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Core Curriculum

SCAI Expert Consensus Statement: Evaluation, Management, and Special Considerations of Cardio-Oncology Patients in the Cardiac Catheterization Laboratory (Endorsed by the Cardiological Society of India, and Sociedad Latino Americana de Cardiologıa Intervencionista)

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In the United States alone, there are currently approximately 14.5 million cancer survivors, and this number is expected to increase to 20 million by 2020. Cancer therapies can cause significant injury to the vasculature, resulting in angina, acute coronary syndromes (ACS), stroke, critical limb ischemia, arrhythmias, and heart failure, independently from the direct myocardial or pericardial damage from the malignancy itself. Consequently, the need for invasive evaluation and management in the cardiac catheterization laboratory (CCL) for such patients has been increasing. In recognition of the need for a document on special considerations for cancer patients in the CCL, the Society for Cardiovascular Angiography and Interventions (SCAI) commissioned a consensus group to provide recommendations based on the published medical literature and on the expertise of operators with accumulated experience in the cardiac catheterization of cancer patients.

Key words: cardio-oncology; PCI; cancer; malignancy; stent thrombosis

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INTRODUCTION

Advances in cancer therapy have resulted in a steady decline in cancer-related mortality since the 1990s. In the United States alone, there are currently approximately 14.5 million cancer survivors, and this number is expected to increase to 20 million by 2020 [1]. In view of these trends, as well as the cardiovascular toxicity potential of radiation and chemotherapy, cancer patients are exposed to cardiovascular morbidity and mortality more than ever before, thus generating the call for "onco-cardiology" or "cardio-oncology." The American College of Cardiology (ACC) recognized cardio-oncology as one of the "top cardiology stories for 2014," and several healthcare institutions have founded onco-cardiology/cardio-oncology departments and fellowship training programs focusing on these issues.

Anticancer therapies can cause significant injury to the vasculature, resulting in angina, acute coronary syndromes (ACS), stroke, critical limb ischemia, arrhythmias, and heart failure (HF), independently from the direct myocardial or pericardial damage that might occur. Moreover, cancer is generally associated with a hypercoagulable state, which increases the risk of acute thrombotic events. Consequently, the need for invasive evaluation and management in the cardiac catheterization laboratory (CCL) for such patients has been increasing. Unfortunately, there are few data on this patient population, because cancer patients have been excluded from national percutaneous coronary intervention (PCI) registries and most randomized PCI clinical trials.

In recognition of the need for a document on special considerations for cancer patients in the CCL, the Society for Cardiovascular Angiography and Interventions (SCAI) commissioned a writing committee to define the landscape and to provide recommendations (level of evidence C) based on published medical literature and expertise of operators with accumulated experience in the cardiac catheterization of cancer patients. As this document is focused on diagnostic and interventional CCL considerations, chemotherapy- and radiotherapy-induced myocardial dysfunction will not be extensively covered.

MECHANISMS OF VASCULAR TOXICITIES IN CANCER PATIENTS

Chemotherapy-Induced Vascular Toxicities

In addition to the known effects on cardiac function, chemotherapeutic agents may injure the vascular system, including coronary and peripheral circulation, causing both acute and long-term consequences (Table I).

The chemotherapeutics notoriously associated with angina and ACS are **5-Fluorouracil (5-FU)** and its oral pro-drug **capecitabine**. The drug 5-FU triggers abnormal vasoreactivity immediately after the initiation of therapy [3], which might be due to endothelial damage and alterations in molecular signaling pathways that control vascular smooth muscle cell tone [6,49–51]. Although myocardial ischemia and arrhythmias are often reversible upon treatment discontinuation, lethal outcomes have been reported.

ACS have also been reported for **paclitaxel** and less for **docetaxel** [9–11]. Vasospasm is the key mechanism, and unrecognized coronary artery disease (CAD) may be a predisposing factor. Unlike 5-FU and capecitabine, cardiac rhythm disturbances including bradycardia are more common than ischemic events [11].

Cisplatin has been uniquely associated with acute coronary thrombosis, sometimes in multiple vascular territories [14,16,17]. Endothelial damage, thromboxane production, platelet activation, and platelet aggregation appear to be the main mechanisms [16,52–54]. Patients who receive platinum-based chemotherapies are at a 1.5- to 7-fold greater long-term risk of CAD and myocardial infarction (MI) [55–60].

Often given in combination with cisplatin, **bleomycin** can aggravate endothelial dysfunction and **vinblastine** can induce endothelial apoptosis [61], increasing the vasotoxic potential of these cancer treatment regimens [12,13,15,18,62].

Finally, **cyclophosphamide** causes toxicity to the endothelial cells, with the induction of Prinzmetal's angina or hemorrhagic peri-myocarditis as the primary presentation [12,63,64].

Vascular endothelial growth factor (VEGF) signaling pathway inhibitors are associated with a two- to sixfold increased risk of acute cardiovascular events [19,21,22]. These events might be due to the induction of endothelial dysfunction and the downstream consequences of vasoconstriction, vascular remodeling, inflammation, and platelet activation. Interference with plaque neovessel formation and integrity is another unique aspect of this class of drugs [30,65–71] Some 70% of patients on sunitinib treatment experience a reduction in coronary flow reserve (on average 1.8 ± 0.4), especially with a longer duration of therapy [28]. In experimental models, sunitinib causes microvascular impairment [27] in conjunction with rarefication of microvascular pericytes and capillaries [72]. Abnormality of the vasofunctional balance due to eNOS uncoupling along with an increase in mitochondrial superoxide production [27,73] and increased endothelin-1 production [74,75] may play an additional role in this alteration.

TABLE I. Chemotherapeutic Agents Associated with Myocardial Ischemia

	Incidence	Presentations	FDA-approved cancer therapy
Antimetabolites			
5-Flourouracil [2–6]	0.1%–19%	Angina, vasospasm, MI, Takotsubo cardiomyopathy	Colorectal, pancreas, gastric, breast, basal cell, and squamous cell cancer of head and neck
Capecitabine [4,7,8]	0.02%–10%	Angina, vasospasm, MI, Takotsubo cardiomyopathy	Colorectal, breast cancer
Anti-microtubule agents			
Paclitaxel [9–11]	0.2%–4%	Angina, vasospasm, MI	Breast, ovarian, non-small lung cancer, Kaposi sarcoma
Vinblastine [12,13]	<5%	Angina, MI	Testicular cancer, Hodgkin's and non-Hodgkin's lymphoma, Kaposi's sarcoma, Mycosis fungoides, breast cancer, and choriocarcinoma
Alkylating agents			
Cisplatin [12–17]	0.2%–12%	Angina, vasospasm, MI, coronary thrombosis, progression of CAD	Bladder, cervical, ovarian, testicular, squamous cell of head and neck, non-small cell lung cancer, and mesothelioma
Antitumor antibiotics			
Bleomycin [12,13,18]	<3%	Angina, vasospasm, MI	Testicular, squamous cell cancer of the vulva, cervix, or head and neck, Hodgkin's and Non-Hodgkin's lymphoma
Monoclonal antibodies			
Bevacizumab [19–22]	1%–6%	Angina, MI, Takotsubo cardiomyopathy	Renal cell, colorectal, cervical, non-small cell lung cancer, glioblastoma
Ramucirumab [23]	1.5%–2%	Angina, MI, cardiac arrest	Gastric/gastroesophageal junction adenocarcinoma
Rituximab [24]	Rare	Vasospasm, angina, MI, Takotsubo cardiomyopathy	Non-Hodgkin's lymphoma, Chronic Lymphocytic Leukemia
Aflibercept	3%	Arterial thromboembolic events	Colorectal cancer
Tyrosine kinase inhibitors			
Sorafenib [25]	1%–2%	Vasospasm, angina, MI	Renal cell, liver, thyroid cancer
Sunitinib [26–31]	1%–13%	Angina, MI, Takotsubo cardiomyopathy, progression of CAD	Renal cell, pancreas cancer, gastrointestinal stromal tumor
Pazopanib [32]	2%–10%	Angina, MI	Renal cell cancer, soft tissue sarcoma
Nilotinib [33–36]	2%–25%	Angina, MI, progression of CAD, peripheral arterial disease	Chronic Myeloid Leukemia (CML)
Ponatinib [37,38]	11%	Angina, myocardial infarction, progression of CAD	CML
Hormone therapy			
Aromatase inhibitors (e.g., anastrozole) [39,40]	1%–2% (12%–17% w/IHD)	Angina, MI	Breast cancer
Anti-androgens (e.g., bicalutamide) [41–44]	2%–5%	Angina, MI, progression of CAD	Prostate cancer
Estrogen/nitrogen mustard [45–47] (Estramustine)	1%–3%	Angina, MI	Prostate cancer
Gonadotropin-releasing hormone agonists [44] (goserelin)	1%–5%	Angina, MI	Prostate cancer
Gonadotropin-releasing hormone antagonists [48] (degarelix)	<1%	MI	Prostate cancer

ACS, acute coronary syndrome; CML, chronic myeloid leukemia; IHD, ischemic heart disease; MI, myocardial infarction.

Sorafenib has been also associated with coronary vasospasm and even more profoundly than **sunitinib** and with involvement of multiple vessels [76–78]. Moreover, sorafenib has been associated with progression of CAD, whereas another report links sunitinib with atherosclerotic plaque rupture due to impaired endothelial healing [79]. In an experimental model, treatment with sorafenib was associated with poorer

TABLE II. Peripheral Arterial Disease Associated with Radiation Therapy

Type of radiation	Peripheral arterial disease
Head and neck radiation	CVA/TIA, carotid arterial disease
Supraclavicular and mediastinal radiation	CVA/TIA, carotid, and subclavian arterial disease
Abdominal and pelvic radiation	Renal arterial disease, lower extremity PAD

CVA/TIA, cerebrovascular accident/transient ischemic attack; PAD, peripheral arterial disease.

survival due to the induction of drug-induced myocyte necrosis [25,26]. Moreover, there is an increased bleeding risk in patients treated with VEGF inhibitors [80].

Progression of atherosclerosis and ischemic events has been noted for two tyrosine kinase inhibitors: **nilotinib** and **ponatinib** [36,81,82]. Some patients develop a series of events in various vascular territories, even when they have no cardiovascular risk factors [33–35]. The mechanism of the preferential effect on the peripheral arterial circulation with nilotinib is unclear. In contrast, cardiovascular events seem to be more common with ponatinib than cerebrovascular and peripheral artery disease (PAD) events (6.2%, 4.0%, and 3.6%, respectively). Overall, arterial thrombotic events are three times more frequent than venous occlusive events. Finally, there are several reports of ACS and reversible apical ballooning syndrome (Takotsubo) with **rituximab** therapy [24,83]. The prognosis of Takotsubo cardiomyopathy induced by chemotherapy agents is unclear.

Increased cardiovascular risk is noted in patients with prostate cancer treated with **androgen deprivation therapy (ADT)** in the form of gonadotropin-releasing hormone (GnRH) agonists [41–44]. A 25% increased risk of cardiovascular events was reported for women receiving **aromatase inhibitors** (anastrozole, letrozole, exemestane) [39]. Randomized, placebo-controlled trials have not indicated an increased cardiovascular risk with tamoxifen [40] (it improves metabolic parameters, endothelial function and slows atherosclerosis disease progression [84]) but have shown an increase in thromboembolic event risk [39].

The effect of the chemotherapeutic agents reviewed above on cardiovascular risk, especially those with a key impact on endothelial cells or stent endothelialization and stent thrombosis risk, remains undefined [56]. Drugs similar to vinblastine that stimulate thromboxane production and platelet reactivity have been reported to cause MI, and platelet activation was suppressed only by high-dose clopidogrel [85]. While VEGF-eluting stents have been linked to decreased stent thrombosis rates, it is unknown whether VEGF inhibition is associated with the opposite effect [86]. Any underlying malignancy by itself may be considered a risk factor for stent thrombosis; some malignancies such as acute promyelocytic leukemia are associated with a high coronary thrombosis risk in general [87–89].

Radiation-Induced Coronary and Peripheral Arterial Disease

Radiation therapy (RT) is received by over 50% of cancer patients. Ionizing radiation affects noncancerous cells and among these, endothelial cells are the most vulnerable. Cholesterol plaques and thrombosis can form within a period of days after radiation exposure in experimental models [90,91]. Fibrosis may evolve over time, involving all three layers of the vessel wall and subsequently manifestations can vary from accelerated atherosclerosis to fibro intimal thickening as well as thrombotic occlusion in areas of infarction [92,93].

More than two decades after RT for Hodgkin's lymphoma, severe stenosis due to the previously mentioned processes of the ostium of the left main and/or right coronary artery is observed in up to 20% of patients. Some stenosis are even undetected with traditional stress testing [91,94–96]. Even in a younger population with a mean age of just 20 years, coronary artery abnormalities were noted in nearly one in five patients [97]. For breast cancer survivors, RT for left-sided breast cancer has been considered to pose a higher risk of stenosis, which occurs as early as 5 years after therapy [98–101]. In addition to macrovascular disease, RT induces microvascular injury, leading to reduced coronary flow reserve, ischemia, and fibrosis.

As with radiation-induced CAD, PAD remains a concern for patients who receive extracardiac treatments for a variety of malignancies, although their sequelae and complications are less often reported than those of CAD. The central mechanism of post-radiation PAD is similar to that of post-radiation CAD (Table II).

In patients with **head and neck** tumors who have received **RT**, an increased risk of ischemic stroke and carotid arterial disease has been reported [102–105]. These findings across a heterogeneous spectrum of malignancies suggest that a predisposition to more vulnerable and accelerated plaque development in the cerebrovascular system may be aggravated by RT. Case series have shown favorable outcomes for carotid artery stenting (CAS) for radiation-induced carotid artery stenosis [106–109].

In patients with a history of **supraclavicular and mediastinal radiation**, several malignancies have been associated with a higher risk of cerebrovascular events

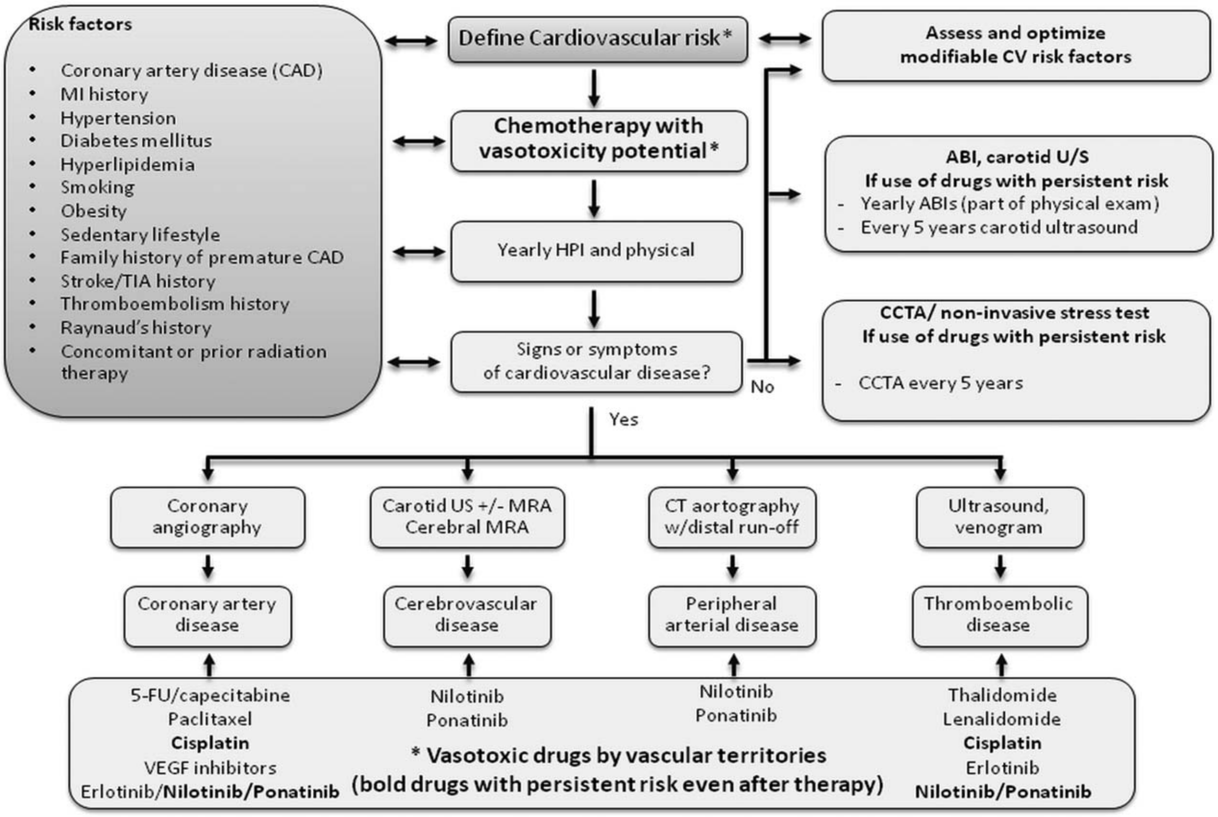

Fig. 1. Suggested SCAI algorithm for the cardiovascular screening of patients on chemotherapy. HPI, history of present illness; TIA, transient ischemic attack; ABI, ankle–brachial index; U/S, Ultrasound; CCTA, cardiac computed tomography angiography. *Pivotal to the sequence is the determination of baseline cardiac risk, including presence of ischemic heart disease, history of myocardial infarction, cardiovascular risk factor profile, and calculated atherosclerotic cardiovascular disease risk, for example, AHA/ACC ASCVD risk calculator, Framingham risk score, or ESC Score.

and carotid artery disease, particularly head and neck malignancies and lymphomas. A retrospective study on 415 patients with a history of Hodgkin's lymphoma showed a 7.4% prevalence of carotid and/or subclavian artery disease at a median of 17 years after RT [110,111].

Radiation-induced renal artery and lower extremity peripheral vascular disease have been less frequently reported in patients who have received **abdominal radiation** for lymphoma, abdominal sarcomas, and genitourinary malignancies [112–116]. Percutaneous transluminal angioplasty and/or stent placement and surgical interventional strategies have been employed with success, but data are extremely limited. Based on limited case reports and case series, PAD has manifested in patients who have received abdominal radiation for genitourinary malignancies as early as 2 years post-treatment [98].

SCREENING AND PREVENTION OF CARDIOVASCULAR DISEASE IN CANCER PATIENTS

Screening for Cardiovascular Disease in Patients to Receive Cancer Therapy (Chemotherapy, RT, and Operative Intervention)

Pre-existing cardiovascular risk factors and cardiovascular injury inflicted by chemotherapeutic agents and radiotherapy can have direct effects on coronary and peripheral arteries and the myocardium. This multifactorial insult can lead to an increased risk of developing cardiomyopathy, myocardial ischemia, vascular disease, or conduction abnormalities as well arrhythmias and QT prolongation [117,118].

Risk assessment and treatment for cancer patients with suspected or known cardiovascular disease should generally follow standing ACC/AHA guidelines, with special considerations described in Figs. 1 and 2.

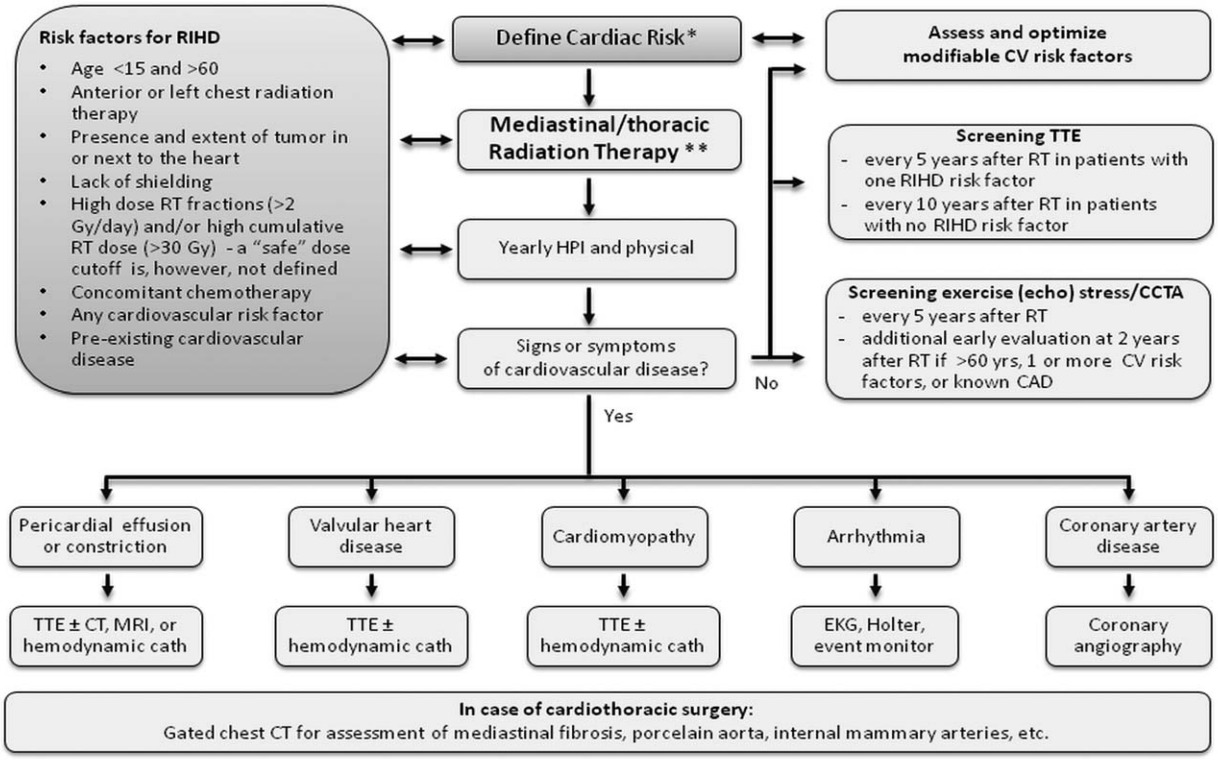

Fig. 2. Suggested SCAI algorithm for the cardiovascular screening of patients on radiation therapy. RIHD, radiation-induced heart disease; HPI, history of present illness; TTE, transthoracic echocardiogram; CCTA, cardiac computed tomography angiography; EKG, electrocardiogram; RT, radiation therapy. *Pivotal to the sequence is the determination of baseline cardiac risk, including presence of ischemic heart disease, history of myocardial infarction, cardiovascular risk factor profile, and calculated 10 year atherosclerotic cardiovascular disease (ASCVD) risk (http://tools.cardiosource.org/ASCVD-Risk-Estimator/), which remain the cohorts at highest risk for overall and early (<5 years) presentation of acute coronary events during follow-up; if established IHD/CAD or 10-year ASCVD risk ≥5.0% and/or patient >60 years, consider further testing and treatment (moderate–high intensity statin) to define the burden of disease prior to radiation therapy. **Potential sequelae of radiation therapy to the head/neck, abdomen/pelvis should also be assessed as outlined in Table II.

Pre-chemotherapy cardioprotection. Although data are limited and such approach remains controversial, the authoring team recommends pre-chemotherapy cardioprotection.

Patients without CAD might benefit from prophylactic treatment with beta-blockers, angiotensin antagonists, statin, or dexrazoxane to reduce cardiotoxicity [119]. The initiation of cardioprotective therapy can be associated with dizziness and fatigue, which might increase due to intravascular volume depletion caused by anorexia, nausea, and vomiting during chemotherapy. Careful volume assessment should be assessed to ensure that the patient remains euvolemic.

For patients with a history of hypertension, blood pressure management is advised as per the eighth Joint National Committee guidelines, with an emphasis on ACE-I and beta blockers (especially carvedilol or nebivolol) as first-line agents. Caution is advised when initiating diuretics and/or angiotensin antagonists due to the propensity to develop electrolyte abnormalities and renal dysfunction.

For patients at intermediate to high cardiovascular risk (based on cardiovascular risk scores) who are potentially undergoing cardiotoxic therapy (i.e., the agents listed in Table I or mediastinal radiation), referral to a cardiologist and/or cardio-oncology program is advised prior to the initiation of treatment.

For patients with established CAD and without contraindications, adding or continuing ACE-I and beta-blockers (preferably carvedilol or nebivolol) might provide additional cardioprotection [120–122].

To identify high-risk patients, intensive and frequent screening for CAD or elevated risk via echocardiographic studies and cardiac biomarkers is encouraged, because the chances of response and recovery are highest with early detection and rapid initiation of therapy [123].

Pre-radiation therapy cardioprotection. Aspirin and statin therapy should be encouraged for patients with established CAD or elevated ASCVD risk in keeping with current guidelines. It should be acknowledged that aspirin may not be tolerated in oncologic patients with high bleeding risk, or statins in patients with impaired liver function or in combination with hepatoxic chemotherapeutic agents. It is reasonable to further assess cardiovascular risk in intermediate-risk patients at suspected or elevated risk for cardiovascular disease with carotid artery intima-media thickness and ankle-brachial index measurements, coronary artery calcium scoring (CAC), and CCTA as per ACC/AHA guidelines [124]. Exposure of the heart to ionizing radiation during radiotherapy for breast cancer increases the subsequent rate of ischemic heart disease. The increase is proportional to the mean dose to the heart, starting within the first 5 years after radiotherapy and continued into the third decade after radiotherapy. Rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per gray (95% confidence interval, 2.9–14.5; $P < 0.001$), with no apparent threshold. The proportional increase in the rate of major coronary events per gray (Gy) was similar in women with and without cardiac risk factors at the time of radiotherapy.

Older patients with head and neck malignancies or lymphoma who are receiving supraclavicular radiation remain at significantly higher short- and long-term risk for cerebrovascular events [125,126] and thus baseline and more aggressive surveillance via carotid artery screening and subsequent treatment should be advised if the prognosis is favorable from an oncologic standpoint.

Traditional stress testing, although advised for long-term surveillance of RIHD, has its limitations in accuracy and CCTA or coronary angiography may be preferable. In regards to CAC, studies have shown that asymptomatic patients with a coronary artery calcium score of 0 have a "warranty period" of up to 5 years with a very low cardiovascular event rate, although further study regarding CAC progression in this specific patient population is warranted [127–129]. Recent data have suggested that lymphoma survivors with a history of mediastinal radiation and/or anthracycline exposure, have a 40-year cumulative incidence of cardiovascular diseases of 50%, with increased risk of cardiovascular events [130]. Thus, the impetus to optimal screening strategies based on epidemiologic data suggests aggressive surveillance before and after treatment.

Screening for Cardiovascular Disease in Cancer Survivors

Given the dynamic state of pharmacotherapy for cancer, with generally dramatic improvements in survival as well as new agents in development (with unclear cardiotoxic properties), it is important that patients are made aware of potential short- and long-term consequences as well as the need to follow up with subspecialists. A retrospective cohort study of the Childhood Cancer Survivor Study demonstrated that adult survivors of childhood malignancies with a history of chemoradiation had a 7-fold higher mortality rate, 15-fold increased rate of HF, 10-fold higher rates of cardiovascular disease, and 9-fold higher rates of stroke compared with their siblings [131]. Cancer survivorship programs and/or cardio-oncology programs provide up-to-date evaluations and appropriate referrals to subspecialists [132]. Periodic annual follow-up in higher risk individuals such as Hodgkin's lymphoma survivors is also advised, based on the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN). Cancer survivors are at increased risk of secondary and recurrent malignancies as well as cardiotoxic sequelae.

The best timing for surveillance initiation for cardiotoxic manifestations is unclear, given the discrepancies in expert opinion and an absence of official guidelines. The Children's Oncology Group recommends an annual follow up and physical examination for patients with a history of total body irradiation, cardiotoxic chemotherapy, total mediastinal radiation of $\geq$20 Gy, or for those who underwent combined chemoradiation. Both serial electrocardiograms and multigated acquisition scan (MUGA) for patients who received treatment $\geq$5 years of age and had both chest radiation and a total anthracycline dose $\geq$300 mg/m^2. For lower risk patients, serial echocardiography is recommended every 2–5 years. Stress testing 5–10 years following radiation exposure to the heart should be considered, along with counseling on lifestyle modifications. A cardiology evaluation and monitoring should be provided to women seeking to become pregnant and who have a history of anthracycline or high dose cyclophosphamide therapy. The International Late Effects of Childhood Cancer Guideline Harmonization Group in 2015 unified several international consensus statements and advised cardiomyopathy screening with "strong" recommendations for echocardiographic surveillance of patients with a history of high dose ($\geq$250 mg/m^2) anthracycline therapy, high dose ($\geq$35 Gy) chest radiation, or a combination of $\geq$100 mg/m^2 cumulative anthracycline and $\geq$15 Gy of chest radiation. There were also recommendations to perform screening for CAD on patients with a history of radiation exposure, although concrete recommendations were not made and were planned for future discussions by the group [133].

The American Society of Echocardiography (ASE) has released an expert consensus statement on the use of multimodality imaging with patients with history of radiotherapy. In their document, screening echocardiography is recommended 5 years after exposure for high-risk patients and 10 years after exposure for all

TABLE III. Cardiovascular Screening Recommendations for Cancer Patients

Cardiovascular screening recommendations for cancer survivors
Referral to a survivorship center/cardio-oncology program is recommended for cancer survivors who are not being actively followed by hematology/oncologist.
Medical record documentation of the patient's chemotherapy and radiotherapy treatment course with cumulative doses should be retrieved.
Transthoracic echocardiography (TTE) should be performed on patients with a history of significant anthracycline dose exposure (>240 mg/m^2) or chest radiation exposure (>30 Gy) starting no later than 2 years after completion of therapy, at 5 years after diagnosis and continued every 5 years thereafter.
In high-risk groups (known coronary artery disease, age >60, one or more CV risk factors) screening after chest radiation therapy should be initiated 2 years after radiation therapy as outlined in Figure 2
Coronary angiography is indicated for symptomatic patients with a history of radiotherapy, risk factors for RIHD, and noninvasive testing (i.e., stress MPI/echo/MRI, CCTA) that suggest a high likelihood of severe ischemic heart disease.
Coronary angiography is reasonable to consider for the evaluation of LV systolic dysfunction after chest radiation and to evaluate for radiation-induced ischemic heart disease.
Right and left heart catheterization is reasonable to evaluate the presence of pericardial constriction and restrictive cardiomyopathy if noninvasive imaging (echocardiography, CT, MR) is insufficient to provide a diagnosis.
Right and/or left heart catheterization and coronary angiography is reasonable to perform as per ACC/AHA guidelines for preoperative planning for patients with severe RIHD.
There is a known association between accelerated coronary artery disease and elevated cardiovascular events and mortality after chest radiation, particularly in high-risk populations such as those with Hodgkin's lymphoma who have undergone mantle field radiation. For these patients, functional imaging and/or CAC/CCTA is reasonable to perform ≥5 years post-radiotherapy, and further workups (e.g., coronary angiography, functional testing) is indicated for risk stratification if there is concern for severe ischemic heart disease.

other patients, with a reassessment every 5 years in asymptomatic patients. Cardiac magnetic resonance imaging (CMR) was recommended if there was a suspicion of pericardial constriction. They also advised stress testing in high-risk patients for CAD detection in asymptomatic individuals 5–10 years after exposure, and a reassessment every 5 years if no new symptoms developed [134].

CAC has attracted interest [135]; however, it is unclear whether these data can be extrapolated to patients with radiation-induced CAD. Another consideration is coronary CT angiography (CCTA), which may be superior to functional stress tests. CCTA offers the advantage of assessing the aorta and internal mammary arteries, which could be affected by RT. Ultimately, the best evaluation technique remains the coronary angiogram with liberal use of intravascular ultrasound (IVUS) and fractional flow reserve (FFR) to reveal diffuse vascular disease and/or lesional physiologic significance respectively. Cardiac catheterization should be considered for hemodynamic evaluation of pericardial, myocardial, and valvular heart disease.

Screening for carotid artery disease by carotid ultrasound should be started 5 years after supraclavicular radiation treatment and repeated every 5 years. Earlier screening (i.e., every 2 years) should occur in older patients (>60 years), in symptomatic patients and/or those with a carotid bruit, those with baseline carotid artery disease, or those on drugs with persistent vascular toxicity risk. Patients with a history of supraclavicular radiotherapy who have neurologic symptoms should undergo carotid artery imaging and be managed in accordance with existing guidelines.

Subclavian arterial ultrasound is recommended in symptomatic patients who have received head, neck, supraclavicular, or mediastinal radiation.

Renal ultrasound should be performed on symptomatic patients who have received abdominal and pelvic radiation.

With regards to lower extremity PAD screening in symptomatic patients, ankle–brachial-index (ABI) screening should be performed annually on those who received RT with potential exposure of the lower extremity vasculature (i.e., abdominal or pelvic radiation exposure) (Table III).

SPECIAL CONSIDERATIONS FOR CANCER PATIENTS WITH THROMBOCYTOPENIA AND ANEMIA

All major clinical trials on antithrombotic therapy have excluded patients with cancer [136]. One reason is the prevalence of thrombocytopenia (TP), which varies from 10% to 25% across the broad range of solid tumor cancer patients treated with intensive chemotherapy (i.e., breast cancer, ovarian, and germ cell) and the majority of acute leukemia, lymphoma, and multiple myeloma patients [137]. Approximately 10% of cancer patients have platelet counts less than 100,000/mm^3. Baseline TP increases the risk of bleeding and other adverse cardiac events [138]. Acquired TP develops frequently in cancer patients and appears to be different from the TP that occurs after the administration of glycoprotein (GP) IIb/IIIa inhibitors, heparin, thrombolytic therapy, and oral antiplatelet medications, which is strongly associated with ischemic and hemorrhagic complications as well as early mortality [139–148].

TP is not believed to protect cancer patients from ischemic events. In fact, TP is associated with an increased propensity for thrombus formation [149–153]. Clinical experience suggests that platelet function rather than platelet count is the determinant factor [154].

Prophylactic platelet transfusion is not recommended if the platelet count is greater than 10,000/mL (Table III). Transfusion at higher levels may be necessary for

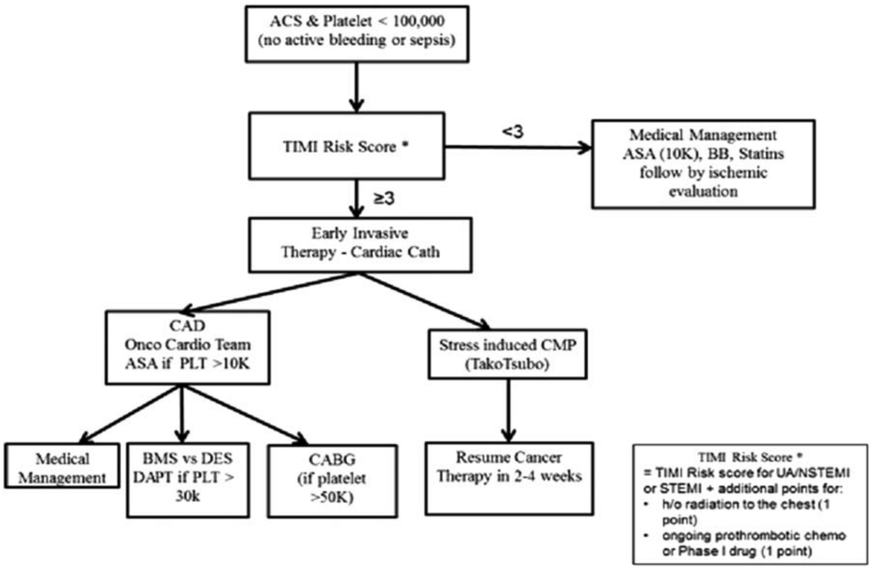

Fig. 3. Recommended revascularization approach used at the MD Anderson Cancer Center.

patients with high fever, hyperleukocytosis, rapid fall in platelet count, or coagulation abnormalities (e.g., acute promyelocytic leukemia) [155]. A prophylactic platelet transfusion should be considered at a threshold of 20,000/mL in patients with solid tumors, who are receiving therapy for bladder, gynecologic, colorectal tumors or melanoma, and for those with demonstrated necrotic tumors, due to the increased risk of bleeding at these sites. When a platelet transfusion is performed, it is critical to repeat the platelet count to ensure that the desired level has been reached. Platelet transfusions should also be available on short notice in case bleeding occurs. For alloimmunized patients, histocompatible platelets must be available.

Because thrombocytopenic patients might have a poor increment after a single transfusion but an excellent response with subsequent transfusions, a diagnosis of refractoriness to platelet transfusion should be made when at least two ABO-compatible transfusions, stored less than 72 hr, result in poor increments. Patients with alloimmune-refractory TP should be managed with platelet transfusions from donors who are HLA-A and HLA-B antigen selected.

On the basis of accumulated clinical experience and a variety of conference consensus documents [156], there is no minimum platelet level that poses an absolute contraindication for a coronary angiogram, and a platelet count of 40,000 to 50,000/mL may be sufficient to perform most interventional procedures with safety, in the absence of associated coagulation abnormalities.

Withholding aspirin (ASA) in thrombocytopenic cancer patients with ACS demonstrated poorer outcomes [153]. Case series of PCI in thrombocytopenic cancer demonstrated minimal bleeding when meticulous access with micropuncture techniques and careful hemostasis were achieved [155,157]. The initial dose of unfractionated heparin given was lowered to 30–50 U/kg when the platelet count was less than 50K, with additional heparin given if ACT was less than 250 sec. The standard dose of unfractionated heparin 50–70 U/kg or bivalirudin were utilized with platelet counts greater than 50K. In terms of dual antiplatelet therapy (DAPT), the only available experience is with clopidogrel. The recommended revascularization approach currently used at the MD Anderson Cancer Center is shown in Fig. 3.

Various platelet function tests are available; however, there is no data on their value for cancer patients with TP to guide platelet transfusion or DAPT therapy duration and intensity. In patients with significant CAD and platelet counts less than 30,000/mL, and in whom there is concern about intracranial bleed, a normal thromboelastography (TEG) may be considered to determine whether a revascularization strategy would be safe. TEG offers a comprehensive evaluation of both platelet and coagulation function. An abnormal TEG might require initial correction with a platelet transfusion or indicated blood products. This limited experience is available from just a few centers and is extrapolated from the cardiovascular as well as liver transplant surgical literature [158,159].

Anemia is common in cancer patients due to decreased red blood cell (RBC) production or increased RBC loss (bleeding) or destruction (hemolysis) as a direct result of the malignancy or secondary to cancer therapy. The optimal management of those patients

TABLE IV. Special Considerations for Cancer Patients with Thrombocytopenia

Special considerations for cancer patients with thrombocytopenia undergoing cardiac catheterization

Prophylactic platelet transfusion is not recommended in patients undergoing cardiac catheterization with thrombocytopenia, unless recommended by the oncology/hematology team for one of the following indications:

1. Platelet count <20,000/mL and one of the following: (a) high fever, (b) leukocytosis, (c) rapid fall in platelet count, (d) other coagulation abnormality
2. Platelet count <20,000/mL in solid tumor patients receiving therapy for bladder, gynecologic, or colorectal tumors, melanoma, or necrotic tumors

Therapeutic platelet transfusions are recommended in thrombocytopenic patients who develop bleeding during or after cardiac catheterization.

Repeat platelet counts are recommended after platelet transfusions.

30–50 U/kg unfractionated heparin is the initial recommended dose for thrombocytopenic patients undergoing PCI who have platelets <50,000/mL. ACT should be monitored.

For platelet counts <30,000/mL, revascularization and DAPT should be decided after a preliminary multidisciplinary evaluation (interventional cardiology/oncology/hematology) and a risk/benefit analysis.

Aspirin administration may be used when platelet counts are >10,000/mL.

DAPT with clopidogrel may be used when platelet counts 30,000–50,000/mL. Prasugrel, ticagrelor and IIB-IIIA inhibitors should not be used in patients with platelet counts <50,000.

If platelet counts are <50,000, the duration of DAPT may be restricted to 2 weeks following PTCA alone, 4 weeks after bare-metal stent (BMS), and 6 months after second or third generation drug-eluting stents (DES) if optimal stent expansion was confirmed by IVUS or OCT .

There is no minimum platelet count to perform a diagnostic coronary angiogram.

with blood product or iron transfusions is unclear and various societies have recommended cut-off levels for transfusion (EORTC, ASH/ASCO) [160–162]. RBC transfusion is generally recommended when hemoglobin is less than 7 g/dL. Consultation with hematology/oncology specialists is recommended for severely anemic cancer patients undergoing cardiac catheterization (Table IV).

VASCULAR ACCESS CONSIDERATIONS FOR CANCER PATIENTS UNDERGOING CARDIAC CATHETERIZATION

Complications of vascular access remain the most common cause of morbidity and are also associated with significant mortality [163]. Specific characteristics of the patient may impact access site complications (i) the effect of cancer and cancer treatment on the hematopoietic system [155,157,164–168], (ii) the presence of a hypercoagulable state [20,169–172], and (iii) the potential interactions between cancer and cardiac drugs [173–175]. Even minor vascular complications may lead to prolonged hospitalization and adverse outcomes [176,177]. Prior to catheterization, all patients should be evaluated for their bleeding diathesis, the prothrombotic state and the potential for infection due to immunosuppression [174]. Access routes should be carefully assessed and the appropriate steps taken to reduce complications associated with each technique (Table IV) [178–180].

Ultrasound guidance, micropuncture needles, and fluoroscopic guidance all contribute to the best possible outcome (Figs. 4 and 5) [180–183].

Femoral Access Site

Femoral artery access has been associated with a higher risk of bleeding, even with the use of vascular closure devices as compared with radial artery access [184]. A controversy exists concerning the need for performing the Allen test before transradial procedure [182]. Oncologic patients who have failed the Allen's test in both arms, who are on hemodialysis, with multiple previous radial procedures or arterial lines, and patients who have undergone bilateral mastectomy are probably better candidates for the femoral approach. Femoral access gives the operator greater flexibility for complex coronary interventions, rotational atherectomy, and the use of mechanical assist devices.

Puncture of the common femoral artery (CFA) at its mid-section should be the goal for optimal vascular access. Access outside that zone may lead to retroperitoneal hemorrhage (RPH), pseudoaneurysm, arteriovenous fistula, thrombosis, or excessive bleeding [185–187], which may be fatal in cancer patients. Therefore, meticulous identification of the inguinal ligament and "lower" access should be preferred to prevent bleeding. Vascular closure devices do not seem to decrease bleeding compared with manual compression, and should be avoided in immunocompromised patients due to the higher risk of local infection or delayed endothelization [188].

Radial Access Site

The radial artery is favored because of the lower bleeding risk and increased patient satisfaction [189]. Reductions in bleeding complications can be attained even in patients with TP who are receiving anticoagulant and antiplatelet therapy [190–192]. Early ambulation after radial access site catheterization favors fewer thrombosis complications. The need for anticoagulant administration remains a limitation for oncologic patients undergoing transradial diagnostic catheterizations.

Depending on the operator's skills, the advantages of radial access may be balanced in some cases by technical difficulty, increased fluoroscopy time, and

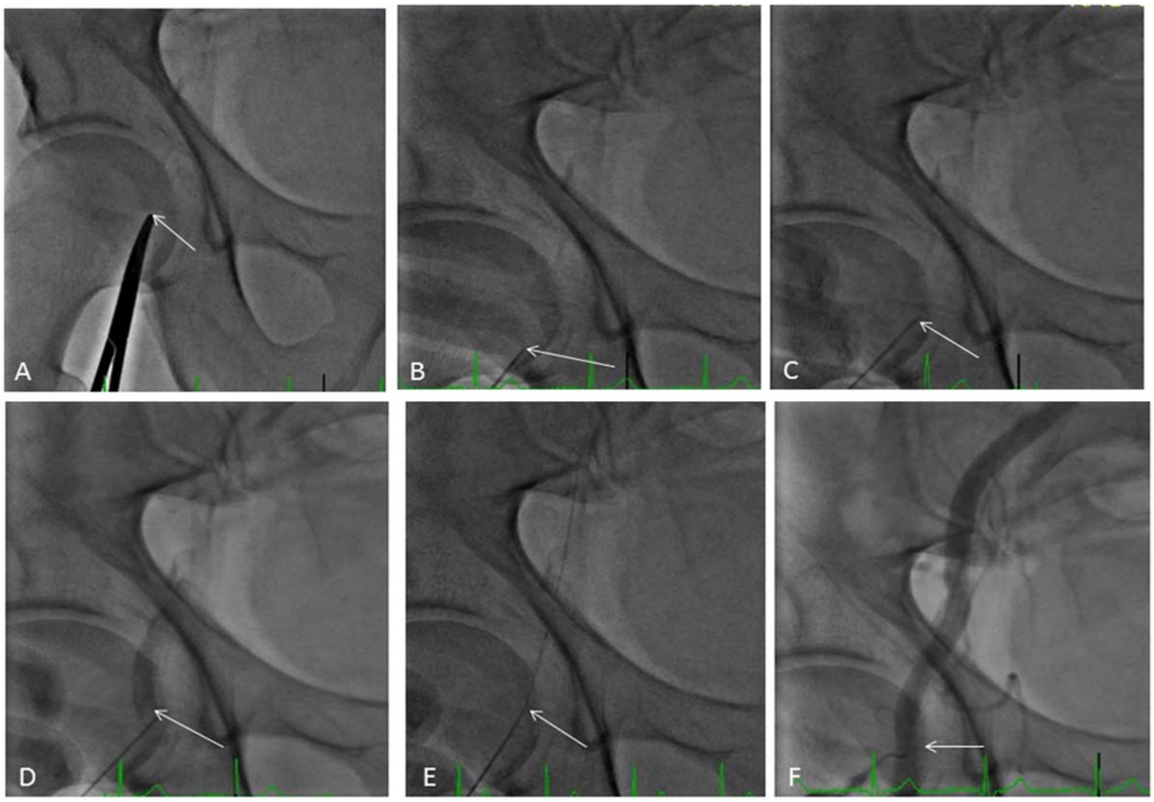

Fig. 4. Use of micropuncture to gain femoral access. (A) Anatomic localization of the femoral head (*white arrow*). (B, C) Micropuncture needle access. (D) Contrast injection through the micropuncture needle. (E) Micropuncture wire placement in the common iliac artery. (F) Common femoral angiogram.

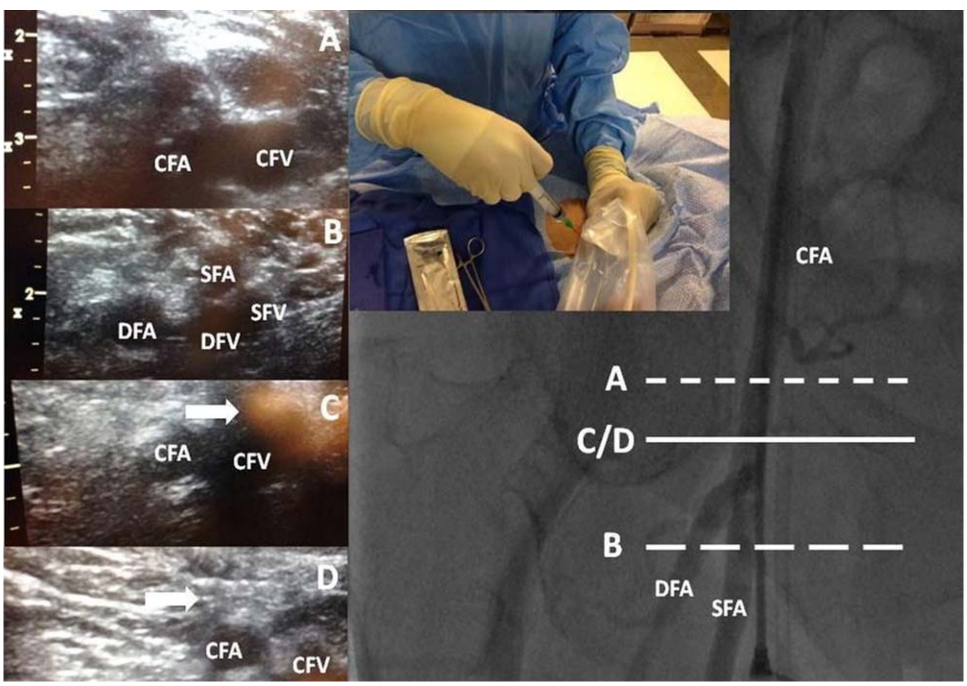

Fig. 5. Ultrasound-guided transfemoral access technique and correlation with femoral angiography. Panel A: Visualization of both the common femoral artery and vein. Panel B: Visualization of vascular structures below the bifurcation of the common femoral artery and vein. Panel C: Ultrasound guided access of the common femoral vein using a micropuncture needle (*arrow*). Panel D: Ultrasound guided access of the common femoral artery using a micropuncture needle (*arrow*). CFA, common femoral artery; CFV, common femoral vein; DFA, deep femoral artery (profunda femoris artery); SFA, superficial femoral artery; DFV, deep femoral vein (profunda femoris vein); SFV, superficial femoral vein (greater saphenous vein). Special thanks to Dr. Timothy Canan for assistance in providing demonstration.

TABLE V. Access Considerations for Cancer Patients Undergoing Cardiac Catheterization

Access considerations for cancer patients undergoing cardiac catheterization
For cancer patients who are excellent candidates for both access types, the radial artery is preferred.Femoral access is the preferred approach for cancer patients on hemodialysis, those with abnormal Allen's tests in both arms, multiple radial procedures or a-lines, bilateral mastectomy or when a complex intervention is anticipated.
The use of smaller sheath sizes, prompt removal of sheaths and early ambulation is recommended.
A lower dose of intra-arterial or intravenous unfractionated heparin at a dose of 50 U/kg or 3.000 units is recommended for cancer patients with thrombocytopenia and platelet count <50k undergoing cardiac catheterization via radial access.
A femoral angiogram is recommended after transfemoral access to promptly identify and address potential access complications.

increased radiation exposure [193,194]. Smaller hydrophilic sheaths and catheters should be used for further reductions in the risk of bleeding [183]. Patent hemostasis must be achieved to reduce the risk of radial artery occlusion, incidence of which is approximately 1%–3% in the general population. The patency of the radial artery should be preserved in case the artery is needed as a conduit for intra-arterial pressure monitoring, coronary artery bypass surgery, or hemodialysis access [195].

Taking into consideration the above special circumstances, for cancer patients who are excellent candidates for both types of access, transradial access should be preferred. Meticulous hemostasis as well as frequent catheter and sheath flushing are required, as cancer patients face the challenge of concomitant increased risk of both bleeding and thrombosis (Table V). Ultimately, operator clinical judgment is paramount in the final decision for the optimal access site.

INVASIVE EVALUATION AND MANAGEMENT OF CAD IN CANCER PATIENTS

Effective clinical risk stratification of patients undergoing cancer surgery must be undertaken prior to the consideration of cardiac catheterization. Breast, endocrine, reconstructive, gynecologic and minor urologic operations are considered low risk; abdominal and urologic operations are considered intermediate risk. The American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) risk calculator has been emphasized in the 2014 ACC/AHA guidelines on perioperative cardiovascular evaluation as an excellent risk assessment tool, and it can be used to stratify cancer patients with underlying cardiovascular disease. Overall, the urgency of cancer surgery and the need for PCI or coronary artery bypass surgery (CABG) should be guided by a collaborative clinical evaluation by oncologists and cardiologists [177]. Furthermore, it is reasonable to consider a staged approach, with an initial coronary anatomy (invasive coronary angiography or coronary CT angiography) and physiology assessment (stress test, cardiac PET, FFR), followed by an interdisciplinary meeting (medical or surgical oncology, RT, and cardiology) to outline the optimal plan (Table VI).

TABLE VI. Special Considerations for Cancer Patients Undergoing Cardiac Catheterization

Special considerations for cancer patients undergoing cardiac catheterization for CAD
Decision making regarding revascularization in patients with active cancer must take into consideration the overall prognosis of the patient.
For cancer patients with an acceptable prognosis, the general revascularization criteria for appropriate use must be carefully evaluated and only the most appropriate indications (scores 7 and above) should be considered [225].
For cancer patients with an expected survival <1 year, percutaneous revascularization may be considered for patients with acute STEMI and high-risk NSTEMI. For patients with stable angina, every effort must be made to maximally optimize medical therapy before resorting to an invasive strategy. This approach must include addressing other cancer-related comorbidities that potentially exacerbate ischemia, such as anemia, infection, hypoxia, etc. Should the patient continue to experience persistently severe angina (CCS Class III or IV), consideration may be given to percutaneous revascularization as a palliative option.
FFR is recommended before non-urgent PCI to justify the need for revascularization.
When invasive approach is indicated:
a. Balloon angioplasty should be considered for cancer patients who are not candidates for DAPT (Platelets <30,000/mL) or when a non-cardiac procedure or surgery is necessary as soon as possible.
b. BMS should be considered for patients with platelet counts >30,000/mL who need a non-cardiac procedure, surgery or chemotherapy which can be postponed for >4 weeks.
c. Newer generation DES should be considered for patients with platelet counts >30,000/mL who are not in immediate need for a non-cardiac procedure, surgery or chemotherapy.
d. Bivalirudin and/or radial approach should be considered to minimize the risk of bleeding.
Post intervention:
Intravascular imaging such as IVUS or optical coherence tomography (OCT) is recommended after stent placement to ensure optimal expansion and an absence of complications given the potential for early DAPT interruption.

Patients with stable angina can be treated medically, as PCI does not offer a survival advantage in most cases [196]. For patients with angina despite medical therapy, the severity of the cardiac disease, stage of the malignancy, and the condition of the patient should determine the strategy for PCI versus CABG. PCI is preferred when the malignancy is aggressive or widespread. CABG can be considered when the malignancy is potentially curable or when the estimated prognosis is acceptable [197].

Cancer patients with STEMI have higher mortality and morbidity compared with those without cancer. Patients with recently diagnosed cancer (<6 months) undergoing primary PCI had threefold higher cardiac mortality compared with those with a prior diagnosis and a control group (adjusted HR 3.3; CI 1.5–7) [165]. Similar findings were reported from the NHLBI registry of ACS patients undergoing PCI where cancer was one of the strongest independent predictors of in hospital death (OR 3.2; CI 1.12–9.4) and 1 year mortality (OR 2.15; 1.3–3.4) [198].

One of the largest series to date, with 456 cancer patients (88% advanced cancer, 61% solid tumors) with ACS (15% STEMI, 85% NSTEMI) from a single institution without onsite catheterization laboratory demonstrated that the presenting symptoms of ACS in cancer patients are dyspnea (44%), followed by chest pain (30.3%), and hypotension (23%) [199]. The majority of those patients were treated medically (ASA 46%; beta blockers 48%; statins 21%) and only 15 (3.3%) underwent percutaneous revascularization. One-year survival was only 26%. The use of aspirin (HR 0.77; 06–0.98) and beta blockers (HR 0.64; 0.51–0.81) were independently predictive of improved survival, whereas there was a trend toward improved survival with catheter-based revascularization (HR 0.57; 0.29–1.10; $P = 0.09$). However, selection bias should be taken into consideration as patients who received antiplatelet therapy and PCI were probably at lower risks than those that did not (bleeding risk, comorbidities, etc.). In another small report from Japan, 18 cancer patients (15 with advanced cancer) with acute MI undergoing PCI (15 BMS; 2 PTCA only; 1 DES) were compared with 59 controls. Both groups had similar procedural success (>97%). There were four in-hospital deaths in the cancer group (1 cardiac; 3 cancer related) and three patients had major bleeding [200]. These studies as well as a small cohort study from Russia [201] suggest the relative safety and efficacy of primary PCI in acute MI patients with advanced cancer.

When performing PCI, it is important to balance lesion characteristics and cancer stage and therapy, recognizing that cancer as a prothrombotic and proinflammatory state is associated with a higher risk of stent thrombosis and possibly in-stent restenosis. We recommend the use of BMS or newer-generation DES, which may have lower rates of stent thrombosis (ST) than BMS. Attempts should be made to avoid bifurcation and overlapping stents, both of which increase the risk of ST. High pressure (≥16 atm), non-compliant balloon inflations and the use of IVUS or optical coherence tomography (OCT) is recommended to assure adequate stent expansion, apposition and lack of edge dissection. Although the use of drug-eluting balloons, bio-absorbable polymers, or scaffolds may reduce the need for DAPT, these devices are not currently available in the United States. The initial experience at a major cancer center using OCT in cancer patients with DES placed for less than 12 months and requiring premature discontinuation of DAPT suggested that many patients had incomplete stent coverage or apposition, underexpansion, or already developed in-stent restenosis. Patients with optimal stent apposition and coverage without in-stent restenosis had no adverse events after premature DAPT discontinuation. However, the recently reported DAPT study suggests that patients treated with either BMS or DES may benefit from 30 weeks of therapy [202], although it is unclear whether a patient population with cancer or ultrasound-guided stent placement would derive a similar benefit. In fact, unrecognized cancer was a significant problem in this study, highlighting the merit of cardio-oncology awareness.

All patients undergoing PCI should receive anticoagulant agents to maintain an activated clotting time of greater than 250 sec during the procedure [182,203]. In oncologic patients with severe TP (<50k platelets), lower doses of unfractionated (50 U/kg) may achieve a therapeutic activated clotting time [182]. Patients with heparin-induced TP should receive intravenous bivalirudin.

If PCI is necessary in patients awaiting cancer surgery, balloon angioplasty without stenting or implantation of BMS is recommended (Table VI), although newer generation DES may also be acceptable. Any interruption of DAPT may lead to in-stent thrombosis, especially in types of cancer with increased propensity for thrombosis.

With chemotherapy, DAPT may need to be extended due to the delayed re-endothelialization of the stent [177]. Some agents are thrombogenic, such as cisplatinum and thalidomide, and require an antithrombotic regimen. Others might induce TP, which hampers the use of DAPT. When urgent surgery is needed shortly after PCI, at least one antiplatelet agent should be continued if at all possible. If oral antiplatelet agents must be discontinued, a short acting intravenous IIb/IIIa receptor blocker could be considered until shortly before non-cardiac surgery; however, data are non-existent and this approach remains controversial. Clopidogrel should be restarted after surgery with a loading dose of 300 mg [177].

Digestive tract tumors can pose different problems. In patients undergoing colonoscopy, the presence of CAD is an independent predictor for advanced colon carcinoma [204,205]. In addition, digestive tract tumors may bleed. When antiplatelet therapy must be stopped due to gastrointestinal bleeding, the cardiac complication rate after PCI increased from 2.4% to 5.8% [206]. Initial treatment with balloon angioplasty followed by delayed stenting after recovery from cancer surgery may be an alternative, but this option has less predictable results [177].

USE OF FFR, IVUS, AND OCT TO AVOID UNNECESSARY CORONARY INTERVENTIONS IN CANCER PATIENTS

The limitations of the coronary angiogram in defining the hemodynamic significance of a lesion are well known [207–210]. For example, coronary angiography may overestimate the significance of ostial or side-branch lesions, leading to unnecessary complex interventions [209,210]. FFR has emerged as a powerful tool to determine the functional importance of the lesion [204–206,209,211].

Experience from an unpublished small case series at MD Anderson suggests that deferring cancer patients with FFR greater than 0.75 in order to expedite cancer care (chemotherapy, radiation, or surgery) may not be associated with increased cardiovascular mortality within 1 year. A similar approach in cancer patients with significant LM disease who were evaluated with FFR or IVUS resulted in improved quality of life, early cancer therapy initiation, and reduced hospital stay and costs.

IVUS and OCT should be liberally used to assure adequate stent expansion, apposition and lack of edge dissection [212,213].

SPECIAL CONSIDERATIONS FOR CANCER PATIENTS WHO HAVE RECEIVED RT

After RT, the distribution of CAD has been associated with the location of radiotherapy: for example left breast/chest wall radiation has been associated with disease of the mid and distal left anterior descending artery and distal diagonal branch [214]. Ostial lesions are also more common. The mean time interval for the development of radiation induced CAD in relation to radiotherapy is approximately 82 months (range 59–104) [93] and it generally presents at younger age than the general population, especially in survivors of childhood and adolescence malignancies treated with mediastinal radiation [215]. There are no specific guidelines in the management of patients with radiation induced CAD. The decision on medical therapy or revascularization depends on patient's symptoms, cancer stage, expected survival, and comorbidities. Regarding revascularization both percutaneous intervention and coronary artery bypass graft (CABG) have been used. During PCI, the use of orbital or rotational atherectomy should be considered for heavily calcified lesions. Surgical revascularization may pose difficulties in these patients because of mediastinal fibrosis, with high incidence of complications. In addition, the use of internal mammary artery as a graft may not always be possible due to radiation disease with this vessel itself [94].

SPECIAL CONSIDERATIONS FOR CABG WITH CANCER PATIENTS

When considering CABG, it is essential to consider the tumor stage and general condition of the patient. CABG is intended to reduce cardiac complications during or after noncardiac surgery [177]. CABG and cancer surgery can be performed simultaneously as a one- or two-stage procedure. If a two-stage procedure is preferred, a recovery of 4–6 weeks should be anticipated [216–218]. Pulmonary tumors can be treated simultaneously with CABG through the same incision. This is not necessarily the case for tumors of the digestive tract, due to the risk of mediastinitis [218–220]. Simultaneous CABG and tumor resection has advantages including reducing hospitalization and costs, repeat thoracotomy, complications, and delay in treating the malignancy [218–220]. When available, minimally-invasive and off-pump CABG is preferred, to shorten the recovery period.

Hematological malignancies, such as chronic lymphatic leukemia (CLL), are associated with a dysfunctional immunological state, bleeding, the need for transfusion, a risk of infection, and mortality after cardiac surgery [221–223]. However, cardiac surgery did not result in a long-term negative impact on the course of this malignancy and CLL is not a contraindication for heart surgery [224].

NON-CORONARY INTERVENTIONAL PROCEDURES IN CANCER PATIENTS

Right Heart Catheterization

Right heart catheterization can accurately assess the presence of left ventricular systolic or diastolic heart failure (HF), restriction or constriction physiology [226] and valvular dysfunction [227] (Table VII). It should be used to diagnose and differentiate complications of cancer therapy (i.e., hypoalbuminemia, intra-alveolar hemorrhage, renal failure) and to monitor the left and right ventricular filling pressures. Prior to catheterization, patients with evidence of tumor invasion of the inferior or superior vena cava should undergo thorough imaging studies. In patients with evidence of pulmonary embolism, pulmonary capillary wedge pressure measurements should be avoided on the side of the

TABLE VII. Indications for Non-Coronary Interventional Procedures in Cancer Patients

Procedure	Indications
Right heart catheterization	Evaluation of heart failure, constrictive or restrictive cardiomyopathy, valvular heart disease, pulmonary hypertension, and pericardial disease.
Endomyocardial biopsy	Evaluation of intracardiac tumors, unexplained heart failure associated with suspected anthracycline cardiomyopathy, infiltrative cardiomyopathies, and myocarditis.
Pericardiocentesis	Evaluation of pericardial effusion and symptomatic relief.
Balloon pericardiotomy	Prevention of large malignant pericardial effusion, especially in poor surgical candidates
Balloon aortic valvuloplasty and TAVR	Palliative measure for symptomatic AS (or as a bridge for SAVR/TAVR)

pulmonary embolus (if the side is known). If the procedure is done in the catheterization laboratory, the use of the micropuncture technique, ultrasound-guided access, and the use of a 5F (French) Swan catheter from the right forearm should be considered to reduce the risk of bleeding complications [228].

Endomyocardial Biopsy (EMB)

EMB is widely used for the surveillance of cardiac allograft rejection and for the diagnosis of unexplained ventricular dysfunction or fulminant myocarditis. Current AHA/ACCF/ESC guidelines recommend EMB for the diagnosis of cardiac tumors (with the exception of cardiac myxomas) if four specific criteria are met: (i) a diagnosis cannot be made in any other way, (ii) the diagnosis with EMB will alter therapy, (iii) the success of a biopsy is believed to be reasonably likely, and (iv) the biopsy will be performed by an experienced operator. Tissue samples should be sent in both formalin and gluteraldehyde for hematoxylin and eosin staining and electron microscopy (EM), as unique features of anthracycline injury are seen only on EM. On Congo Red staining for cardiac amyloidosis, EM identifies specific features that confirm the diagnosis of amyloidosis. Frozen sections should be examined to ensure adequate tissue samples for analysis. The use of transthoracic echocardiographic, transesophageal echocardiography (TEE), or intracardial echocardiography (ICE) guidance in combination with fluoroscopy might result in better quality samples, the use of less radiation and early detection of complications [229]. Data on ICE for this purpose is currently limited.

EMB is reasonable in the setting of unexplained HF with suspected anthracycline cardiomyopathy (Class IIa indication, Level of evidence C) as it may result in changes in the chemotherapeutic dose and/or regimen [229]. EMB should not be used for routine monitoring after anthracycline or other chemotherapy treatment.

Pericardiocentesis

The drainage of malignant pericardial effusion is frequently performed on cancer patients for symptom relief or diagnostic purposes. Pericardiocentesis alone is generally inadequate for malignant effusions, given that only one-third of the effusions are controlled and re-accumulation frequently occurs within 24–48 hr [230]. We recommend that pericardiocentesis should be performed in the catheterization laboratory under fluoroscopic and echocardiographic guidance. The access site should be determined by echocardiography based on the route with the shortest and easiest access to the pericardial space. Echocardiographic assistance also allows for the detection of early complications. If a subxyphoid approach is used, care should be taken to avoid trauma to the left lobe of the liver. For intercostal approaches, placement of the needle above the specific rib margin is necessary to avoid damage to the intercostal areas [231]. The use of micro-puncture needle and small sheath size is recommended to minimize procedural risks. The pericardial drain should be maintained for a minimum of 3 days (optimally 5 days) [232].

Balloon Pericardiotomy

Malignant pericardial effusion has a high recurrence rate after pericardiocentesis. Percutaneous balloon pericardiotomy is a simple, safe technique that can be effective in the prevention of recurrence in patients with large malignant pericardial effusion, especially in poor surgical candidates. Several centers have actually adopted that strategy as the initial preferred treatment with low complication rates similar to simple aspiration. The subxiphoid is the standard approach. A dilating balloon containing 30% radiographic contrast medium is advanced over the guide wire to the pericardial border and it is manually inflated to create the window [233,234]. Post-procedure echocardiography and chest radiography are recommended to monitor for possible re-accumulation of pericardial fluid or development of an iatrogenic left pleural effusion.

Balloon Aortic Valvuloplasty and TAVR

Balloon aortic valvuloplasty (BAV) was once the only percutaneous option for severe, symptomatic aortic stenosis (AS). Today BAV is mainly used in combination or as a bridge to surgical aortic valve replacement (SAVR), or transcatheter aortic valve replacement (TAVR). Data

APPENDIX A. Author Relationships with Industry and Other Entities (Relevant)

Committee Member	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational or Other Financial Benefit	Expert Witness
Konstantinos Marmagkiolis, MD	None	None	None	None	None	None
Cezar Iliescu, MD	None	None	None	None	None	None
Cindy Grines, MD	None	None	None	None	None	None
Joerg Herrmann, MD	None	None	None	None	None	None
Eric Yang, MD	None	None	None	None	None	None
Mehmet Cilingiroglu, MD	None	None	None	None	None	None
Konstantinos Charitakis, MD	None	None	None	None	None	None
Massoud Leesar, MD	None	None	None	None	None	None

This table presents the relevant healthcare relationships of committee members with industry and other entities that were reported by authors at the time this document was under development. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of $\geq$5% of the voting stock or share of the business entity, or ownership of $\geq$\$10 000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships no financial benefit is also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.

on TAVR in cancer patients are currently unavailable and cancer patients are excluded in most TAVR programs [235] A recent case series of six cancer patients demonstrated the feasibility of BAV when urgent, noncardiac surgery was necessary [236]. TAVR may be a viable option in cancer patients with acceptable prognoses and severely symptomatic AS. Furthermore, cancer patients may be at higher perioperative risk of mortality with traditional surgical aortic valve replacement due to prohibitive anatomy (i.e., mediastinal fibrosis, severe lung disease, porcelain aorta, and prior thoracic surgeries).

CONCLUSION

The cardio-oncology patient population has been increasing in recent years, with better quality of life and improved survival rates. Invasive cardiac assessment is important for the evaluation and management of concomitant heart disease. This SCAI consensus document aims to indicate special considerations to be addressed by interventional cardiologists when managing this frail patient subgroup. Collaboration between cardiologists and hematologists/oncologists is of prime importance. Further research involving cancer patients is also needed to optimize the care of oncology patients in the CCL.

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