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Multi-Modality Imaging to Detect Ischemic and Valvular Heart Disease in Adult Cancer Patients

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Received: 2 October 2024 | **Revised:** 21 October 2024 | **Accepted:** 27 October 2024

Keywords: cancer survivors | cancer therapy-related cardiovascular toxicity | computed tomography coronary angiography | coronary functional imaging | ischemic heart disease | multidisciplinary decision-making | valvular heart disease

ABSTRACT

Thanks to impressive advances in the field of oncology over the last 30 years, there has been a significant rise in cancer survivors. Nowadays, cardiovascular disease is one of the leading causes of death in this patient population. Coronary artery disease (CAD) is a major problem due to shared risk factors, an aging population and in many cases induced and/or accelerated atherosclerosis by antitumoral treatment during and even decades after the end of cancer therapy. Furthermore, the presence of CAD or valvular heart disease (VHD) at the time point of cancer diagnosis largely increases the risk of any cancer therapy-related cardiovascular toxicity (CTR-CVT). It is therefore of utmost importance to detect CAD and VHD before, during, and after certain types of chemotherapy, target therapies, and radiotherapy. Multimodality cardiovascular imaging plays a central role in this vulnerable population where individual risk stratification and multidisciplinary decision-making are critical.

1 | Introduction

Over the past three decades, we have seen remarkable progress in anticancer treatment and as a direct consequence an impressive increase of cancer survivors [1]. However, many of the conventional chemotherapeutic agents as well as the more recent targeted molecular therapies come with organ toxicity, including cardiovascular toxicity. In fact, cardiovascular disease (CVD) is among the leading underlying etiologies in this population; ischemic heart disease (IHD) being one of the main reasons [2]. Multiple mechanisms leading to myocardial ischemia have been described in cancer patients and include direct toxicity affecting coronary arteries, as well as an accelerated process of atherosclerosis, and an increasing burden of classical cardiovascular risk factors (CVRF). Indeed, cancer patients are particularly at risk for atherosclerosis due to common pathogenesis (including systemic inflammation), shared risk factors (tobacco and alcohol consumption), aging and (treatment-induced) arterial hypertension (HTN), diabetes, and hypercholesterolemia.

It is the aim of the rapidly growing field of cardio-oncology to enable optimal cancer therapy for each patient while mitigating the deleterious short- and long-term effects on the CV system. Whereas European society of cardiology (ESC) guidelines for

Abbreviations: 5-FU, 5-fluorouracil; ACS, acute coronary syndrome; CAC, coronary artery calcification; CACs, coronary artery calcium scoring; CAD, coronary artery disease; CMR, cardiac magnetic resonance; CTCA, computed tomography coronary angiography; CTRCD, cancer therapy-related cardiac dysfunction; CTR-CVT, cancer therapy-related cardiovascular toxicity; CVD, cardiovascular disease; CVRF, cardiovascular risk factors; ECG, electrocardiography; ESC, European society of cardiology; GP, general practitioner; Gy, gray; HL, Hodgkin lymphoma; HSCT, hematopoietic stem cell transplantation; HTN, hypertension; ICI, immune checkpoint inhibitor; LAD, left anterior descending artery; LCX, left circumflex artery; LGE, late gadolinium enhancement; MACE, major cardiovascular event; PET, positron emission tomography; RCA, right coronary artery; RT, radiotherapy; TTE, transthoracic echocardiography; VHD, valvular heart disease.

cardio-oncology published in 2022 [3] give structured recommendations about echocardiographic follow-up in patients at risk of cancer treatment-related cardiac dysfunction (CTRCD), the detection of coronary artery disease (CAD) and myocardial ischemia in this population has not been well standardized. The European guidelines on acute coronary syndrome (ACS) [4] recommend treating cancer patients indifferently from the general population highlighting the importance of multidisciplinary discussion considering fragility, bleeding risk, and overall prognosis. In the very recent ESC guidelines on chronic coronary syndrome, multimodality cardiac imaging plays a central role in the diagnostic process but there are no specific recommendations for cancer patients [5].

This article aims to offer a review of oncologic treatments related to IHD and VHD, to discuss the type and timing of cardiac imaging through clinical cases as well as the challenges of diagnostic multimodal imaging pathways in this population.

2 | Approach to Ischemic and Valvular Heart Disease Before Antitumoral Treatment

The aim of cardio-oncology is to optimize the individual risk profile and decrease the risk of cancer therapy-related cardiovascular toxicity (CTR-CVT) before, during, and after cancer therapy. Individual risk stratification before starting anticancer treatment plays a very important role in cardio-oncology since patients with concomitant CVD or CVRF at baseline are particularly prone to suffer from cardiotoxicity.

CTRCD being the most frequent toxicity, echocardiography is the pillar of cardio-oncologic follow-up in patients at risk. Recommendations on CTRCD prevention, detection, and treatment (mostly due to anthracycline and anti-HER2 therapies) are increasingly implemented, owing to the ESC Guidelines for Cardio-oncology published in 2022 [3]. Transthoracic echocardiography (TTE) at baseline further allows identification of preexisting VHD which is also important since severe valvular pathology increases the risk of CTRCD. Decision on indication, timing, and type of valve intervention (surgical vs. percutaneous) in patients requiring oncologic treatment always implies a multidisciplinary discussion. Treatment of severe VHD such as artic stenosis might sometimes be mandatory for patients to have access to high-risk tumor surgery, especially if the oncological treatment has a curative intent [6, 7].

On the other hand, evidence-based recommendations are scarce concerning screening for CAD in cancer patients. Observational studies clearly show an association between baseline CVRF and/or CAD with coronary events during antitumoral treatment, particularly for certain agents (Table 1). Therefore, it seems beneficial to intensively manage CVRF and actively screen for CAD in symptomatic patients as well as in high-risk asymptomatic individuals aiming to decrease cancer-treatment-related coronary events which could cause the interruption of lifesaving antitumoral therapy. It should be highlighted that screening for CAD does not primarily aim to identify targets for coronary revascularization but rather to detect subclinical atherosclerotic disease that could be targeted by aggressive risk factor management and medical anti-ischemic treatment.

A very recent study on more than 2000 Austrian patients with newly diagnosed cancer showed a hazard ratio of 4.3 for 2-year MACE risk in the presence of CAD at baseline [8]. Proposed scores for pre-test probability of chronic coronary syndrome tend to underestimate the risk in the oncologic population and the imaging threshold should be low. Every patient planning to receive an agent at risk of inducing coronary events (Table 1) should therefore be screened for CVRF, anginal symptoms, and signs of atherosclerotic disease. A chest computed tomography (CT) scan is often available as it is frequently performed for tumor staging and should be checked for atherosclerotic burden through coronary calcium scoring (CACs) which helps to stratify the risk and can be easily done retrospectively. Further testing should be discussed in a multidisciplinary team and should take into account the patient's preference.

Even though many recommendations in cardio-oncology are based on experts' consensus, some evidence exists for the utility of CT coronary angiography (CTCA) and CACs in patients planned for radiotherapy (RT) as it allows for the identification of CAD and has prognostic utility in identifying subjects at increased risk for all-cause death. Since coronary artery calcification (CAC) appears during the development of CAD, non-contrast CT allows for its detection and quantification. A calcific lesion is defined by a CT density of 130 Hounsfield units having an area $\geq$ 1 mm. CAC can be quantified by Agatston score, with a result of 0 meaning absence of CAD, 1–10 minimal evidence of CAD, 11–100 mild evidence of CAD, 101–400 moderate evidence of CAD, and >400 extensive CAD. CAC assessment on non-gated chest CT has been shown to correlate well with gated CT-studies and cardiovascular outcomes in the general population [9]. Moreover, the early recognition of increased atherosclerotic disease is important because lipid-lowering medications such as statins are generally underused in cancer patients [10]. CTCA can be used to screen patients undergoing RT with a negative study being predictive of an extremely low-risk of cardiac death [11].

In the case of known CAD and/or symptomatic patients with intermediate to high pre-test probability for obstructive CAD further testing is usually done by functional imaging which evaluates myocardial ischemia. Depending on local expertise and patient's characteristics transthoracic stress echocardiography, perfusion cardiac magnetic resonance (CMR), or positron-emission tomography-CT (PET-CT) achieve similar diagnostic precision concerning prognostically significant myocardial ischemia. The choice of modality can therefore be tailored to the individual patient's characteristics and preferences (such as echogenicity, heart rhythm, renal function, claustrophobia).

Hence, before initiating diagnostic tests, one always needs to consider the consequences of potential findings and appreciate the patient's life expectancy. For instance, it is certainly not beneficial to revascularize a coronary stenosis of a minor coronary vessel or in chronic coronary syndrome in a patient planned for chemotherapy with a risk of severe thrombocytopenia or in a patient with metastatic cancer in palliative care. Multidisciplinary and pragmatic decisions based on precise quantification of the extent of ischemia, patient prognosis, and quality of life are of paramount importance in this case. Intensification and optimization of medical treatment should be the first step (and sometimes, the only one) after the detection of significant

TABLE 1 | Treatments increasing risk of coronary events and postulated mechanisms.

	Vasospasms	Accelerated atherosclerosis, plaque rupture	Coronary thrombosis
Conventional therapies			
Platinum based (cisplatin)			x
Alkylating agents (cyclophosphamide, ifosfamide)			x
Bleomycin	x		
Antimetabolites (5-fluorouracil, capecitabine, cytarabine)	x		x
Taxanes (paclitaxel, docetaxel)			x
Vinca alkaloids (vinblastine, vincristine, vinorelbine)	x		
Immunomodulatory drugs (lenalidomie, thalidomide)			x
Targeted molecular therapies			
VEGF antibodies (bevacizumab)			x
VEGF TK inhibitors (sunitinib, pazopanib, sorafenib)	x	x	x
HER-1 inhibitor (erlotinib)			x
BCR-ABL TK inhibitors (nilotinib, ponatinib)		x	x
Anti-CD20 monoclonal Antibodies (rituximab, obinutuzumab)			x
Immune check-point inhibitors (PD-1 inhibitors: pembrolizumab, nivolumab, PDL-1i: atezolizumab, durvalumab, CTLA-4i: ipilimumab)		x	x
Other therapies			
Androgen deprivation therapy (leuprolide, goserelin, flutamide, abiraterone)		x	
Aromatase inhibitors (anastrozole, letrozole, exemestane)		(x)	
Chimeric antigen receptor T cell therapy		(x)	
Hematopoietic stem cell transplantation		(x)	
Radiation		x	
Steroids		x	

ischemia in symptomatic patients. Recent studies have underscored the importance of medical management in the presence of significant CAD as an alternative to coronary intervention [12].

Table 1 gives a summary of specific antitumoral therapies at risk of inducing IHD and the mechanisms that are postulated based on existing evidence. Proposed screening and imaging modalities at baseline, during, and after the end of cancer treatment are summarized in Table 2.

Figures 1–3 present three real-world cases that illustrate typical situations encountered in our practice before the start of antitumoral treatment at risk.

3 | Management of Acute Coronary Events During Antitumoral Treatment

Several antitumoral agents are known to cause acute coronary events during the treatment phase by different mechanisms including arterial thrombosis, vasospasms, endothelial dysfunction, or rapidly progressive atherosclerosis due to cancer-induced hypercoagulable state. According to the European Guidelines on ACS, approach in cancer patients presenting with chest pain should not differ from the general population, except for favoring conservative strategies in patients with poor overall prognosis (<6 months). Non-invasive multimodality imaging by TTE, CCTA, and/or functional stress imaging is recommended in patients with chest pain and intermediate risk of CAD by European and American practice guidelines. In general, a non-invasive anatomical study with or without functional testing should be favored in clinical scenarios where chest pain is atypical, ECG abnormalities are inconclusive, and troponin increase is mild [4, 13].

The assessment and diagnosis of ACS in cancer patients is often particularly difficult due to the lack of typical symptoms. This is frequent with only 30% of patients presenting with chest pain and 44% with dyspnea [14]. In addition, work-up is complicated by anemia, thrombocytopenia, and coagulation disorders that come with a higher risk of complications during invasive coronary exploration. Therefore, in case of diagnostic uncertainty or very high bleeding risk, an ECG-gated cardiac CT can be utilized as a triple rule-out strategy [15] in acute settings. In case of asymptomatic troponin rise or ECG changes a coronary calcium

55-year-old man with gastric cancer, planned for treatment with 5-FU. Known for a sedentary lifestyle with dyspnea NYHA II; history of type 2 MI due to arterial hypertension and severe anemia 6 months ago without further work-up. BP 150/89 mmHg. ECG showed sinus rhythm with inverted T-waves, normal TTE, troponin level T hs 10 ng/ml, LDL-cholesterol level 4,2mmol/l. Panels A-M illustrate semi-automated calculation of coronary artery calcification on unenhanced chest CT : 143 Agatston units (percentile rank 84 for age/gender; moderate risk of MACE with a relative risk ratio of 4.3) Perfusion CMR : no stress induced ischemia (Panels N-Q), absence of scar/macroscopic fibrosis (Panel R). The patient was treated by intensive risk factor management including statins and preventive calcium channel blockers with good tolerance of 5-FU therapy.

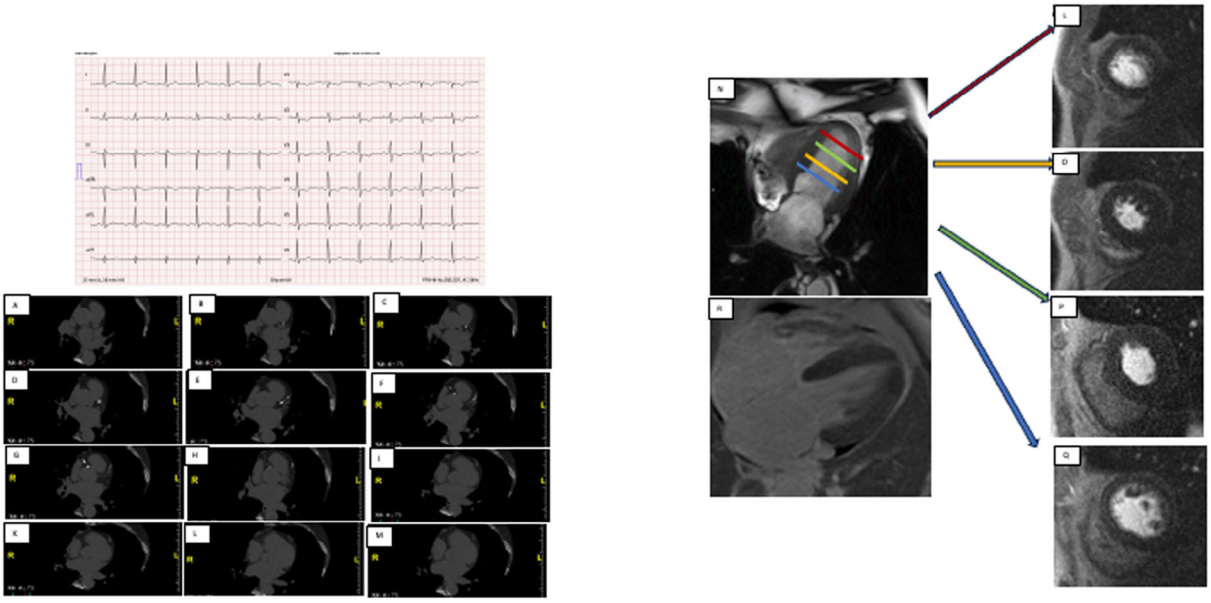

FIGURE 1 | Case 1. 55-year-old man with gastric cancer, planned for treatment with 5-fluorouracil (5-FU). Known for a sedentary lifestyle with dyspnea NYHA II; history of type 2 MI due to arterial hypertension and severe anemia 6 months ago without further work-up.

65-year-old woman with ovarian cancer diagnosed 6 months ago, known for HTN, obesity, cancer progression under cisplatin, planned for second-line bevacizumab, chest tightness during exertion. TA during examination 165/95mmHg, LDL-cholesterol 3.6mmol/l.
Baseline tests: normal ECG and troponins, mildly elevated nt-proBNP, TTE revealed LV-remodeling, diastolic dysfunction with high filling pressures. (Panels A-D). CCTA with calcified <50% LAD stenosis (Panel E). CMR showed absence of stress-induced ischemia, no late Gadolinium enhancement, mildly elevated ECV (32%) due to diffuse interstitial fibrosis probably due to HTN. The patient was treated by intensive risk factor management including statins and combined HT treatment by ACE-inhibitors and calcium-channel blocker.

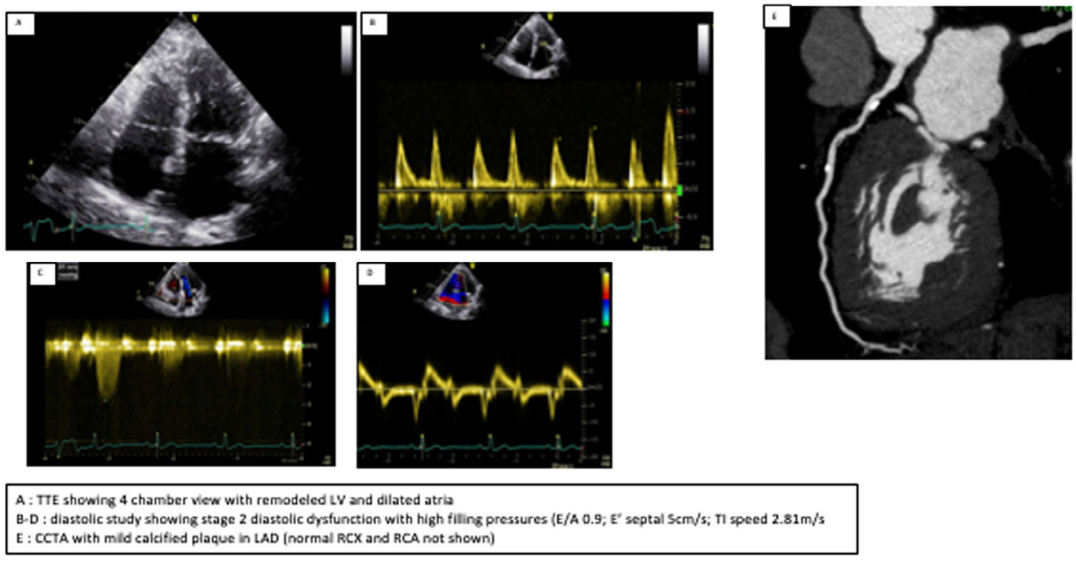

FIGURE 2 | Case 2. 65-year-old woman with ovarian cancer diagnosed 6 months ago, known for hypertension (HTN), obesity, cancer progression under cisplatin, planned for second-line bevacizumab, chest tightness during exertion.

TABLE 2 | Suggested screening and imaging modality at baseline, during, and after end of cancer treatment.

	Before start of treatment	During and after cancer treatment
Conventional therapies		
Platinum based (cisplatin)		
Alkylating agents (cyclophosphamide, ifosfamide)		
Bleomycin		
Antimetabolites (5-fluorouracil, capecitabine, cytarabine)	TTE if CVD, CTCA and/or FT if high risk	Regular CVRF screening
Taxanes (paclitaxel, docetaxel)		
Vinca alkaloids (vinblastine, vincristine, vinorelbine)		
Immunomodulatory drugs (lenalidomie, thalidomide)		
Targeted molecular therapies		
VEGF antibodies (bevacizumab)	TTE	
VEGF TK inhibitors (sunitinib, pazopanib)	TTE	
HER-1 inhibitor (erlotinib)		
BCR-ABL TK inhibitors (nilotinib, ponatinib)	TTE	
Anti-CD20 monoclonal antibodies (rituximab, obinutuzumab)		
Immune check-point inhibitors (PD-1 inhibitors: pembrolizumab, nivolumab, PDL-1i: atezolizumab, durvalumab, CTLA-4i: ipilimumab)	TTE if known CVD or if combined treatment	
Other therapies		
Androgen deprivation therapy (leuprolide, goserelin, flutamide, abiraterone)		Active CVRF screening every 6 months
Aromatase inhibitors (anastrozole, letrozole, exemestane)		
Chimeric antigen receptor T cell therapy	TTE (+ stress if high risk)	
Hematopoietic stem cell transplantation	TTE (+ stress if high risk)	
Radiation	CACs or CTCA if chest CT done	TTE + CTCA ± FT starting at 5 years
Steroids		

Abbreviations: CACs, coronary artery calcium score; CTCA, coronary CT angiography; CVRF, cardiovascular risk factors; FT, Functional testing: (according to local expertise: stress echocardiography, CMR, or PET-CT); TTE, transthoracic echocardiography.

score (CAC) of zero confers a high negative predictive value for obstructive epicardial CAD [16].

During or after several days of treatment with fluoropyrimidines (5-FU, capecitabine) chest pain is the most common symptom with an incidence reported between 2% and 9% [17, 18]. Symptoms are mostly transitory and self-amending and involve significant ECG changes in two-thirds of patients while troponin changes occur in around half of the cases. The most described mechanism of fluoropyrimidine-induced myocardial ischemia is coronary spasm concerning patients with and without underlying CAD. Still, preexistent CAD and prior mediastinal RT are clear risk factors for serious cardiac events [19]; therefore, cardiac imaging helps to adopt an individualized preventive strategy. A combination of TTE to detect wall motion abnormalities and CAC score on a recent chest CT if available, or CTCA, should be part of the diagnostic work-up. If these results are pathologic, then further testing by functional stress imaging identifies patients at high-risk who could benefit from an invasive coronary angiogram (ICA). In the absence of obstructive CAD, antimetabolites might be continued, depending on the individual's risk and awaited benefit of the therapy. Preventive anti-ischemic therapy, such as calcium-channel blockers and/or nitrates with an adapted treatment dosing and schedule [18] are suggested even though consistent evidence for its benefit is lacking.

Myocardial ischemia and infarction have been reported in rare cases within 2 weeks of administration of paclitaxel in patients with HTN and CAD [20].

VEGF-inhibition has become a widely used treatment of various cancers with the most frequent class-associated side effect being HTN. Serious arterial thrombotic events including myocardial infarction are significantly increased (up to 5%) in patients treated with such molecules, especially bevacizumab, sunitinib, and sorafenib [21–23]. One observation single-center study even showed symptomatic cardiac events in 18% of patients, mostly without any underlying CAD but responding well to prophylactic

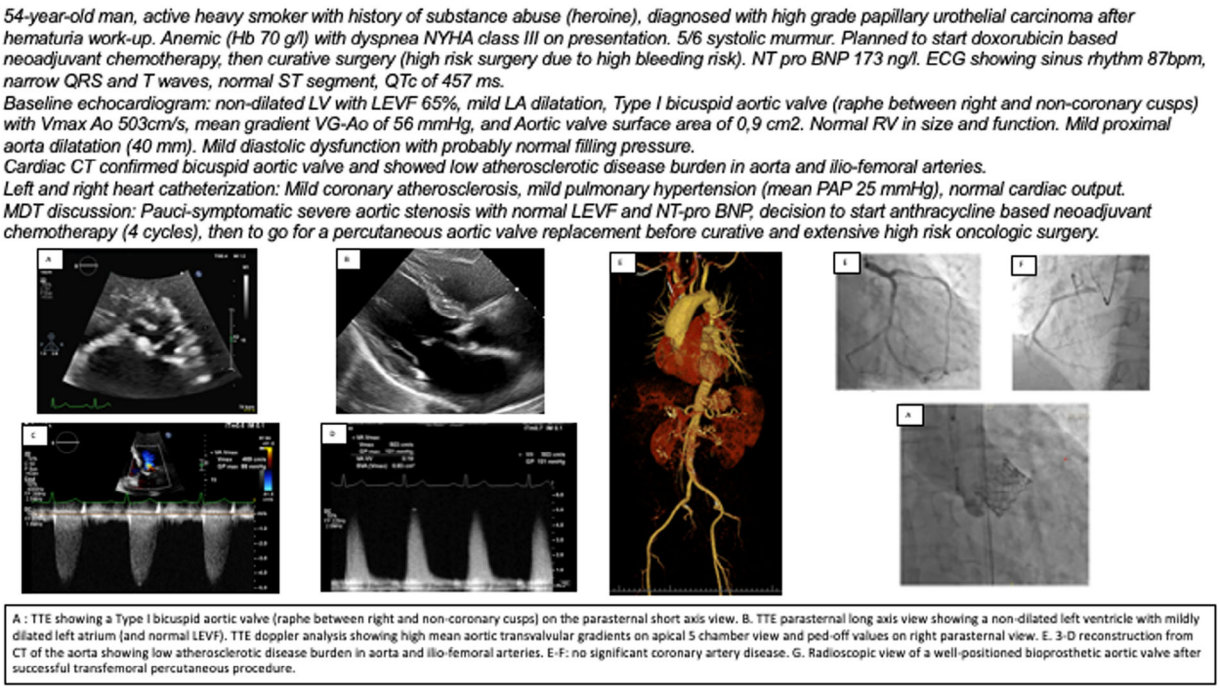

FIGURE 3 | Case 3. 54-year-old man, active heavy smoker with history of substance abuse (heroine), diagnosed with high grade papillary urothelial carcinoma after hematuria work-up.

treatment (beta-blockers) when rechallenged [23]. Some other molecular targeted therapies as erlotinib, nilotinib, and ponatinib increase the risk of coronary events during therapy [24]. Pretreatment TTE and risk-factor evaluation is therefore recommended [3] with a special attention to HTN and anginal symptoms. In symptomatic patients anatomical and/or functional imaging needs to be considered.

Several small and one large single-center studies have shown an association of immune checkpoint-inhibitor (ICI) therapy with myocardial infarction (HR 7.2) and coronary revascularization (HR 3.3) over a 2-year follow-up period [25]. On the other hand, ICI therapy is particularly feared for its risk of myocarditis [26], and has also been shown to induce takotsubo syndrome and non-inflammatory CTRCD [27]. Since clinical presentation tends to be similar in all these cases, CMR is extremely useful in the diagnostic pathway for its potential of tissue characterization. Application of revised Lake Louise Criteria, including late Gadolinium enhancement (LGE) combined with parametric T1- and T2-mapping has shown to be of excellent diagnostic and prognostic value in diagnosing ICI-related myocarditis in a retrospective single-center study [28].

In case of new left ventricular dysfunction detected during echocardiographic follow-up in patients under anthracyclines or anti-HER2 therapies IHD needs to be excluded which can also be done by CMR.

De novo VHD as a direct consequence of cancer therapy is rarely encountered. New onset VHD detected during cancer treatment is mostly due to endocarditis, which can affect any valve. Endocarditis during cancer therapy should be managed according to the specific ESC guidelines on endocarditis [29], with special considerations discussed by a multidisciplinary team around immunosuppressive status, and a higher threshold for surgical intervention in the setting of advanced cancer with poor prognosis. Secondary or functional VHD is more often encountered due to dilated cardiomyopathy of any origin including toxic etiologies. This mainly involves mitral or tricuspid regurgitation. Management usually involves correction of the triggers such as tachyarrhythmias, and medical management of the underlying cardiomyopathy, and rarely percutaneous valvular interventions (edge-to-edge techniques).

We developed an algorithm for the management of patients with acute chest pain during cancer treatment (Figure 4) based on the AHA/ACC Clinical Practice Guideline on Management of acute chest pain 2021 [13] and current European recommendations on ACS and cardio-oncology [3, 4].

Figures 5 and 6 illustrate two real-world case presentations that illustrate patients presenting chest pain during antitumoral treatment at risk.

4 | Surveillance of Ischemic and VHD in Long-Term Cancer Survivors

Due to the dynamic nature of CTR-CVT, the 2022 ESC guidelines on cardio-oncology [3] recommend risk reassessment during the first year following the end of cancer therapy in patients with good long-term prognosis. The aim is to identify high-risk individuals and to determine a personalized long-term cardiac surveillance plan. This task is made difficult due to the heterogenous list of long-term cardiac affections which depend on the type of cancer therapy and preexisting cardiovascular comorbidities. These entities include CTRCD, arrhytmias, pericardial

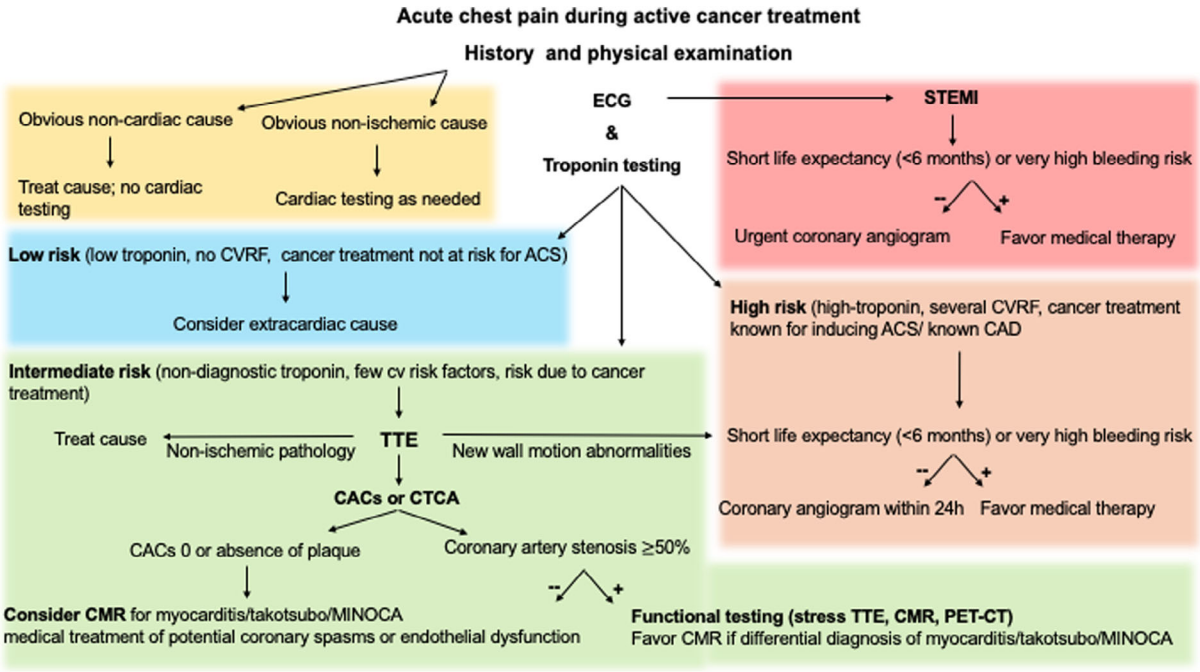

FIGURE 4 | Proposed algorithm in case of acute chest pain during cancer therapy (adapted from AHA/ACC Clinical Practice Guideline on Management of acute chest pain 2021 [13].

80-year-old woman with mesothelioma under double ICI treatment (ipilimumab/nivolumab), admitted for chest pain with troponin rise, and subtle ECG changes. TTE showed mildly reduced EF with apical ballooning and hyperdynamic basal segments (Panels A-C), and moderate aortic stenosis. CCTA showed absence of coronary plaque in LAD (Panel D), LCX (Panel E), RCA (Panel F), mild aortic valve calcification (E-F). CMR 1 month later showed normal wall motion and LVEF, absence of edema (normal T2-mapping Panel I) and absence of myocardial scar (Panel G-H) confirming takotsubo syndrome. Initially patient was admitted for rhythm surveillance with interruption of ICI for 1 month until normalized CMR, followed by further ICI treatment with preventive tocilizumab which was well supported without further events.

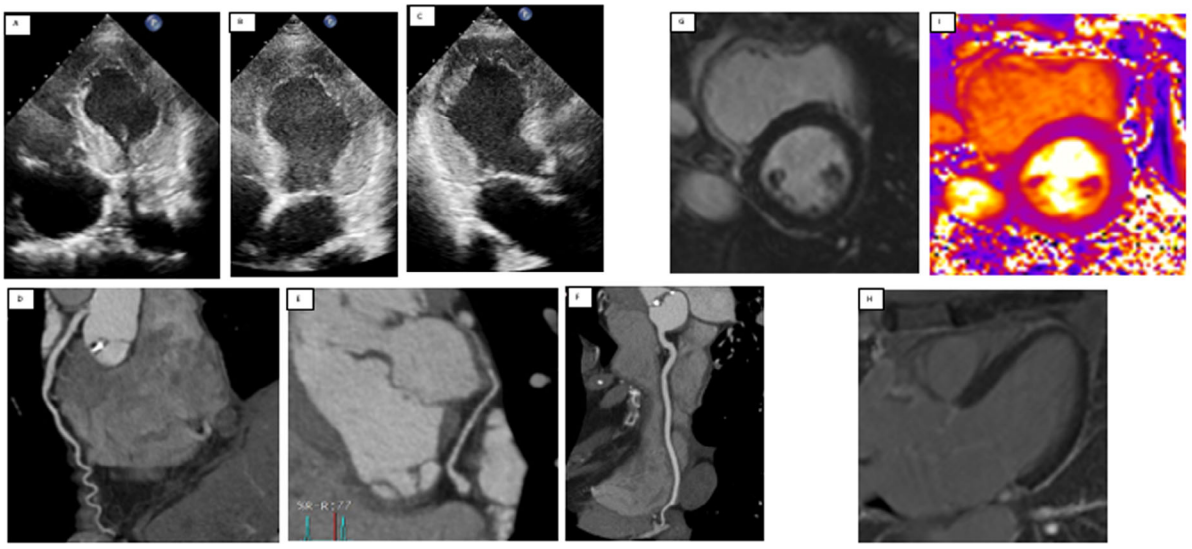

FIGURE 5 | Case 4. 80-year-old woman with mesothelioma under double ICI treatment (ipilimumab/nivolumab), admitted for chest pain with troponin rise, and subtle ECG changes. ECG, electrocardiography; ICI, immune checkpoint inhibitor.

diseases, IHD, VHD, and can co-exist. Patients presenting a high or very high cardiovascular risk when starting antineoplastic treatment, or who undergo treatment with high dose anthracyclines, total mean heart radiation, or hematopoietic stem cell transplantation, or who experience moderate or severe CTR-CVT during cancer treatment are at high-risk of long-term CTR-CVT.

Long-term cancer survivors who experience new or worsening symptoms suggestive of myocardial ischemia or new onset heart failure/cardiac dysfunction should be assessed for CAD as per the specific guidelines on chronic coronary syndrome [5]. Functional imaging assessment using CMR, PET/CT, coronary CT, or stress echocardiography depends on the pre-test probability as well as on local expertise and availability of these imaging tools.

45-year-old woman with CVRF with relapsing renal cell carcinoma treated by sunitinib for 4 weeks when admitted to ER with acute chest pain and blood pressure 200/100mmHg. ECG showed sinus rhythm with ST-depression from V4-V6 and elevated troponins T hs 0 and 1 hour 45-58ng/ml. Angio-CT excluded aortic dissection and pulmonary embolism and TTE revealed normal LVEF (suboptimal echogenicity). Functional imaging by Rb-82 PET/CT was chosen because of claustrophobia. Semi-quantitative analysis of myocardial perfusion showed no perfusion deficit (Panel A). ECG-gated acquisition confirmed normal LVEF at peak stress and rest, with a physiologic LVEF increase between stress and rest (panel B). Dedicated non-contrast CT acquisition for calcium scoring showed no calcification (C). Quantitative analysis of the myocardial perfusion with normal global and regional myocardial perfusion at stress and rest, as well as normal myocardial perfusion reserve and normal coronary flow capacity (D). Antihypertensive treatment was rapidly titrated allowing for sunitinib to be continued.

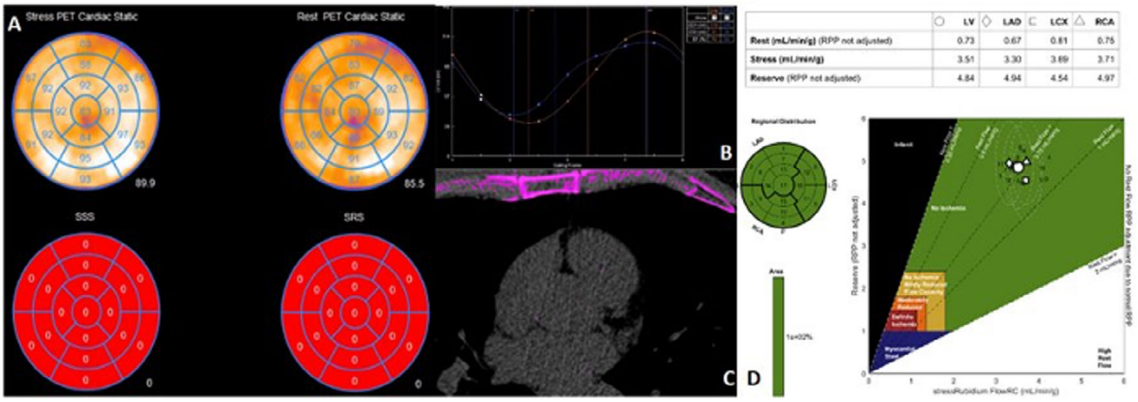

FIGURE 6 | Case 5. 45-year-old woman with cardiovascular risk factors (CVRF) with relapsing renal cell carcinoma treated by sunitinib for 4 weeks when admitted to ER with acute chest pain and blood pressure 200/100 mm Hg.

Exposure to high mean heart radiation doses (>15 Gy) as well as exposure to specific cancer therapies associated with accelerated atherosclerosis and/or vascular toxicity (Table 1) should be considered when assessing pre-test probability of CAD. CCTA is particularly valuable in patients with low- to intermediate pre-test probability of CAD due to its very high negative predictive value [30]. In addition, the combination of a normal left atrial volume index and global longitudinal strain on a resting echocardiogram also has a good negative predictive value for the exclusion of significant CAD and may be considered in low pre-test probability settings as an alternative to CCTA [31].

In long-term-cancer survivors, who are evaluated to be at high or very-high risk cardiovascular risk at baseline, echocardiography-based surveillance to detect CTRCD and IHD should be considered and performed every 2 years during the first 5 years following the end of cancer treatment. There are no consensus guidelines or recommendations for systematic and generalized screening for CAD, although CCTA seems to be a promising tool in this setting [32]. Rather than focusing on cardiac imaging, clinicians must target lifestyle and behavioral factors associated with an increased cardiovascular risk and aggressively treat modifiable CVRF. Proactive ischemia testing should be considered in high or very high-risk patients, even in the absence of symptoms, every 5–10 years, starting from year 5 after exposure to high mean heart radiation dose (>15 Gy), especially in the setting of poorly controlled traditional CVRF. The choice of the imaging modality for ischemia testing in asymptomatic cancer survivors depends on patient characteristics such as claustrophobia and echogenicity, as well as local expertise and availability of the tests. Asymptomatic long-term cancer survivors with preexisting CAD should be assessed as per the ESC guidelines on chronic coronary syndromes [5].

Long-term cancer survivors include individuals living with chronic stable cancer with good long-term prognosis or in complete remission. This population of patients should be offered personalized annual CV risk stratification and long-term CV surveillance. Despite ongoing research in this setting, some cancer-targeted treatments used for long-term cancer control are known to potentially accelerate atherosclerosis. Such therapies include ICIs, and tyrosine kinase inhibitors such as ponatinib, nilotinib, as well as androgen deprivation therapy, aromatase inhibitors, and hematopoietic stem cell transplantation (HSCT).

Late-occurring valvular morphologic and functional abnormalities are well described with certain types of cancer therapies, mainly exposure to high mean heart radiation dose (>15 Gy). Calcification and fibrosis leading to dysfunction of the aortic and/or mitral valves typically occurs 10 years after exposure to radiation and increases progressively with hazard ratios of 2.7 for IHD and even 6.6 for VHD according to a retrospective Dutch study on >2500 HL patients [33]. Highest relative risks were in patients treated before the age of 25 years and in the elderly. Another recent analysis of 274 lymphoma survivors treated with anthracycline containing chemotherapy and HSCT found a significant association between valvular degeneration and cancer treatment [34]. These valvular abnormalities are readily assessed through regular echocardiography performed in high and very high-risk cancer survivors. The threshold for percutaneous or surgical valvular interventions depends on the severity of the valvular dysfunction and symptoms, as per specific 2021 ESC guidelines on VHD [35]. Particular attention needs to be paid in these cases on the aspect of the thoracic aorta which is diffusely diseased and fragilized in many cases ("porcelain aorta"). A CT scan of the aortic valve and aorta are useful in the pre-operative assessment followed by multidisciplinary valve-board discussion. In long-term cancer survivors, a careful assessment of VHD severity and its link to symptoms is required due to the co-existence of radiation-induced CAD, pericardial disease, and CTRCD. Cardiac catheterization to assess hemodynamics, and CMR or CT assessment of pericardial involvement are useful.

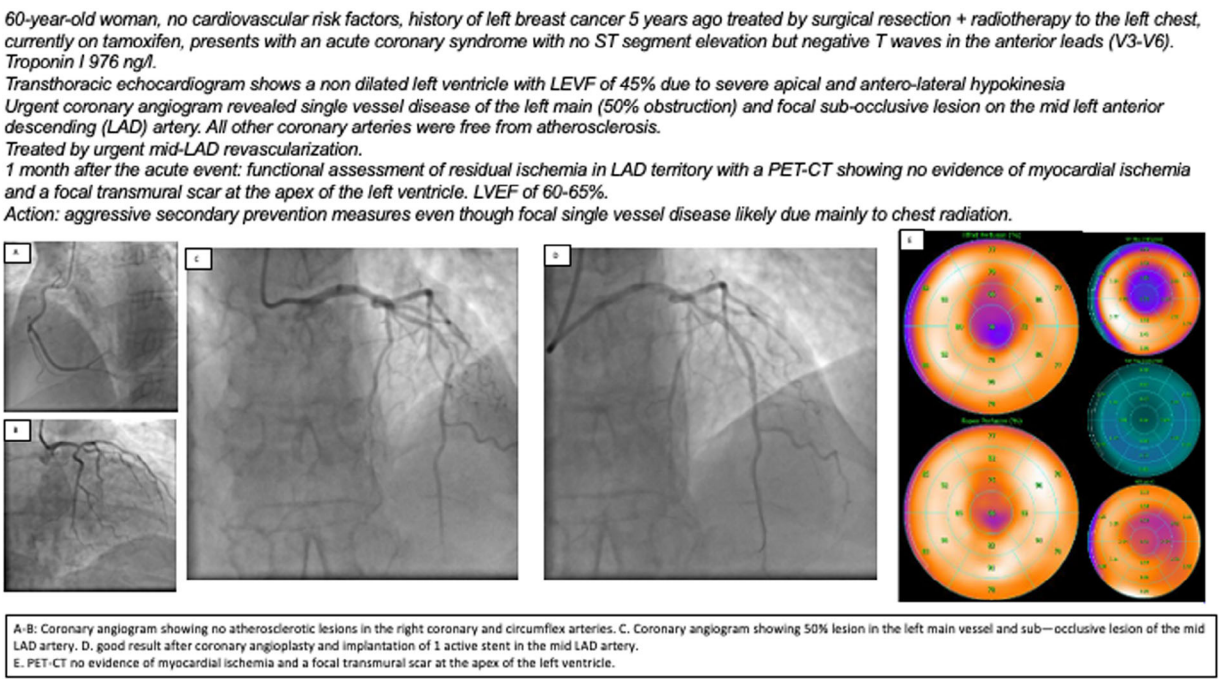

FIGURE 7 | Case 6. 60-year-old woman, no cardiovascular risk factors, history of left breast cancer 5 years ago treated by surgical resection + radiotherapy to the left chest, currently on tamoxifen, presents with an acute coronary syndrome with no ST segment elevation but negative T waves in the anterior leads (V3–V6). Troponin I 976 ng/L.

Secondary mitral and/or tricuspid valve regurgitation due to arrhythmic cardiomyopathy, amyloidogenic light-chain cardiomyopathy, and severe forms of CTRCD with LV cavity enlargement are all readily assessed by echocardiography often combined with CMR.

Right-sided valve disease due to the vasoactive substances secreted by neuroendocrine tumors in the setting of carcinoid heart disease should be screened for and monitored by echocardiography 2–4 times a year depending on circulating serotonin metabolite levels (5HIAA) and NT-proBNP levels [36]. Pulmonary and tricuspid regurgitation are the most common valve dysfunctions in this setting [37]. Left-sided valve involvement, although rare, is possible in the presence of direct entry into the systemic circulation of the vasoactive substances through patent foramen ovale, or porto-systemic shunts. Transesophageal echocardiography is usually required during the pre-operative assessment. PET-CT scans are useful for the detection and follow-up of cardiac metastases. Cardiac CT and CMR are helpful in assessing pericardial involvement and right heart size and function.

Figure 7 illustrates a real-world case presentation on the management of IHD in long-term cancer survivors.

5 | Challenges

The diversity in imaging technologies and techniques can lead to variations in diagnostic accuracy. Establishing standardized protocols for multimodality imaging tailored specifically to cancer patients is therefore crucial to ensure consistent detection of ischemic and VHD. Moreover, some patients may lack access to multimodal imaging and there is a need to address these disparities based on socioeconomic status, geographic location, and healthcare resources to ensure timely diagnosis and management of severe heart disease for all cancer patients. Although advanced imaging techniques entail significant costs, the potential benefits include early detection, enabling timely management which in the end might reduce the costs induced by severe CVD. Further, the value of maintaining a patient's quality of life through effective cardiovascular management should not be underestimated.

Nevertheless, discussions with oncologists and patients concerning the risk-benefit ratio of diagnostic imaging modalities are crucial. First, the added value of imaging techniques that involve radiation must be carefully evaluated, particularly in young patients, considering the potential risks of increased secondary malignancies. Second, screening for IHD can deliver false positives that may lead to unnecessary invasive procedures. Treatment decisions arising from imaging findings should therefore involve shared decision-making between patients and healthcare providers. Later is of particular importance in patients with reduced life expectancy, where conservative treatment should often be favored and carefully weighed against aggressive interventions. We strongly recommend a pragmatic individualized approach respecting patients' values and preferences, especially in palliative situations where quality of life comes first.

Establishing multidisciplinary teams involving cardiologists, oncologists, and radiologists will facilitate comprehensive management of cancer patients, ensuring that both oncological and cardiovascular health needs are addressed.

Finally, a huge effort in the education of doctors and patients is necessary concerning the importance of CVRF management (especially HTN) in cancer patients. Although in a significant proportion of non-oncologic patients' treatment goals are not reached the situation seems even worse in cancer patients due to neglect of this matter from a doctor's side.

Future research should focus on the long-term cardiovascular outcomes of cancer survivors, particularly those with diagnosed IHD, VHD, or multiple CVRF. Long-term effects on atherosclerotic vascular disease of new-generation targeted therapies need particular attention since they are increasingly used as a chronic treatment to maintain a good treatment response or remission. This knowledge will guide surveillance strategies and improve patient management. The utility of a formal and standardized screening strategy for CAD in asymptomatic cancer survivors needs to be evaluated. Artificial intelligence (AI) deserves attention since applied in image analysis it might improve efficiency, diagnostic accuracy, streamline workflows, and enhance the early detection of cardiac dysfunction, allowing for better risk stratification, and timely intervention.

6 | Conclusion

IHD and VHD occurring during and after cancer treatment imply multiple mechanisms including patient-, cancer-, and cancer treatment-related factors. Comprehensive multi-modality CV morphological imaging and myocardial functional assessment are central in risk stratification, at baseline for identification of high-risk patients to optimize preventive strategies, during antitumoral therapy for detection, and follow-up of acute CTR-CVT, and after the end of oncologic treatment for screening of asymptomatic high-risk cancer survivors, and work-up of symtpomatic patients. Research is needed to create specific evidence-based recommendations on detection and management of IHD and VHD in cancer patients.

Ethics Statement

As a review article, this manuscript does not involve human or animal participants and thus did not require formal ethical approval. The article adheres to ethical guidelines for reviewing literature, including the accurate citation of sources and avoidance of plagiarism. All relevant studies have been discussed objectively, and no unpublished or sensitive data has been included.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this review. No financial or personal relationships with individuals or organizations have influenced the content of this article. Any funding sources that supported the research or writing of this review have been acknowledged, and the sponsors had no role in the selection of articles reviewed, interpretation of findings, or decision to submit the manuscript for publication.

Data Availability Statement

This review article does not involve original data collection or analysis. All data supporting the findings and conclusions are derived from previously published studies, which are available in the public domain or through subscription-based journals. Relevant sources and references have been cited throughout the manuscript. Any further inquiries regarding specific data or studies discussed in the review can be directed to the corresponding author.

References

1. R. L. Siegel, A. N. Giaquinto, and A. Jemal, "Cancer Statistics, 2024," *CA: A Cancer Journal for Clinicians* 74, no. 1 (2024): 12–49.

2. H. Strongman, S. Gadd, A. Matthews, et al., "Medium and Long-Term Risks of Specific Cardiovascular Diseases in Survivors of 20 Adult Cancers: A Population-Based Cohort Study Using Multiple Linked UK Electronic Health Records Databases," *Lancet* 394, no. 10203 (2019): 1041–1054.

3. A. R. Lyon, T. Lopez-Fernandez, L. S. Couch, et al., "2022 ESC Guidelines on Cardio-Oncology Developed in Collaboration With the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS)," *European Heart Journal* 43, no. 41 (2022): 4229–4361.

4. R. A. Byrne, X. Rossello, J. J. Coughlan, et al., "2023 ESC Guidelines for the Management of Acute Coronary Syndromes," *European Heart Journal – Acute Cardiovascular Care* 13, no. 1 (2024): 55–161.

5. C. Vrints, F. Andreotti, K. C. Koskinas, et al., "2024 ESC Guidelines for the Management of Chronic Coronary Syndromes," *European Heart Journal* 45, no. 36 (2024): 3415–3537.

6. A. Lind, M. Totzeck, A. A. Mahabadi, et al., "Impact of Cancer in Patients Undergoing Transcatheter Aortic Valve Replacement: A Single-Center Study," *JACC CardioOncology* 2, no. 5 (2020): 735–743.

7. G. Santangelo, S. Moscardelli, L. Barbieri, A. Faggiano, S. Carugo, and P. Faggiano, "Aortic Valve Stenosis and Cancer: Problems of Management," *Journal of Clinical Medicine* 12, no. 18 (2023): 5804.

8. S. Kraler, L. Liberale, S. Nopp, et al., "Biomarker-Enhanced Cardiovascular Risk Prediction in Patients With Cancer: A Prospective Cohort Study," *Journal of Thrombosis and Haemostasis* 22, no. 11 (2024): 3125–3136.

9. P. Greenland, M. J. Blaha, M. J. Budoff, R. Erbel, and K. E. Watson, "Coronary Calcium Score and Cardiovascular Risk," *Journal of the American College of Cardiology* 72, no. 4 (2018): 434–447.

10. S. Cuddy, D. L. Payne, D. J. Murphy, et al., "Incidental Coronary Artery Calcification in Cancer Imaging," *JACC CardioOncology* 1, no. 1 (2019): 135–137.

11. J. H. Lee, A. Rizvi, B. O. Hartaigh, et al., "The Predictive Value of Coronary Artery Calcium Scoring for Major Adverse Cardiac Events According to Renal Function (From the Coronary Computed Tomography Angiography Evaluation for Clinical Outcomes: An International Multicenter [CONFIRM] Registry)," *American Journal of Cardiology* 123, no. 9 (2019): 1435–1442.

12. D. J. Maron, J. S. Hochman, H. R. Reynolds, et al., "Initial Invasive or Conservative Strategy for Stable Coronary Disease," *New England Journal of Medicine* 382, no. 15 (2020):1395–1407.

13. M. Gulati, P. D. Levy, D. Mukherjee, et al., "2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines," *Circulation* 144, no. 22 (2021): e368–e454.

14. S. W. Yusuf, N. Daraban, N. Abbasi, X. Lei, J. B. Durand, and I. N. Daher, "Treatment and Outcomes of Acute Coronary Syndrome in the Cancer Population," *Clinical Cardiology* 35, no. 7 (2012): 443–450.

15. A. C. Burris 2nd, J. A. Boura, G. L. Raff, and K. M. Chinnaiyan, "Triple Rule Out Versus Coronary CT Angiography in Patients With Acute Chest Pain: Results From the ACIC Consortium," *JACC Cardiovascular Imaging* 8, no. 7 (2015): 817–825.

16. H. Hecht, M. J. Blaha, D. S. Berman, et al., "Clinical Indications for Coronary Artery Calcium Scoring in Asymptomatic Patients: Expert Consensus Statement From the Society of Cardiovascular Computed Tomography," *Journal of Cardiovascular Computed Tomography* 11, no. 2 (2017): 157–168.

17. C. C. Meyer, K. A. Calis, Burke, C. A. Walawander, and T. H. Grasela, "Symptomatic Cardiotoxicity Associated With 5-Fluorouracil," *Pharmacotherapy* 17, no. 4 (1997): 729–736.

18. S. A. Jensen and J. B. Sorensen, "Risk Factors and Prevention of Cardiotoxicity Induced by 5-Fluorouracil or Capecitabine," *Cancer Chemotherapy and Pharmacology* 58, no. 4 (2006): 487–493.

19. E. Van Cutsem, P. M. Hoff, J. L. Blum, M. Abt, and B. Osterwalder, "Incidence of Cardiotoxicity With the Oral Fluoropyrimidine Capecitabine is Typical of That Reported With 5-Fluorouracil," *Annals of Oncology* 13, no. 3 (2002): 484–485.

20. S. G. Arbuck, H. Strauss, E. Rowinsky, et al., "A Reassessment of Cardiac Toxicity Associated With Taxol," *Journal of the National Cancer Institute Monographs* 15 (1993): 117–130.

21. F. A. Scappaticci, J. R. Skillings, S. N. Holden, et al., "Arterial Thromboembolic Events in Patients With Metastatic Carcinoma Treated With Chemotherapy and Bevacizumab," *JNCI: Journal of the National Cancer Institute* 99, no. 16 (2007): 1232–1239.

22. B. Escudier, "Sorafenib [Corrected] in Kidney Cancer," *Annals of Oncology* 18, no. S9 (2007): ix90–ix93.

23. M. Schmidinger, C. C. Zielinski, U. M. Vogl, et al., "Cardiac Toxicity of Sunitinib and Sorafenib in Patients With Metastatic Renal Cell Carcinoma," *Journal of Clinical Oncology* 26, no. 32 (2008): 5204–5212.

24. M. J. Moore, D. Goldstein, J. Hamm, et al., "Erlotinib Plus Gemcitabine Compared With Gemcitabine Alone in Patients With Advanced Pancreatic Cancer: A Phase III Trial of the National Cancer Institute of Canada Clinical Trials Group," *Journal of Clinical Oncology* 25, no. 15 (2007): 1960–1966.

25. J. T. Vuong, A. F. Stein-Merlob, A. Nayeri, T. Sallam, T. G. Neilan, and E. H. Yang, "Immune Checkpoint Therapies and Atherosclerosis: Mechanisms and Clinical Implications: JACC State-of-the-Art Review," *Journal of the American College of Cardiology* 79, no. 6 (2022): 577–593.

26. Z. D. Drobni, R. M. Alvi, J. Taron, et al., "Association Between Immune Checkpoint Inhibitors With Cardiovascular Events and Atherosclerotic Plaque," *Circulation* 142, no. 24 (2020): 2299–2311.

27. M. D'Souza, I. M. Svane, G. Gislason, and M. Schou, "Immune Check Point Inhibitors are Associated With a Spectrum of Cardiac Events in Patients With Cancer," *European Heart Journal* 42, no. 16 (2021): 1636.

28. P. Thavendiranathan, L. Zhang, A. Zafar, et al., "Myocardial T1 and T2 Mapping by Magnetic Resonance in Patients With Immune Checkpoint Inhibitor-Associated Myocarditis," *Journal of the American College of Cardiology* 77, no. 12 (2021): 1503–1516.

29. V. Delgado, N. Ajmone Marsan, S. de Waha, et al., "2023 ESC Guidelines for the Management of Endocarditis," *European Heart Journal* 44, no. 39 (2023): 3948–4042.

30. S. Rosmini, A. Aggarwal, D. H. Chen, et al., "Cardiac Computed Tomography in Cardio-Oncology: An Update on Recent Clinical Applications," *European Heart Journal – Cardiovascular Imaging* 22, no. 4 (2021): 397–405.

31. S. Jinno, A. Yamada, K. Sugimoto, et al., "Resting Echocardiographic Parameters Can Exclude Significant Coronary Artery Disease: A Comparison With Coronary Computed Tomography Angiography," *Echocardiography* 40, no. 11 (2023): 1251–1258.

32. R. Velusamy, M. Nolan, A. Murphy, P. Thavendiranathan, and T. H. Marwick, "Screening for Coronary Artery Disease in Cancer Survivors State-of-the-Art Review," *JACC: Cardiooncology* 5, no. 1 (2023): 22–38.

33. F. A. van Nimwegen, M. Schaapveld, C. P. Janus, et al., "Cardiovascular Disease After Hodgkin Lymphoma Treatment: 40-Year Disease Risk," *JAMA Internal Medicine* 175, no. 6 (2015): 1007–1017.

34. K. Murbraech, T. Wethal, K. B. Smeland, et al., "Valvular Dysfunction in Lymphoma Survivors Treated With Autologous Stem Cell Transplantation: A National Cross-Sectional Study," *JACC Cardiovascular Imaging* 9, no. 3 (2016): 230–239.

35. A. Vahanian, F. Beyersdorf, F. Praz, et al., "2021 ESC/EACTS Guidelines for the Management of Valvular Heart Disease," *European Heart Journal* 43, no. 7 (2022): 561–632.

36. C. Delhomme, T. Walter, D. Arangalage, et al., "Carcinoid Heart Disease in Patients With Midgut Neuroendocrine Tumours," *Journal of Neuroendocrinology* 35, no. 4 (2023): e13262.

37. G. Suc, A. Cachier, O. Hentic, et al., "Management and Outcomes of Carcinoid Heart Disease With Liver Metastases of Midgut Neuroendocrine Tumours," *Heart* 110, no. 2 (2023): 132–139.