounding structures, including the aortic annulus, subvalvular apparatus, and the aorto-mitral curtain. Calcification of the aorto-mitral curtain is considered a typical complication of cardiac radiation exposure, and severe calcification is a strong predictor of mortality in patients undergoing cardiac surgery.

The adverse effects of radiotherapy affect not only the aortic valve but also a significant portion of the ascending aorta together with the branches of the aortic arch. Almost 60% of such patients develop significant atherosclerosis of the ascending aorta, while porcelain aorta is seen in about 15% of patients [36]. Severe calcification of the ascending aorta may preclude cardiac surgery. At the same time, endovascular aortic procedures remain feasible but are associated with higher risk of complications, such as stroke or peripheral embolism. Patients with severe AS and previous radiotherapy are at higher long-term mortality risk after surgical aortic valve replacement (SAVR) than those without previous radiotherapy [36]. The higher short-term and long-term risk may be caused by worse pulmonary ventilation due to radiation-induced pulmonary fibrosis, the need for simultaneous mitral valve replacement and coronary artery bypass grafting, as well as fibrosis of the pericardial and right ventricular free wall.

Surgical risk assessment in patients with cancer poses a significant challenge. Surgical risk scores are limited because they do not include a history of cancer or previous chest radiation. According to the 2017 ESC guidelines for the management of VHD, the decision between SAVR and TAVI in patients with risk factors such as frailty, porcelain aorta, or previous chest radiation should be guided by the Heart Team discussion and follow a careful assessment of the individual patient. TAVI is preferable in patients when transfemoral access is possible, especially in those at older ages [37]. The more recent 2021 guidelines generally recommend TAVI if comorbidities preclude SAVR [4]. Current data on SAVR vs TAVI in patients with previous chest radiotherapy come from small retrospective studies or subanalyses of larger studies [38]. Therefore, each patient after chest radiotherapy requires a personalized approach.

The most recent ESC guidelines on cardio-oncology recommend that patients with severe AS are managed according to current clinical knowledge while considering cancer-related prognosis. TAVI should be considered in patients with symptomatic radiation-induced AS and intermediate surgical risk (class IIa) [1].

Another important aspect is the management of patients with severe symptomatic AS and newly diagnosed cancer. Compared with TAVI, cardiac surgery with extracorporeal circulation may significantly delay cancer treatment. Therefore, the treatment choice should be based on the risk-benefit assessment and individualized based on cancer stage and prognosis. TAVI will be a more common strategy in this scenario because it reduces recovery time and delays in starting cancer treatment. Therapeutic decision-making should consider the higher risk of surgical complications in patients with cancer due to higher rates of hemostatic disorders such as thrombocytopenia, coagulopathy, or hypercoagulation. In selected cases, patients with relatively good long-term prognosis (at least 1-year survival after cancer treatment) may be considered for balloon aortic valvuloplasty (BAV) as a bridge to definitive valve repair. Temporary hemodynamic improvement after BAV reduces the risk of cancer surgery. Usually, aortic valve replacement, most often TAVI, can be safely performed a few weeks after BAV [39]. In patients with poor cancer-related prognosis and severe symptomatic AS, BAV can be performed as a palliative treatment to improve the quality of life [40].

TRANSCATHETER HEART VALVE INTERVENTIONS IN PATIENTS WITH CANCER: MITRAL, TRICUSPID, AND PULMONARY VALVES

The presence of VHD is associated with increased risk of perioperative CV complications in patients undergoing noncardiac surgery (NCS), such as cancer surgery [41]. As described in the section on the management of patients with VHD undergoing NCS, the mode of treatment depends on the type of valve disease, urgency of NCS, and the risk of perioperative complications [42]. Also, in patients with cancer treated with medical therapy (cytostatic drugs, biological drugs) or radiotherapy, the choice of valve disease treatment should be guided by efforts to minimize the risk of death and HF as well as to improve the quality of life without exposing the patient to the excessive risk associated with the intervention. Cardiac surgery in these patients may be challenging, particularly with previous chest radiotherapy (fibrosis, delayed wound healing, and higher risk of infection, including endocarditis). Transcatheter valve repair and replacement seem to be the safest option for these patients. An important consideration is the need for anticoagulant and antiplatelet treatment after valve repair/replacement. Anticoagulation and antiplatelet treatment can increase the bleeding risk in patients with drug-induced or radiation-induced coagulopathies (bone marrow suppression, increased risk of gastrointestinal bleeding). Antiplatelet treatment in patients with cancer is associated with a 1.6-fold higher bleeding risk compared with patients without cancer. It seems justified to avoid the combination of oral anticoagulation and dual antiplatelet therapy. Good communication among the MDT members is essential [43].

Transcatheter mitral valve edge-to-edge repair

Eligibility: (1) the presence of HF symptoms in patients with severe primary MR not eligible for surgical valve repair and fulfilling criteria suggesting an increased chance of responding to the treatment; (2) HF symptoms despite optimal medical therapy and cardiac resynchronization therapy according to the ESC guidelines for the management of HF in patients with moderate or severe MR fulfilling criteria suggesting an increased chance of responding to the treatment (COAPT inclusion criteria); (3) patients not fulfilling all the clinical criteria but who may derive clinical benefit from mitral TEER as per the Heart Team's judgment [4]. In conclusion, the presence of cancer itself should not constitute a contraindication to TEER unless the estimated life expectancy is less than 12 months. Reduction of HF symptoms can improve the quality of life and facilitate cancer treatment [1].

The technique is similar to standard transcatheter valve repair, but extra caution is advised when obtaining vascular access in patients with thrombocytopenia or coagulation disorders. Ultrasound-guided femoral puncture, frequent monitoring of activated clotting time during the procedure (recommended value of about 300 s), and maintenance and frequent monitoring of hemostasis (at least two hemostatic systems should be considered, i.e., vascular suture and hemostatic suture [a figure-of-eight suture] or two vascular systems) are recommended. The atrial septal puncture should be guided by transesophageal echocardiography to reduce the risk of tamponade.

The choice of medical therapy after the procedure should consider the benefits (prevention of thromboembolic complications in patients with atrial fibrillation [AF]) against the risks (bleeding). In the absence of a high bleeding risk, standard medical therapy is recommended (antithrombotic treatment with non-vitamin K antagonist oral anticoagulants [NOACs]) in patients with indications for long-term anticoagulation plus an antiplatelet drug for 1 to 3 months or dual antiplatelet therapy for 1 month, with one of the drugs maintained for 3 to 6 months. In patients at high bleeding risk with indications for anticoagulation, the treatment should be limited to NOACs and a single antiplatelet therapy for 3 months. However, these recommendations are not based on evidence from randomized controlled trials [1].

Transcatheter tricuspid valve edge-to-edge repair

Eligibility: symptoms of right HF in inoperable patients with severe tricuspid regurgitation (TR) fulfilling anatomical criteria, when the clinical benefit of the procedure is

expected according to the Heart Team evaluation. Specific cases include patients with TR associated with carcinoid syndrome, where a decision on TEER should be based on a multidisciplinary team discussion, including life expectancy as assessed by the treating oncologist. As in mitral TEER, the technique is similar to standard transcatheter valve repair, except that a higher risk of bleeding complications can be expected in patients with right HF and secondary liver failure. Medical therapy after the procedure should follow the same criteria as for mitral TEER. Interventions that are unlikely to result in clinical improvement should be avoided (severe right ventricular dysfunction, systolic pulmonary artery pressure [SPAP] >70 mm Hg) [4].

Transcatheter interventions in pulmonary valve disease

The eligibility criteria for transcatheter interventions in patients with pulmonary valve disease and cancer are the same as for patients without cancer. The key considerations include reducing the risk of bleeding complications during the procedure and assessment of potential benefits in life expectancy, clinical status, and quality of life [4].

HEART VALVE SURGERY IN PATIENTS WITH CANCER

Both cancer survivors and those with active cancer may require heart valve surgery.

It was estimated that from 2% to 4% of patients undergoing heart valve surgery were previously treated for cancer. Most patients (70%–80%) presented with solid cancer (mainly breast, large intestine, prostate, and bladder cancer), while hematological malignancies were less common. Previous chemotherapy is generally not associated with increased surgical risk unless chemotherapy-related cardiotoxicity results in permanent cardiac damage. Knowledge of specific treatment-related side effects facilitates an appropriate surgical risk assessment. Cancer therapy-related CV toxicity, as well as the potential for reversibility, was summarized in the 2022 ESC guidelines on cardio-oncology [1].

Also, previous radiotherapy has implications for heart valve surgery, especially in the case of radiation to the chest. The side effects of radiotherapy that should be considered before surgery include pericarditis (with possible pericardial adhesions or effusion) and myocardial and pulmonary fibrosis. Other important aspects include radiotherapy-induced injury to the internal mammary artery used as a conduit for revascularization procedures as well as injury to the aortic and mitral valves themselves, which may adversely affect the repair. Radiation-induced CV toxicity can also include aortic pathology, such as aortic wall calcification (porcelain aorta), which may significantly limit, or even preclude, the cross-clamping procedure or even extracorporeal circulation. The risk of radiation-induced CV toxicity is higher in patients receiving higher radiation doses and young patients. Importantly, radiotherapy can also cause esophageal fibrosis, which increases the risk of esophageal perforation during perioperative transesophageal echocardiography. In patients with previous radiotherapy, chest CT for pulmonary and CV assessment should be an indispensable part of the preoperative planning or even the Heart Team/MDT decision-making.

In patients with active cancer, the decision on management strategy should be based on multidisciplinary team discussions involving a cardiologist, cardiac surgeon, interventional cardiologist, oncologist, and anesthesiologist. The most important factor to be considered in the decision-making process is life expectancy. Valve surgery is usually unwarranted if cancer is associated with shorter expected survival than VHD. According to the ESC/EACTS guidelines [4], heart valve surgery in patients with symptomatic VHD is not indicated if no improvement in the quality of life can be expected or if life expectancy is less than 12 months. In patients with a good cancer prognosis, the most important aspect to consider is which procedure to perform first (oncological or cardiac surgery), bearing in mind that cardiac surgery will most likely delay cancer treatment by about 1 month. Based on the ESC and European Society of Cardiac Surgery guidelines, non-cardiac cancer surgery (NCOS) is safe in asymptomatic patients with VHD, including those with severe disease. The presence of symptoms or LV dysfunction should prompt consideration of valvular surgery before cancer surgery, but NCOS can be performed first, especially in patients with valvular regurgitation.

Concomitant cancer and cardiac surgery can also be considered. Good outcomes of concomitant surgery were reported in case-series studies, particularly in patients with lung and gastrointestinal cancer. If lung resection is performed simultaneously with cardiac surgery, the thoracic part of the procedure is usually performed first. Relatively good outcomes of a combined approach were reported for minor cancer surgery (stage I or II lung cancer, partial gastrectomy) and relatively good cardiac function. In the case of more advanced cancer, major surgeries, and more advanced CVD, cardiac surgery should be performed first, followed by cancer surgery.

Notably, both cancer treatment and cancer itself are often linked with a prothrombotic state. Cancer often induces the release of tissue factor and other factors that can indirectly activate factor X. Myeloproliferative neoplasms, such as chronic myeloid leukemia, are also associated with higher risk of disseminated intravascular coagulation. Therefore, appropriate thromboprophylaxis is an important consideration in the perioperative management of patients with cancer.

Notably, unequivocal evidence to support a link between cardiac surgery with extracorporeal circulation and the risk of cancer spread is lacking.

In conclusion, a multidisciplinary approach to the management of patients with cancer, with careful consideration of the above factors and planning of the subsequent stages of treatment, is important for individual patient outcomes.

MINIMALLY INVASIVE/ROBOT-ASSISTED PROCEDURES FOR VALVULAR HEART DISEASE IN PATIENTS WITH CANCER

The most common cause of heart valve intervention in patients with cancer is the progression of pre-existing VHD, previous endocarditis, and LV remodeling. As mentioned before, radiotherapy-induced fibrosis and calcification most often affect the aortic valve leaflets, followed by the mitral valve leaflets, but also the aorta, mediastinum, and pericardium, which is associated with a higher surgical risk [8, 26, 44–46].

Minimally invasive procedures, including robot-assisted procedures, are possible in highly specialized centers. Considering pre-existing CVD in patients with cancer, minimally invasive procedures seem to offer a greater benefit.

The gold standard for aortic valve and ascending aortic surgery is upper mini-sternotomy, in which an incision is made only in the upper one-third of the sternum. This approach provides good access to the aortic valve, allowing valve replacement or repair. It also spares the lower two-thirds of the sternum, which helps maintain shoulder girdle stability and facilitates rehabilitation. In a selected group of patients, this surgery can also be performed through right anterior mini-thoracotomy. In this technique, sternal incision is not required, and access is obtained by small incisions and openings in the intercostal space. Patients who undergo right anterior mini-thoracotomy can be mobilized and rehabilitated already on the first day after surgery [47]. Minimally invasive procedures can also be performed in patients with mitral and tricuspid valve disease. Mitral and tricuspid valve surgeries are performed using right lateral mini-thoracotomy or a full thoracoscopic approach. In most patients, the skin incision is done at places where scars occur naturally, for example, around the nipple in men. This makes the surgical scar almost invisible. In centers specializing in minimally invasive cardiac surgery, such procedures are performed with 3D technology, which uses high-resolution equipment and increases procedural precision. The use of 3D glasses allows the surgeon to access views from inside the chest [48].

So far, the robotics technology has been the greatest achievement in the field of minimally invasive surgery. However, it requires considerable experience. In robot-assisted surgeries, there is no need to do an incision, and transthoracic access is obtained via skin ports into which the robot arms are introduced. Such surgeries are unique in that the surgeon-operator is not present at the operating table but sits at the robot console and performs the procedure by navigating the robot's arms inside the chest (Figure 4). The advantage of robot-assisted surgeries over thoracoscopy is the extraordinary mobility of the robot's arms. The arms have a very wide field of view and can reach locations that are unattainable with a thoracoscope [49].

Minimally invasive and robot-assisted procedures shorten recovery and hospital stay; they also reduce postoperative pain. Other benefits include a less frequent need for blood products, reduced incidence of arrhythmia, and in some populations, lower mortality rates [50]. The sternal-sparing approach is also associated with lower risk of severe local infections. Also, a shorter recovery time helps prevent infections (e.g., lung infection that is frequently observed in these patients). Finally, faster recovery reduces the time between cardiac surgery and subsequent cancer therapy.

MANAGEMENT OF PATIENTS WITH VALVULAR HEART DISEASE SCHEDULED FOR ONCOLOGIC SURGERY

The risk of perioperative CV complications is higher in patients with known VHD. The highest risk is observed in patients with AS and mitral stenosis (MS). The risk increases with the severity of VHD and depends on the type of planned surgery. According to Glance et al. [41], in most cases, NCOS is associated with intermediate or high risk of CV death, thus the presence of VHD may be problematic in a significant number of patients with cancer.

Compared with open surgery, endoscopic procedures are associated with lower complication rates, reduced fluid shifts, and better postoperative pulmonary ventilation, which is important in patients with VHD. Thus, it is important to consider these factors when deciding on the access site.

Echocardiographic evaluation is recommended in all patients scheduled for elective intermediate- or high-risk NCOS to determine the type and severity of VHD. The association of clinical symptoms with VHD and cancer stage should be assessed (class I, level C) [42].

In patients with severe VHD, time-sensitive surgery should be performed with close hemodynamic monitoring, and decisions on elective NCOS should consider the presence of VHD-related symptoms and CV comorbidities (coronary artery disease, reduced LV systolic function). A surgical risk assessment by the Heart Team should consider the patient's preferences and should be communicated to the surgical team. In general, severe symptomatic MS or AS should be treated before both time-sensitive and elective NCOS because they are associated with the highest CV risk. If NCOS can be safely delayed, the repair of severe AR and MR with concomitant HF should be considered.

Severe aortic stenosis

The key aspects to consider in patients with severe AS scheduled for elective NCOS include clinical symptoms, LVEF, and coronary artery disease. Eligibility is determined using the same criteria as in patients without planned NCOS. The measurement of biomarkers (NT-proBNP and troponin) may be useful in asymptomatic patients or in the presence of atypical symptoms. Symptomatic patients scheduled for intermediate- or high-risk NCOS should undergo SAVR or TAVI (according to the 2021 ESC/EACTS

Figure 4. Robot-assisted surgery with the Da Vinci robot (Intuitive Surgical, Sunnyvale, CA, US)

guidelines for the management of VHD) (class I, level C) [4]. In patients scheduled for time-sensitive NCOS, TAVI should be considered. In patients at high risk of valve replacement, with the presence of contraindications, with lack of consent to cardiac surgery, or in need of time-sensitive NCOS, BAV may be considered as a bridge to definitive valve repair (class IIb, level C). In asymptomatic patients with severe AS and preserved LVEF, low- and intermediate-risk NCOS can be safely performed. Similarly, in asymptomatic patients with LVEF <50%, low- and intermediate-risk NCOS can be safely performed with perioperative hemodynamic monitoring.

Severe mitral stenosis

In patients with mild MS (valve area >1.5 cm^2) or in asymptomatic patients with moderate to severe MS (valve area ≤1.5 cm^2) and SPAP <50 mm Hg, NCOS is associated with low CV risk.

In asymptomatic patients with moderate to severe MS and SPAP >50 mm Hg and in symptomatic patients with MS, percutaneous mitral commissurotomy (PMC) or valve surgery is recommended before high-risk NCOS (class I, level C). Low- and intermediate-risk NCS in asymptomatic patients with severe MS can be performed with appropriate perioperative hemodynamic monitoring if PMC is unfeasible due to valve morphology.

Aortic regurgitation

Patients with mild to moderate AR can undergo NCOS at no additional CV risk. In symptomatic patients with severe AR or asymptomatic patients with severe AR eligible for valve intervention, the intervention is recommended before elective intermediate- or high-risk NCOS (class I, level C).

Mitral regurgitation

In patients with symptomatic severe primary MR or asymptomatic severe primary MR with LV dysfunction, surgical or transcatheter valve intervention should be considered before elective intermediate- or high-risk NCOS (class IIa, level C).

In patients with severe secondary MR who remain symptomatic despite optimal medical therapy, surgical or transcatheter valve intervention should be considered before NCS (class IIa, level C).

In patients with AR or MR with significantly reduced LVEF, peri- and postoperative monitoring with a special focus on rate and fluid control is recommended to optimize cardiac output and reduce MR severity.

Transcatheter valve interventions in patients with cancer — summary

1. In patients referred for time-sensitive NCOS, TAVI should be considered in patients with severe AS.
2. In patients at high risk of valve replacement, with contraindications, lack of consent to cardiac surgery, or in need of time-sensitive NCOS, balloon aortic valvuloplasty may be considered as a bridge to definitive valve repair.
3. In asymptomatic patients with severe AS and preserved LVEF, low- and intermediate-risk NCS can be safely performed. Similarly, in asymptomatic patients with LVEF <50%, low- and intermediate-risk NCOS can be safely performed with perioperative hemodynamic monitoring.
4. In asymptomatic patients with moderate to severe MS and SPAP >50 mmHg and in symptomatic patients with MS, PMC or valve surgery is recommended before high-risk NCOS.
5. In symptomatic patients with severe AR or in asymptomatic patients with severe AR eligible for valve intervention, the intervention is recommended before elective intermediate- or high-risk NCOS.
6. In patients with symptomatic severe primary MR or asymptomatic severe primary MR with LV dysfunction, surgical or transcatheter valve intervention should be considered before elective intermediate- or high-risk NCOS.
7. In patients with severe secondary MR who remain symptomatic despite optimal medical therapy, surgical or transcatheter valve intervention should be considered before NCOS.

Heart valve surgery in patients with cancer — summary

1. In patients with previous radiotherapy, chest CT for pulmonary and CV assessment should be an indispensable part of the preoperative planning.
2. Notably, unequivocal evidence to support a link between cardiac surgery with extracorporeal circulation and the risk of cancer spread is lacking.
3. Minimally invasive and robot-assisted procedures shorten recovery and hospital stay; they also reduce postoperative pain. Sternal-sparing procedures also reduce the risk of severe local infections.
4. When determining eligibility for surgery, estimated life expectancy/prognosis as well as the risk-benefit ratio should be considered.
5. Surgical risk can be assessed using the STS-PROM score, as it considers previous chest radiotherapy and previous cancer (as opposed to other risk scores).

MANAGEMENT OF AORTIC DISEASE IN PATIENTS WITH CANCER

Management of patients with aortic dilatation

Cancer treatment in patients with thoracic aortic dilation (ascending aorta diameter, 35–55 mm; descending aorta diameter, 35–60 mm) is the same as in patients without aortic disease, and thoracic aortic dilatation is not a contraindication to conservative treatment (chemotherapy or radiotherapy) or surgical treatment. Each patient with aortic dilatation and hypertension should receive oral β-blockers (if not contraindicated) as the only oral drugs that reduce the dp/dt ratio, thus lowering the risk of acute aortic syndrome. Some chemotherapeutics used for cancer treatment can significantly increase blood pressure and the risk of acute aortic syndrome (acute aortic dissection, aortic rupture, intramural aortic hematoma). This particularly refers to angiogenesis inhibitors. Patients receiving such medications should be closely monitored for blood pressure, and aggressive antihypertensive treatment should be administered if needed. Increased blood pressure is observed only during cancer treatment and can be successfully managed with antihypertensive drugs.

Aortic dilatation ranging from 45 to 55 mm for the ascending aorta and from 50 to 60 mm for the descending aorta is associated with only slightly higher risk of acute aortic syndrome and is not a contraindication to cancer treatment and should not delay such treatment. If conservative or surgical cancer treatment is required, blood pressure should be closely monitored, aggressive antihypertensive treatment should be started, and the patient should be instructed to avoid heavy physical activity, especially isometric training. During the delivery of anesthesia for surgery, blood pressure should be monitored, preferably with invasive blood pressure monitoring, which offers a more precise real-time measurement. During surgery, blood pressure should not be higher than 130 mm Hg.

Management of patients with aortic aneurysms

The management of patients with an aortic aneurysm (ascending aorta diameter >55 mm or descending aorta diameter >60 mm) and cancer requires an individualized approach. The decision on treatment strategy should follow a multidisciplinary team discussion involving an oncologist, cardiologist, and cardiac surgeon. The decision should be based on assessment of:

- The risk of surgical aortic aneurysm repair
- The size and site of aortic aneurysm
- The risk of cancer treatment and its cardiotoxicity
- Cancer prognosis.

The final decision should always take into consideration patients' preferences and their willingness to accept higher-risk treatment.

In patients with smaller aortic aneurysms, it is possible to avoid surgical treatment so that cancer treatment is not delayed. The risk of acute aortic syndrome is higher with larger aneurysms. Therefore, in patients with large aneurysms (>6 cm for the ascending aorta), surgery should be performed before cancer treatment. In-vitro and in-vivo studies showed that extracorporeal circulation can cause significant immunosuppression. Despite previous concerns, there is no evidence that extracorporeal circulation is associated with cancer spread or increased cancer progression and mortality. The need for rehabilitation after cardiac surgery may delay cancer treatment. Patients with cancer are at higher risk of severe complications during and after surgery.

Management of patients with Stanford aortic dissection

Ascending aortic dissection is a life-threatening condition requiring emergency surgery. In patients with cancer, the decision on the management strategy should be made immediately based on all the available data and with consideration of the patient's preferences. If technically feasible, minimally invasive interventions should be considered, including endovascular procedures. In patients with cancer with a poor prognosis or at very high surgical risk due to poor clinical status, a decision not to perform surgical repair can be considered. Each patient with aortic dissection should be closely monitored and receive aggressive antihypertensive treatment.

Management of patients with aortic aneurysms — summary

1. The management of patients with aortic aneurysms (ascending aorta diameter >55 mm or descending aorta diameter >60 mm) and cancer requires an individualized approach. The decision on treatment strategy should follow a multidisciplinary team discussion involving an oncologist, cardiologist, and cardiac surgeon.

INFECTIVE ENDOCARDITIS AND NONBACTERIAL THROMBOTIC ENDOCARDITIS IN PATIENTS WITH CANCER

The reported incidence of cancer in patients with infective endocarditis (IE) ranges from 5.6% to 17.6%. It is more prevalent in men and elderly patients. Patients with IE may either have active cancer or previous cancer history although this is not always reflected in studies [51–54].

Infective endocarditis is more common in patients with cancer than in the general population. This may be due to immune disorders and prothrombotic state as well as the need for numerous invasive diagnostic and therapeutic procedures (e.g., catheters, central ports, various devices) that increase susceptibility to bacteremia (port of entry), including IE. Other causes include a higher risk of local and systemic infections, elderly age, and a higher incidence of CV comorbidities, including pre-existing VHD. Immunosuppression is also affected by the type of cancer (blood cancer, metastases) and the type of cancer treatment. Nevertheless, the prevention of endocarditis in patients with cancer should follow the same guidelines as in the general population. In particular, it is limited to preventive measures before oral procedures, even though invasive procedures constitute the port of entry for bacteria [51].

In patients with cancer, IE is associated with higher mortality and can adversely affect treatment outcomes, for example, by prompting a decision not to use or to delay chemotherapy or to modify aggressive treatment. In patients with cancer, IE can have atypical clinical presentation as compared with patients without cancer, characterized by less frequent fever, a new heart murmur, and a higher risk of complications such as acute kidney failure with subsequent thrombotic events and HF [51, 53, 54].

In patients with cancer, IE affects mainly the mitral and aortic valves. The most common causative pathogen, also associated with the worst prognosis, is Staphylococcus aureus, followed by *Enterococcus*. On the other hand, IE caused by *Streptococcus gallolyticus* (previously *S. bovis*) and *Enterococcus fecalis* was associated with a higher incidence of colorectal cancer or neoplasms. Therefore, colonoscopy is recommended in these patients [55–57], and IE may be an early marker of colorectal cancer and other types of cancer [52, 57]. IE is more common in elderly patients with colorectal, lung, and prostate cancer, as compared with individuals without cancer. Although gastrointestinal and lung cancer, as well as hematological malignancies, were linked to IE, specific management strategies are lacking [53].

Patients with advanced cancer may develop nonbacterial thrombotic endocarditis. This particularly refers to lung cancer, pancreatic cancer, and gastrointestinal adenocarcinomas. Valvular vegetations in nonbacterial thrombotic endocarditis are usually small (<1 cm), have an irregular shape, and typically involve left-sided valves. Vegetations are found on damaged and undamaged valves but may also involve the tendinous cords, left atrial appendage, and the remaining endocardium. In these patients, nonbacterial thrombotic endocarditis usually leads to embolic events in the central nervous system or another important organ [52, 58, 59].

The diagnosis of IE in patients with cancer is the same as in patients without cancer. Echocardiography is the first-line imaging modality as the safest method with no radiation exposure. The role of CT, PET/CT, and CMR is also emphasized. However, differentiation between inflammatory, cancer, metastatic, and thrombotic lesions remains challenging or even unfeasible [59, 60].

Patients with IE and treatable cancer should receive guideline-based empiric antibiotic therapy depending on the type and location of the microorganism as well as the

type of cancer treatment. Research shows that patients with IE and cancer are more often treated with amoxicillin, ceftriaxone, and daptomycin than with vancomycin [53, 54].

Indications for surgical treatment of IE in patients with cancer are the same as in patients without cancer. Mortality at 1 year in patients with cancer was higher than in patients without cancer (18.0% vs. 10.2%; P <0.001), and the risk factors included creatinine levels higher than 2 mg/dl, HF, and no surgery despite indications [54]. Bioprosthetic valves were more common in patients with cancer versus those without. However, it was reported that cardiac surgery is less often performed in patients with cancer despite indications [51, 54], and this is also linked to higher mortality rates in patients with IE and cancer. Pugalenthi et al. [53] argued that cardiac surgery should be performed in patients with treatable cancer (with no metastases) in the absence of contraindications. This is supported by the fact that some malignancies (i.e., prostate, breast, and colorectal cancer) are often associated with long survival [58]. On the other hand, often the reason why surgery is not performed is not cancer itself but other factors such as surgical risk, patient's death, or the lack of consent [53].

A recent algorithm for the management of patients with IE and cancer suggests that in patients with previous or current treatable cancer with no metastases, IE should be treated according to the guidelines, irrespective of the causative pathogen. In the remaining cases, medical therapy is recommended. If IE is caused by S. Gallolyticus or Enterococcus, colonoscopy is recommended [54].

Infective endocarditis and nonbacterial thrombotic endocarditis in patients with cancer — summary

1. In patients with cancer, IE can have atypical clinical presentation as compared with patients without cancer, characterized by less frequent fever, a new heart murmur, and a higher risk of complications such as acute kidney failure with subsequent thrombotic events and HF.
2. In patients with cancer, IE affects mainly the mitral and aortic valves. The most common causative pathogen, associated also with the worst prognosis, is Staphylococcus aureus, followed by Enterococcus.
3. Patients with advanced cancer may develop nonbacterial thrombotic endocarditis. This particularly refers to lung cancer, pancreatic cancer, and gastrointestinal adenocarcinomas.
4. Indications for antibiotic and surgical treatment of IE in patients with cancer are the same as in patients without cancer.

CARDIAC TUMORS WITH VALVULAR INVOLVEMENT

Cancer significantly affects the natural course of pre-existing VHD [61, 62]. On the other hand, chemotherapy (CTRCD) and radiotherapy adversely affect the valvular structures, accelerating degeneration and increasing susceptibility to IE.

Carcinoid tumor is a type of malignancy that directly affects valvular morphology and function. It is a neuroendocrine tumor that releases serotonin and is found in the liver or the ovary [61]. Increased amounts of serotonin are released consequent to impaired serotonin degradation by liver cells due to metastatic liver involvement. In 20% to 50% of patients, carcinoid tumor causes heart damage, usually VHD, with myocardial metastases or pleural effusion being less common. Carcinoid heart disease more often involves right-sided valves (typically the tricuspid valve) than left-sided valves. This is because monoamine oxidase in the lungs degrades serotonin limiting its release into the circulation. However, in patients with patent foramen ovale, concomitant atrial septic defect, hormonally active tumor in the lungs, or poorly controlled carcinoid syndrome, the involvement of the left-sided valves is also observed (one-third of patients with carcinoid heart disease). Valve damage is caused by serotonin, which stimulates valvular myofibroblasts to excessive collagen and glycosaminoglycan production by acting on the serotonin receptors 5-HT2B. This leads to the thickening of valvular leaflets and subvalvular apparatus, with the formation of carcinoid plaque. The typical feature is the absence of calcified foci in the valvular structures. In terms of morphological lesions, carcinoid syndrome causes increased regurgitation with retracted and immobile leaflets. The main cause of death in patients with carcinoid syndrome is right HF due to endocardial fibrosis of the right ventricle and volume overload following severe tricuspid or pulmonary regurgitation.

The prognosis of patients with carcinoid heart disease has improved after the introduction of somatostatin analogs and new surgical techniques for liver metastases. In patients with well-controlled symptoms and metastatic foci and with a cancer prognosis longer than 12 months, tricuspid valve replacement is recommended (class I). The choice between bioprosthetic and mechanical valves should be guided by individual patient and disease characteristics, as both types of valves have their pros and cons in carcinoid heart disease. The decision on surgery should follow a multidisciplinary team discussion (cardiologist, cardiac surgeon, anesthesiologist, oncologist, endocrinologist) and should take into consideration the risk of carcinoid crisis among other factors (class I, ESC guidelines) [61, 62].

Tumors that directly affect the heart valves include papillary fibroelastoma, and less commonly, myxoma and metastatic tumors [61, 63]. Papillary fibroelastoma is a mild tumor that constitutes about 11.5% of all primary cardiac tumors and three-fourths of all tumors associated with valvular dysfunction. The tumor is composed of elastic fibers and collagen with an endothelial covering. It is attached to the endocardium of the aortic and mitral valves (less commonly the tricuspid valve) by a short connective tissue pedicle. In contrast to vegetations, fibroelastomas

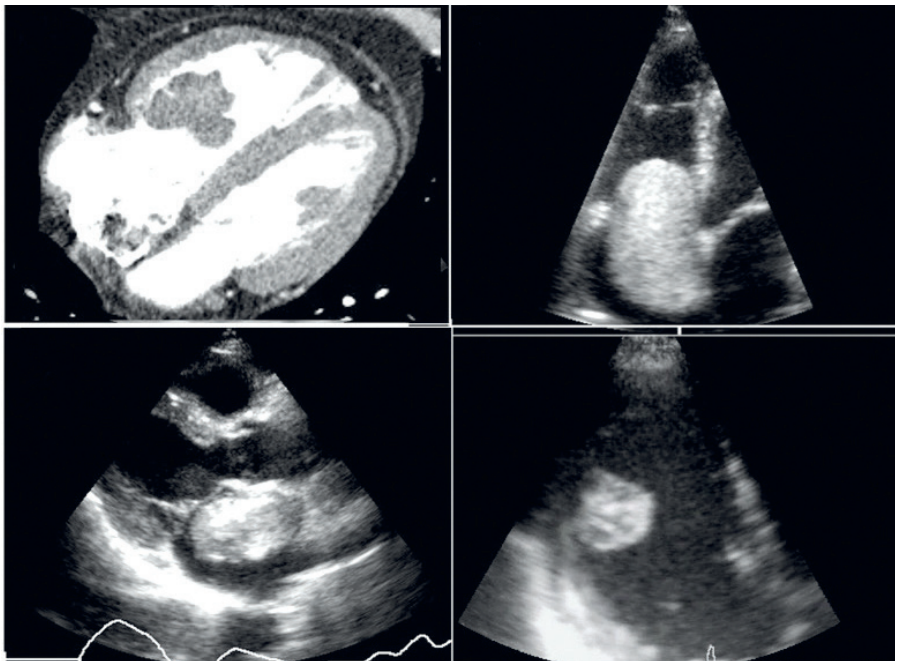

Figure 5. Changes in the topography and morphology of cardiac myxomas. **A.** A tumor with ragged "cluster-of-grapes" appearance in the inflow portion of the right ventricle, partially connected to the subvalvular apparatus of the tricuspid valve (contrast-enhanced CT). **B.** A large cylindrical pedunculated tumor narrowing the orifice of the tricuspid valve. **C.** Left atrial tumor limiting mitral leaflet mobility. **D.** Pedunculated lobular tumor in the left atrial appendage

are found on the ventricular side of the mitral valve or the aortic side of the aortic valve. Fibroelastomas usually do not cause valvular dysfunction, but patients may present with neurological complications following left-sided peripheral embolism. Due to its small size, characteristic "sea anemone" appearance, and free movement on the pedicle, papillary fibroelastomas are not easily identified on transthoracic and transesophageal echocardiography. If the results are inconclusive, CT and magnetic resonance imaging should be used as additional diagnostic tests.

Surgical treatment of papillary fibroelastoma is recommended for tumors greater than 1 cm in diameter and found on the left-sided valves in patients at low surgical risk or during cardiac surgery for other indications. Tumors on the tricuspid and pulmonary valves are usually treated conservatively unless they block the orifice or pose a risk of paradoxical embolism (leaky heart valve). If the patient is ineligible for surgical treatment, antiplatelet therapy should be considered [63].

Myxoma is the most common mild cardiac tumor (about 30% of all mild primary cardiac tumors). Although myxoma does not directly involve the valve structures, it may lead to atrioventricular valve dysfunction when located in the atria. This most often leads to functional stenosis with all the hemodynamic sequelae of mitral and tricuspid stenosis. Myxoma usually occurs as a single tumor. In 75% of cases, it is found in the left atrium; in 15%, in the right atrium; and in 5%, in the left and right ventricles (Figure 6 [64]). Multiple sites are rare. The characteristic feature of myxoma is its connection with one is correct the interatrial septum via a mobile pedicle. The tumor surface is usually regular and smooth but often has a rugged "cluster-of-grapes" appearance with a tendency for fragmentation and the risk of embolism. There are two types of myxoma: sporadic and familial (about 5%–10% of cases). Compared with sporadic tumors, familial myxomas more often have multiple foci, are more often found in the ventricles, and have higher recurrence rates. Familial myxomas may be associated with Carney syndrome that encompasses multiple myxomas in the heart and other locations, endocrine disorders, skin pigmentation, thyroid cancer, and Sertoli cell tumors of the testis. In most cases, an initial diagnosis of myxoma and its hemodynamic consequences can be made by transthoracic and transesophageal echocardiography. The tumor location in the right heart may necessitate additional CT, especially if peripheral embolism is the dominant clinical symptom. In each case of a suspected cardiac myxoma, surgical resection should be performed. The final diagnosis is made on the basis of histopathological findings. Considering high recurrence rates, patients after surgical resection should be followed with regular echocardiographic assessment.

ANTICOAGULATION IN PATIENTS WITH CANCER AND VALVULAR HEART DISEASE

The incidence of VHD, particularly degenerative valve disease, increases with age. Also, cancer is more prevalent among elderly patients and is associated with a worse prognosis. The management of patients with cancer and VHD constitutes a considerable challenge. Evidence-based guidelines that could facilitate therapeutic decision-making are lacking. Patients with cancer who also have VHD, AF, and a history of heart valve interventions require long-term or short-term anticoagulant and antiplatelet treatment.

There is limited evidence on anticoagulation in patients with cancer. Known factors to be considered in anticoagulation decisions in this population include the use of non-vitamin K antagonist oral anticoagulants (NOACs);

thrombocytopenia, which is common in cancer patients and increases bleeding risk; drug-drug interactions; intracerebral and liver metastases; low protein levels; eating disorders caused by nausea, vomiting, and anorexia; and interruptions of medical therapy due to invasive procedures [65].

Atrial fibrillation is common in patients with VHD, and it can also be induced by cancer drugs. Research shows that the CHA2DS2-VASc score, a standard tool for predicting the risk of thromboembolism in patients with AF, provides different results for patients with cancer versus those without. Therefore, the CHA2DS2-VASc score should be used with caution, and treatment should be individualized and take bleeding risk into consideration [66]. In patients with AF and moderate or severe MS, as well as in those with mechanical prosthetic valves, anticoagulation with vitamin K antagonists (VKAs) guided by the international normalized ratio (INR) is indicated. In the remaining patients with AF, the few available studies confirm the safety of anticoagulation with NOACs. NOACs are preferable to VKAs or heparins in patients with newly diagnosed AF who receive chemotherapy, except for patients with gastrointestinal cancer and noninvasively treated primary tumors or active gastrointestinal mucosal lesions [67]. In emergencies, such as a time-sensitive surgery or life-threatening bleeding, anticoagulation treatment should be discontinued immediately. The effects of dabigatran can be reversed with a specific reversal agent – idarucizumab. Andexanet alfa, a reversal agent for all direct factor Xa inhibitors and selected indirect factor Xa inhibitors (unfractionated heparin, low-molecular-weight heparin [LMWH], and fondaparinux) is currently unavailable in Poland. In patients receiving rivaroxaban and apixaban, fresh frozen plasma or prothrombin complex concentrate can be used. In patients on VKAs, vitamin K, fresh frozen plasma, or prothrombin complex concentrate are used.

In patients with low platelet count (25–50 × 109/l), half-dose LMWH can be used, and platelet transfusion can be considered. In patients with platelet count <25 × 109/l, individualized treatment is indicated.

The number of patients with prosthetic heart valves and concomitant cancer has been increasing. Anticoagulation in these patients differs depending on the type and location of the valve. The most recent 2021 ESC/EACTS guidelines on the management of VHD recommend lifelong anticoagulation with VKAs guided by the INR in patients with mechanical prostheses. During the perioperative period, bridging with unfractionated heparin or LMWH can be used. There is evidence on the use of a therapeutic dose of LMWH as bridging therapy in patients with increased thrombocytopenia or thrombocytosis or increased bleeding risk. However, the safety of this strategy was not confirmed in randomized controlled trials [68]. The ESC/EACTS guidelines recommend strict anti-factor Xa monitoring to ensure optimal LMWH dosing, which may help balance the risks against the benefits in patients with cancer. Anticoagulation with NOACs is not recommended in patients with mechanical prostheses.

Bioprosthetic valves do not require long-term anticoagulation, irrespective of the position. Current guidelines recommend VKAs during the first 3 months in all patients with bioprosthetic mitral or tricuspid valves. In patients after bioprosthetic aortic valve surgery, acetylsalicylic acid (75–100 mg/d) or a VKA in the first 3 months should be considered. After 3 months, NOACs, rather than VKAs, are indicated in patients with AF and surgical bioprosthesis.

Patients with cancer have a higher thrombotic and bleeding risk. Therefore, decisions on interventions requiring anticoagulant or antiplatelet treatment may be quite challenging. Factors to be considered in a multidisciplinary team discussion include the hemodynamic status of the patient as well as the type and stage of cancer. If recommendations on management are lacking, an individualized approach is warranted. TAVI is a common procedure in patients with AS and cancer. Lifelong single antiplatelet therapy is recommended in patients after TAVI without indications for oral anticoagulation. Immunosuppressive therapy was not associated with a higher rate of vascular access complications or CV events in patients during a short-term (median, 567 days) and long-term (6 months to 5 years) follow-up [69, 70].

All patients with cancer requiring anticoagulant or antiplatelet treatment should undergo regular assessment for thromboembolic and bleeding risk, which may change over time.

Anticoagulant and antiplatelet treatment — summary

1. There is limited evidence on anticoagulation in patients with cancer. Known factors to be considered in anticoagulation decisions in this population include the use of direct oral anticoagulants; thrombocytopenia, which is common in cancer patients and increases bleeding risk; drug-drug interactions; and intracerebral and liver metastases.
2. In patients with low platelet count (25–50 × 10^9/l), half-dose LMWH can be used, and platelet transfusion can be considered. In patients with platelet count <25 × 10^9/l, individualized treatment is indicated.
3. Lifelong single antiplatelet therapy is recommended in patients after TAVI without indications for oral anticoagulation. In the presence of indications for oral anticoagulation, anticoagulant monotherapy is recommended, except for patients with coronary stent implantation <3 months before TAVI. In such cases, a combination of anticoagulant and antiplatelet treatment is recommended.
4. Patients with mechanical prosthetic valves should receive lifelong anticoagulation with VKAs guided by INR monitoring.

Article information

Conflict of interest: None declared.

Funding: None.

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