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Authors

Baldassarre, Lauren A
Yang, Eric H
Cheng, Richard K
et al.

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Commentary

Cardiovascular Care of the Oncology Patient During COVID-19: An Expert Consensus Document From the ACC Cardio-Oncology and Imaging Councils

Lauren A. Baldassarre, MD,[1] Eric H. Yang, MD,[2] Richard K. Cheng, MD, MSc,[3] Jeanne M. DeCara, MD,[4] Susan Dent, MD,[5] Jennifer E. Liu, MD,[6] Lawrence G. Rudski, MD,[7] Jordan B. Strom, MD, MSc,[8] Paaladinesh Thavendiranathan, MD, SM,[9] Ana Barac, MD, PhD,[10] Vlad G. Zaha, MD, PhD,[11] Chiara Bucciarelli-Ducci, MD, PhD,[12] Samer Ellahham, MD,[13] Anita Deswal, MD, MPH,[14] Carrie Lenneman, MD, MSCI,[15] Hector R. Villarraga, MD,[16] Anne H. Blaes, MD, MS,[17] Roohi Ismail-Khan, MD, MSc,[18] Bonnie Ky, MD, MSCE,[19] Monika J. Leja, MD,[20] Marielle Scherrer-Crosbie, MD, PhD[21,*]

[1]Affiliations of authors: Section of Cardiovascular Medicine, Department of Medicine, Department of Radiology and Biomedical Imaging, Yale University School of Medicine, New Haven, CT, USA; [2]UCLA Cardio-Oncology Program, Division of Cardiology, Department of Medicine, University of California at Los Angeles, Los Angeles, CA, USA; [3]Cardio-Oncology Program, Department of Medicine, Division of Cardiology and Department of Radiology, University of Washington, Seattle, WA, USA; [4]Section of Cardiology, Department of Medicine, University of Chicago, Chicago, IL, USA; [5]Duke Cancer Institute, Department of Medicine, Duke University, Durham, NC, USA; [6]Cardiology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [7]Azrieli Heart Center, Department of Medicine, Jewish General Hospital, McGill University, Montreal, QC, Canada; [8]Richard A. and Susan F. Smith Center for Outcomes Research in Cardiology, Division of Cardiovascular Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA; [9]Ted Rogers Program in Cardiotoxicity Prevention, Division of Cardiology, Peter Munk Cardiac Centre, University Health Network, University of Toronto, Toronto, ON, Canada; [10]Medstar Heart and Vascular Institute, Georgetown University, Washington, DC, USA; [11]Cardio-Oncology Program, Harold C. Simmons Comprehensive Cancer Center, Division of Cardiology, Internal Medicine, UT Southwestern Medical Center, Dallas, TX, USA; [12]Bristol Heart Institute, Bristol National Institute of Health Research (NIHR) Biomedical Research Centre, University Hospitals Bristol NHS Trust and University of Bristol, Bristol, UK; [13]Heart and Vascular Institute, Cleveland Clinic-Abu Dhabi, Abu Dhabi, United Arab Emirates; [14]Department of Cardiology, Division of Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [15]Division of Cardiology, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA; [16]Department of Cardiovascular Diseases, Mayo Clinic College of Medicine, Rochester, MN, USA; [17]Division of Hematology and Oncology, University of Minnesota, Minneapolis, MN, USA; [18]Cardio-Oncology Program, Division of Oncologic Sciences, H. Lee Moffitt Cancer Center, University of South Florida, Tampa, FL, USA; [19]Division of Cardiology, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [20]Division of Cardiovascular Medicine, Department of Medicine, University of Michigan, Ann Arbor, MI, USA and [21]Division of Cardiology, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

*Correspondence to: Marielle Scherrer-Crosbie, MD, PhD, Perelman Center for Advanced Medicine, University of Pennsylvania Cardiovascular Medicine Division, 11-131 South Tower, 3400 Civic Center Blvd, Philadelphia, PA 19104, USA (e-mail: mariellesc110@gmail.com).

Abstract

In response to the coronavirus disease 2019 (COVID-19) pandemic, the Cardio-Oncology and Imaging Councils of the American College of Cardiology offers recommendations to clinicians regarding the cardiovascular care of cardio-oncology patients in this expert consensus statement. Cardio-oncology patients—individuals with an active or prior cancer history and with or at risk of cardiovascular disease—are a rapidly growing population who are at increased risk of infection, and experiencing severe and/or lethal complications by COVID-19. Recommendations for optimizing screening and monitoring visits to detect cardiac dysfunction are discussed. In addition, judicious use of multimodality imaging and biomarkers are proposed to identify myocardial, valvular, vascular, and pericardial involvement in cancer patients. The difficulties of diagnosing the etiology of cardiovascular complications in patients with cancer and COVID-19 are outlined, along with weighing the advantages against risks of exposure, with the modification of existing cardiovascular treatments and cardiotoxicity surveillance in patients with cancer during the COVID-19 pandemic.

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The first case of coronavirus disease 2019 (COVID-19) was reported to the World Health Organization on December 31, 2019, and at the time of this writing, there are more than 40.6 million confirmed cases worldwide—8.27 million of which are in the United States—with more than 1.1 million reported deaths (1,2). Cardiovascular complications of COVID-19 were recognized early in the pandemic and include myocardial injury that can be due to acute coronary syndrome; myocarditis; disseminated intravascular coagulation or cytokine storm; cardiac arrhythmias, including malignant arrhythmias; arterial and venous thromboembolism; heart failure; and cardiogenic shock (3). Recent data also demonstrate subclinical myocardial dysfunction early post recovery from the infection (4).

Cardio-oncology patients (patients with active/prior cancer at risk for, or with cardiovascular disease [CVD]) are a rapidly growing population who are at increased risk both of infection by COVID-19 and of experiencing severe and even lethal complications when infected. It is well recognized that immunocompromised individuals, such as patients with cancer or diabetes, are more prone to viral infections (5). Patients with cancer have reduced physiologic reserve from underlying disease and, in many cases, prior cardiotoxic exposure, resulting in a higher risk for cardiovascular complications (6). A nationwide analysis from China demonstrated that 1.1% of patients hospitalized with COVID-19 had a history of cancer (7). A subsequent review of 13 studies (2 in Italy, 11 in China), encompassing close to 5000 patients with symptomatic COVID-19, reported that the pooled prevalence of cancer cases in COVID-19–infected patients was 4.5% (95% confidence interval = 3.05% to 5.74%) (8).

In COVID-19–infected patients, the presence of cardiovascular risk factors, established CVD, and cancer have been associated with increased severity of COVID-19–related disease and mortality (7,9). In a meta-analysis of 6 studies including 1527 hospitalized patients, the risk of being in the intensive care unit was threefold higher for patients with cardiac or cerebrovascular disease and twofold higher for patients with hypertension (10). The adverse effect of cardiovascular risk factors and cardiac diseases on the prognosis of patients with COVID-19 has been confirmed in studies from Italy (11) and the United States (12). A report of the World Health Organization–China Joint Mission on COVID-19 showed that individuals at highest risk for severe disease and death from COVID-19 included those with CVD or cancer. Although patients with no comorbidities had a case-fatality rate of 1.4%, rates were much higher for those with hypertension, CVD, or cancer, with case-fatality rates of 8.4%, 13.2%, and 7.6%, respectively (13). More recently, 2 multicenter studies of more than 800 patients each have been published, emphasizing the association of cancer with increased COVID-19 severity and death (14,15). The COVID-19 and Cancer Consortium registry, based in the United States, Canada, and Spain, reported 13% mortality within 30 days of COVID-19 diagnosis in patients with a median age of 66 years old and with cancer. The UK Coronavirus Cancer Monitoring project reported 28% mortality within 30 days, a higher rate possibly explained by older and sicker patients. In comparison, unselected patients aged 60-69 years have a mortality rate attributed to COVID-19 of 6.7% (16). Therefore, cardio-oncology patients are at heightened risk from COVID-19.

Cardio-oncology patients require targeted cardiovascular screening and monitoring, particularly if they are being actively treated with or have had past exposure to potentially cardiotoxic therapies. The COVID-19 pandemic raises specific questions regarding how to conduct screening, surveillance, and treatment of this unique population, especially because many patients will need ongoing cancer treatment. Such recommendations must be weighed against the risk of exposure to COVID-19.

In this expert consensus document, the Cardio-Oncology and Imaging Councils of the American College of Cardiology offers recommendations to clinicians regarding the cardiovascular care of cardio-oncology patients at the time of the COVID-19 pandemic (Table 1).

Consultations for the Cardio-Oncology Patient

Cardio-oncology patients have complex medical issues that require multidisciplinary involvement from their healthcare providers. Given the risks of exposure to both provider and patient with in-person consultation, consideration should be given to the need for and acuity of consultations on an individual basis guided by an ongoing discussion of risks and benefits. Should a consultation be deemed necessary, telehealth and other web-based platforms should be preferentially used if the reason for consultation permits. From the patient perspective, telehealth may streamline the process of meeting with providers from different subspecialties and cardio-oncologists, particularly if they are at different locations, while minimizing potential exposure. For outpatient diagnostic testing, some services, including ambulatory rhythm monitoring to assess for arrhythmias, can be sent to the patient's residence. Additionally, wearable devices used to assess performance status may have utility, as they have been shown to predict clinical outcomes in cancer patients (17). If a face-to-face encounter is necessary, proper personal protective equipment (PPE) should be donned by staff with universal masking of cardio-oncology patients to avoid droplet transmission. Sparing and judicious use of diagnostic testing is recommended to facilitate necessary and time-sensitive treatments that are expected to directly affect patient outcomes. If testing availability permits, cardio-oncology patients undergoing elective but necessary procedures and/or hospital admission should be tested for COVID-19 beforehand. Procedures such as cardiac surgery, transcatheter structural valvular interventions, and cardioversion for arrhythmias should be reserved for patients who are symptomatic and/or hemodynamically unstable despite medical therapy. When needed, procedures such as pericardiocentesis should ideally be carried out in a negative pressure setting with staff donning the appropriate PPE. Further published recommendations have been discussed in other society statements (18-20).

Multimodality Cardiac Imaging in Oncology Patients During the COVID-19 Pandemic

During the era of the COVID-19 pandemic, when most oncology patients continue to receive cancer treatment and remain at elevated risk both for cardiotoxic exposure and infection, certain considerations for indicated cardiac imaging studies warrant addressing. Here, we highlight the different cardiac imaging modalities and specific clinical scenarios most applicable to cardio-oncology patients. Given the need to protect patients and service providers from spreading the virus, proposed modifications to the current practice of cardiac screening and monitoring during cancer treatment are discussed. In addition, it is important to be aware of the dynamic changes in the choice of cancer treatment, such as prioritization of surgery or neoadjuvant chemotherapy, depending on the cancer type and stage, response to treatment, and the patients' individual goals of

Table 1. Special considerations for the cardio-oncology patient during the COVID-19 pandemic[a]

Cardio-oncology aspect of care	Areas of concern	Proposed strategies to mitigate COVID-19 exposure
Patients undergoing or about to initiate cancer treatments (eg, chemotherapy, targeted therapies, immunotherapy, SCT, CAR-T) or oncologic-related surgery	Compromised immune systems may make patient more susceptible to COVID-19 Certain cancer types (ie, lung) and treatments may put patients at increased risk of severe COVID-19 infection Cancer treatments may require healthcare facility or inpatient stay exposing patient to asymptomatic carriers (ie, HCW) Inpatient beds used for cancer treatments may be diverted to accommodate COVID-19 patients in a "surge" Delaying of potential critical, life-prolonging surgery because it may be considered "elective"	Universal PPE and social distancing during cancer treatments in outpatient and inpatient settings and with family members Multidisciplinary discussion of optimizing timing of cancer treatments or surgery to minimize exposure to inpatient healthcare setting Preprocedural and preadmission screening and testing for COVID-19 Consideration of telemedicine for routine follow-up cardio-oncology or oncology visits if no active clinical issues
Cardiotoxicity experienced during cancer treatments (eg, cardiomyopathy, arrhythmias, ischemic events)	Further delay of cancer treatments and cardio-oncology evaluation because of COVID-19 may increase comorbidity and mortality Cardiac imaging may be delayed due to reallocation of resources Cardiac imaging and testing may cause further exposure to asymptomatic carriers and depletion of PPE	Inpatient admission and noninvasive or invasive evaluation as clinically indicated for severe symptoms from arrhythmias, heart failure, or acute coronary syndrome Telemedicine for patients for routine monitoring, such as CVD risk factor modification, and/or patients who are clinically stable Preemptive aggressive treatment for suspected symptoms related to CAD, arrhythmias, or HF, and deferring of imaging unless clinically necessary Ambulatory rhythm monitors for patients to evaluate suspected or known arrhythmias
Cardiotoxicity surveillance in cancer patients during and after treatment	Some cancer treatments (eg, clinical trial drugs, anti-HER2 treatments) require frequent surveillance of cardiac function Patients with known cardiotoxicity or known treatments that can cause long-term cardiotoxicity (ie, anthracyclines, radiation) may not receive timely surveillance cardiac imaging	Reserve cardiac imaging for patients who are high risk or symptomatic or who require imaging to proceed with cancer therapy Multidisciplinary discussion with hematologist or oncologist about widening surveillance intervals if or when possible Limited imaging protocols to evaluate LVEF to minimize acquisition time Telemedicine for patients with medical issues that do not likely require face-to-face evaluation (ie, blood pressure, lipid management, stable CHF) Defer asymptomatic long-term cancer survivor surveillance (ie, assessment of LVEF and valvular function)
Education and research efforts of cardio-oncology field	Possible detrimental effects on education of trainees and healthcare workers with less face-to-face time with patients and related cardiac imaging studies Decreased revenue from lower patient volume may affect programmatic and research support Less access to didactics related to cardio-oncology	Emphasis on telemedicine in allowing more patient exposure to trainees and healthcare workers interested in cardio-oncology Virtual educational cardio-oncology didactics on local, institutional, and national level as well as "attending" virtual national meetings using video-based platforms Usage of platforms to hold multidisciplinary meetings regarding patient care Multi-institutional collaborations and grant applications evaluating effects of COVID-19 pandemic on cardio-oncology population and systems of care

[a]CAD = coronary artery disease; CAR-T = chimeric antigen receptor therapy; COVID-19 = coronavirus disease 2019; CVD = cardiovascular disease; HCW = healthcare workers; HF = heart failure; LVEF = left ventricular ejection fraction; PPE = personal protective equipment; SCT = stem cell transplantation.

Table 2. Recommended modifications to LVEF surveillance during the COVID-19 pandemic[a]

Stage of cancer treatment	Anthracycline	Anthracycline→anti-HER2	Anti-HER2 (no anthracycline)
Baseline (before treatment)[b]	All patients: check LVEF	All patients: check LVEF	All patients: check LVEF
During treatment[b]	Check LVEF at doxorubicin equivalent dose >250 mg/m^2 Repeat LVEF at doxorubicin equivalent dose ≥400 mg/m^2, then every 1-2 cycles thereafter	All patients: check LVEF at 3, 6, and 12 months	High risk[d]: check LVEF at 3, 6, and 12 months Non–high risk[e]: check LVEF at 6 and 12 months Beyond 12 months (metastatic disease), defer[c]
After completion of treatment	Defer LVEF assessment[c]	—	—

[a]These recommendations only apply to patients with no prior cardiac dysfunction, those who maintain normal cardiac function during surveillance (LVEF ≥ 55%), and those without any cardiac symptoms. Any question of case-specific surveillance for a patient, especially if there is any concern of cardiac disease or symptoms, should prompt a cardio-oncology consultation. Additionally, beyond patient- and treatment-specific risks, all of these recommendations depend on the time and regional variance of COVID-19 risk. CAD = coronary artery disease; COVID-19 = coronavirus disease 2019; LVEF = left ventricular ejection fraction.

[b]Recommend medical providers to coordinate LVEF with other appointments to minimize exposure.

[c]Duration of deferral is based on time-dependent regional prevalence of COVID-19 pandemic and risk of exposure.

[d]Patient-specific risk factors that are considered high risk for developing cardiac dysfunction include any of the criteria: older age (>60 years), 2 or more traditional cardiovascular risk factors (smoking, hypertension, diabetes, hyperlipidemia, obesity), prior cardiotoxic cancer therapy or mediastinal irradiation, compromised cardiac function (LVEF < 55%, more than moderate valvular heart disease, or CAD).

[e]Patients are considered nonhigh risk if they do not meet any of the following criteria: older age (>60 years), 2 or more traditional cardiovascular risk factors (smoking, hypertension, diabetes, hyperlipidemia, obesity), prior cardiotoxic cancer therapy or mediastinal irradiation, or compromised cardiac function (LVEF < 55%, more than moderate valvular heart disease, or CAD).

care. These conditions remain dynamic, and such recommendations are subject to change as the COVID-19 crisis evolves.

The following summary and recommendations are proposed as a clinical approach to adopt during the pandemic while optimizing cardio-oncology care. Currently published statements from cardiac imaging societies delineate the timing and prioritization of cardiac imaging studies in the general patient population during the COVID-19 pandemic, including recommendations for laboratory safety and PPE use (18,21-26). However, the urgency and timing of imaging studies specifically in cardio-oncology patients must be carefully considered, especially because cancer treatment must be continued in many patients, as holding these treatments may decrease survival (27).

In both COVID-19–positive and –negative oncology patients, the risk-vs-benefit decision for obtaining cardiac imaging studies for each individual case should be carefully evaluated when considering modifications from standard practice. Additionally, there may be variations in institution protocols and recommendations to decrease exposure, which should be followed. Finally, it is important to be aware of geographic variability of COVID-19 infections, which can affect changes to practice. Our goal is to provide a framework and facilitate optimal use and coordination of cardiac imaging studies to minimize risk and meet cancer treatment needs during the pandemic.

Transthoracic echocardiography (TTE) is the mainstay tool in the detection and surveillance of cancer therapy–related cardiac dysfunction (CTRCD) (28,29) because of its availability, feasibility, and cost-effectiveness. It is also the most affected modality by the pandemic given its high use and associated risk of transmission due to proximity of the performing staff to the patient. Point-of-care ultrasound (POCUS) allows for a limited cardiac ultrasound at the bedside, and these small devices are easier to disinfect and potentially limit viral transmission. An initial POCUS study can screen and diagnose important cardiovascular findings and help guide need for follow-up TTEs. Specifically in cardio-oncology patients with known or suspected COVID-19, it can help to distinguish between cardiac and/or pulmonary etiologies of dyspnea, which can stem from several potential sources in a cancer patient, including left ventricular (LV) dysfunction from exposure to cardiotoxic therapies, malignant or inflammatory pericardial effusions, heart failure, or other COVID-19–related sequelae. POCUS has also been used for assessment of venous thromboembolism, and given COVID-19 has been associated with an increased risk of thrombosis (30), oncology patients may be particularly at risk for venous thromboembolism in the setting of their underlying malignancy, compounded by COVID-19 infection (31).

Transesophageal echocardiography is considered an aerosol-generating procedure, and it is advisable to reserve transesophageal echocardiography for circumstances in which the information obtained is deemed imminently essential to the management of the patient and the information cannot be obtained from other modalities. Due to its high accuracy for LV ejection fraction (LVEF) assessment and ability to assess pericardial disease, myocardial inflammation, fibrosis, and scar burden, cardiac magnetic resonance (CMR) imaging has a unique role in cardio-oncology (32,33). Although the routine use of multigated radionuclide angiography in cardio-oncology is declining because of concerns of cumulative radiation exposure, it offers an alternative assessment of LVEF with minimal contact between patients and technicians (34). Cardiac computed tomography (CCT) has emerging clinical value in cardio-oncology for pretreatment CVD risk assessment, evaluation of CVD or suspected toxicity during cancer treatment, and in survivors post treatment (35). CCT may function as an alternate to stress testing to assess coronary artery disease (CAD) in low- to intermediate-risk patients.

Imaging for Cardio-Oncology-Specific Clinical Scenarios

Screening and Monitoring of Cardiac Function Before, During, and After Cancer Therapy

Early recognition of CTRCD provides an opportunity to mitigate cardiac injury and risk of late cardiac events, which is the centerpiece of cardio-oncology care. Current expert consensus–based surveillance strategies during cardiotoxic

Table 3. Imaging choices in cardio-oncology scenarios

Patient case scenario	Imaging modalities to consider
New-onset cardiomyopathy while on cardiotoxic treatment (ie, anthracyclines, anti-HER2, proteasome inhibitors) (29)	TTE[a] CMR[a] MUGA CCTA (to evaluate for underlying ischemia)
Myocarditis (ie, immune checkpoint inhibitors, or secondary to COVID-19) (41)	TTE[a] CMR[a] (should be performed because patients with myocarditis can have a normal LVEF) (42–44) PET (limited data) (45)
Cardiac masses (ie, metastatic vs primary tumors)	TTE [a] CMR[a] TEE PET CCTA
Atrial fibrillation and intracardiac thrombus [cancer is an independent risk factor for atrial fibrillation (46) as well as some cancer therapies (ie, ibrutinib)] (47).	CCTA[a] to assess left atrial appendage thrombus (48) TEE (typically first line, but due to concern for aerosolization CCT can be an option) TTE with agitated saline injection for patent foramen ovale (in setting of stroke) CMR if concern for ventricular thrombus
Ischemic heart disease [preexisting, as many cancer patients with increased risk of CAD (49) vs acquired from cancer therapy (radiation, tyrosine kinase inhibitors including ponatinib) (50), evaluation of chest pain from 5-FU]. Routine CAD screening, such as for asymptomatic survivors of childhood cancers and others with radiation exposure, can be deferred (51).	CCTA[a] Functional stress testing (exercise less ideal given concern for aerosolization, pharmacologic preferred via nuclear [PET, SPECT] or CMR) (52)
Valvular disease, including endocarditis [valvular disease can be a consequence of radiation and chemotherapy treatment for cancer (53)] and infective endocarditis can occur in oncology patients and is associated with worse outcomes (54).	TTE[a] TEE (for endocarditis evaluation, consider deferral if transthoracic echocardiogram imaging adequate; can consider if information from transesophageal echocardiogram will imminently change management) CCT (paravalvular abscess assessment) or CMR (structural assessment)
Pericardial diseases	TTE[a] CMR[a] CCT
Pulmonary hypertension, preexisting vs acquired (ie, tyrosine kinase inhibitors including desatinib) (55)	TTE[a] CMR (can provide accurate right ventricular function and myocardial tissue characterization)

[a]Modalities are considered first line. However, ultimately, there should be multidisciplinary discussions with cardiology or cardio-oncology to decide the most high-yield and safest imaging modality of choice for a patient's specific disease state. CAD = coronary artery disease; CCT = cardiac computed tomography; CCTA = cardiac computed tomography coronary angiography; CMR = cardiac magnetic resonance; COVID-19 = coronavirus disease 2019; MUGA = multigated acquisition scan; PET = positron emission tomography; TEE = transesophageal echocardiogram; TTE = transthoracic echocardiogram; SPECT = single photon emission computed tomography.

therapy are largely guided by treatment-related risks and patient-specific risk factors (29,36). However, the exact frequency and intervals of monitoring vary among clinical practice. Baseline imaging for ventricular function before treatments is ideal to perform, because the incidence of cardiotoxicity remains elevated in modern clinical trials. The CECCY trial, which comprised anthracycline chemotherapy, had an incidence of 13.5%-14.5% (37), and Guglin et al. (38) showed a 29%-32% incidence of cardiotoxicity—defined as a decline in LVEF—in patients receiving trastuzumab with and without anthracyclines, all defined as an decline in LVEF. In addition, insurance coverage for cancer treatments may require LVEF assessment before initiating treatment. Thus, risks and benefits of widening the frequency and type of cardiotoxicity surveillance should be individually weighed and determined for each patient, depending on their risk factor profile, with the imaging and PPE resources available.

The following expert consensus for screening and monitoring of cardiac function in patients treated with anthracyclines and/or trastuzumab is summarized in Table 2.

It is acknowledged that current guidelines mostly focus on anthracyclines and HER2-targeted agents but provide limited if any guidance for cardiac monitoring of other anticancer agents. This is mostly due to the limited and short-term cardiovascular data from clinical trials of those other agents. However, it is reasonable to obtain baseline LVEF assessment in those considered to be at high risk for CTRCD, with repeat LVEF assessment during therapy if indicated for cardiac-related symptoms. Patient-specific risk factors that are considered high risk are older age (>60 years), 2 or more traditional cardiovascular risk factors (smoking, hypertension, diabetes, hyperlipidemia, obesity),

prior cardiotoxic cancer therapy or mediastinal irradiation, and compromised cardiac function (LVEF < 55%, more than moderate valvular heart disease, or CAD).

LV strain assessment can be important in the identification of CTRCD. However, it should only continue to be performed if it does not notably lengthen the acquisition time of the TTE.

Monitoring with serial troponin and/or brain natriuretic peptide (BNP) has been proposed to reduce frequency of imaging (39), and promising data have been collected in the research setting (40). The European Society of Medical Oncology recommends measurements of troponin-I or troponin-T, BNP or N-terminal pro-BNP every 3 to 6 weeks or before each cycle, with 99% upper limit of normal being the threshold (39). The optimal timing of the blood draw and recommendations on therapeutic decisions based on the results are lacking. However, if serum biomarkers are checked, it is recommended they coincide with patient routine treatment–related blood draws to minimize healthcare setting exposures during the pandemic.

Other clinical scenarios are summarized in Table 3.

The Patient With Cancer and COVID-19: What Are the Specific Challenges?

Cancer patients are at high risk of developing more severe COVID-19–related disease than noncancer patients. However, it is not known if prior exposure to potentially cardiotoxic anticancer treatment may modify the cardiac response to COVID-19 infection.

The Cancer Patient With Suspected or Confirmed COVID-19 Infection

Before cancer treatment, the decision and timing of when to start should be based on the likelihood that urgent therapy and/or surgery will be disease modifying. The need to mitigate exposure risk to healthcare workers and other cancer patients must be considered (56). Additionally, given the concerns of known cardiovascular injury with COVID-19 (7,61-64), active treatment with cardiotoxic agents should be avoided if possible until resolution of COVID-19 infection in cancer patients. For most patients, cancer therapy will likely be held in the setting of active COVID-19 infection (57).

Even in the absence of active cancer treatment, patients with CVD and cancer who are infected with COVID-19 are at increased risk of severe disease and require close surveillance. Modern technology platforms should be used for remote monitoring.

For patients on active cancer treatment who are infected with COVID-19, holding cancer therapy will be considered in most patients, especially those with cardiovascular risk factors.

The interplay of inflammation, cancer, and CVD is complex. Although there is an underlying proinflammatory state in patients with cancer or CVD (58), modern cancer therapies can exhibit complex immunological effects by not only directly targeting malignant cells with “on-target” effects but also depleting circulating or tumor-infiltrating immunosuppressive cell populations resulting in immunomodulation via “off-target” effects (59). In COVID-19 patients with acute myocardial injury, a subset of patients demonstrates hyperinflammation consistent with cytokine storm (60). Thus cardio-oncology patients with COVID-19 should be closely monitored for these inflammatory states.

Many diagnostic dilemmas in cardio-oncology can occur, which pose more challenges in the setting of the COVID-19 pandemic. For example, elevations in cardiac biomarkers are common, and cardiomyopathy can occur with COVID-19 infection (7,61-64). Troponin levels can be elevated in the setting of COVID-19 infection, which may be suggestive of worse outcomes (61). Cardio-oncology patients with COVID-19 with recent cancer treatment may demonstrate elevations in troponin or LV dysfunction, making it challenging to differentiate between COVID-19–mediated injuries, cancer therapy–related cardiotoxicity, and acute coronary syndrome.

Conversely, though biomarker elevation denotes an increased risk in cardio-oncology patients receiving cardiotoxic chemotherapy (65), their elevation in COVID-19–infected patients may not imply a similarly elevated oncologic-specific risk, but may be relatedto the infection instead.

Additionally, an elevated troponin or BNP may be nonspecific for acute ischemic or thrombotic pathology if the patient is undergoing active anthracycline and/or anti-HER2 treatments; in which case, this elevation may be a marker of subclinical cardiotoxicity (66).

Other agents, such as certain tyrosine kinase inhibitors (ie, ponatinib) or fluoropyrimidines (5-fluorouracil–based agents) can induce actual ischemic events via thrombotic or vasospastic mechanisms, which may require more invasive diagnostic modalities (55,67). COVID-19 infection may, as do other severe viral infections, increase the risk of plaque rupture and the occurrence of acute coronary syndrome (68).

In addition, biomarker elevations with some treatments have been associated with clinically significant declines in cardiac function or worse outcomes, such as proteasome inhibitor cardiotoxicity (ie, carfilzomib) (69) or cytokine release syndrome during chimeric antigen receptor therapy (70), which may warrant more intensive monitoring and management.

Patients undergoing immune checkpoint inhibitor (ICI) therapy also may exhibit elevated cardiac biomarkers, which may be nonspecific but may raise the concern of ICI-associated myocarditis (42). It is important to recognize ICI-associated myocarditis early and treat with immunosuppressant medications (ie, steroids). The difficulty in proceeding with immunosuppressant agents is compounded by the fact that COVID-19 itself can manifest with clinical features of myocarditis (3). Thus, a thorough multidisciplinary evaluation, factoring in duration and timing of prior ICI treatment, signs of cardiac inflammation (eg, abnormal electrocardiographic findings, arrhythmias, abnormal TTE and/or CMR findings), and assessment of other signs of ICI toxicity (71) should be performed (72). Noninvasive imaging modalities, such as CMR and CCT coronary angiography, are preferred as the first imaging approach in a patient with suspected ICI-associated myocarditis and possible or confirmed COVID-19 infection. However, if the diagnosis cannot be established, pursuing endomyocardial biopsy should be considered, particularly in patients with hemodynamic instability and if it will change management of the patient.

Following cancer treatment, patients may be at increased risk for cardiovascular injury related to direct effects of treatment or immunological effects of therapy. Those with active COVID-19 infection should self-isolate but be more cognizant of signs or symptoms suggesting progressive disease, with a low threshold to seek medical care.

There are no data on the effect of COVID-19 on patients with chemotherapy-induced cardiomyopathy, but underlying CVD may be associated with higher risk for adverse outcomes. Risk factors that have been associated with chemotherapy-induced

cardiomyopathy such as hypertension, diabetes, and CAD have also been associated with worse prognosis with COVID-19 infection (7,61-64).

The Cancer Patient With Resolved COVID-19 Infection

Postrecovery from active COVID-19 infection, cancer patients with either overt or subclinical myocardial injury should undergo repeat cardiac imaging before their next treatment cycle.

It is reasonable to image recovered cancer patients with risk factors for cardiotoxicity (hypertension, diabetes, CAD). Cardiac biomarkers can be considered and compared with those that may have been drawn during the course of the COVID-19 infection.

Registry data of recovered COVID-19–positive patients receiving cancer treatments will allow a better understanding of the short and intermediate risk for cancer therapy–related cardiotoxicity.

Modification of Cardiovascular Treatments

The principles of cardioprotective pharmacologic intervention for the cardio-oncology patient remain unchanged and should be guided by an assessment of an individual patient's risk profile; however, in the COVID-19 era, additional complexities have arisen regarding overlapping cardiac medications and COVID-19 infection.

Angiotensin Converting Enzyme Inhibitors or Angiotensin Receptor Blockers

Initial concerns were raised about the use of angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) in COVID-19 infection (73). The causative pathogen in COVID-19, the Severe acute respiratory syndrome coronavirus-2 virus (74), binds to the spike protein of angiotensin-converting enzyme 2, a membrane-bound immunopeptidase highly expressed in lung and heart tissue, facilitating viral entry into the respiratory epithelium (75,76). Because angiotensin-converting enzyme 2 levels may be elevated in patients on ACEi and ARBs (75) and a higher risk of adverse complications has been noted in patients with preexisting CVD (62,77), there was initial controversy surrounding continued ACEi and ARB use in COVID-19 infections. Society guidelines recommend against withdrawal of these therapies due to the risk of hypertension and resulting kidney injury that may result (78,79). Moreover, the results of 2 meta-analyses, 31 observational studies, and interim results from at least 1 randomized controlled trial indicate that ACE inhibitors and ARBs are not associated with either the incidence or severity of COVID-19 infection (80,81). Although there is a signal toward improved outcomes among patients with COVID-19 who continue these medications, the risk-vs-benefit decision of newly initiating these therapies in the context of COVID-19 is an area of active study. Although not stipulated, such guidelines should also apply to angiotensin receptor-neprilysin inhibitors or other medications containing ACE inhibitors or ARBs. Beta blockers can be considered as first line for cardioprotective therapy in patients treated with cardiotoxic therapy and/or with CTRCD. In individuals with chemotherapy-induced LV dysfunction already prescribed ACE inhibitors or ARBs, these medications may contribute to positive ventricular remodeling (82) and should be continued in the setting of COVID-19 infection.

Anticoagulants

Based on multiple reports (62,83), elevated clotting factors such as D-dimer, PT, and fibrinogen have been associated with worsened septic coagulopathy and outcomes in COVID-19–infected patients. Among cancer patients with COVID-19, 1 study found that 39% have an elevated D-dimer (84). The International Society of Thrombosis and Haemostasis has put forth guidelines recommending the use of low–molecular-weight heparin (LMWH) for thromboprophylaxis in all hospitalized patients (including those noncritically ill) with COVID-19 in the absence of contraindications (ie, active bleeding or platelet count $<25 \times 10^9$/L) (85). In 1 study, individuals with a sepsis-induced coagulopathy score 4 or greater or a D-dimer value greater than sixfold the upper limit of normal had a lower in-hospital mortality with LMWH prophylaxis (86). Additionally, LMWH has been shown to have antiinflammatory properties that may be useful adjunctively in treating COVID infection (87). Continuation of anticoagulation post hospitalization can be considered in some patients considered at low risk for bleeding and at high risk for VTE, although it is not routinely recommended in all patients upon discharge (88). As with all anticoagulants in cancer patients, the benefits of treatment must be weighed against the risk of hemorrhage on an individual basis and warrant further study (89).

QT Interval Prolongation From COVID-19 or Cancer-Related Treatments

Several agents being investigated in the treatment of COVID-19 (eg, chloroquine, hydroxychloroquine, lopinavir, ritonavir, and azithromycin) have been implicated in corrected QT (QTc) prolongation and sudden cardiac death; caution is advised in starting these medications, and drug–drug interactions should be evaluated (90). Cardio-oncology patients may be receiving QT-prolonging cancer therapy (eg, arsenic) or medications (eg, antifungals and antiemetics) at baseline and therefore may be more susceptible to electrolyte disturbances that can cause further QTc prolongation. To reduce the risk of torsade de pointes, QT-prolonging COVID-19 medications should not be initiated in patients with a baseline QTc of 500 milliseconds or longer or with known congenital long-QT syndrome (90). Aggressive repletion of electrolytes (ie, potassium, magnesium) should be performed in all patients. For cardio-oncology patients starting QTc-prolonging agents, it is reasonable to monitor their QT interval with more frequent electrocardiograms and withdraw the medication if the QTc exceeds 500 milliseconds (90,91).

What Happens After the Pandemic?

The COVID-19 crisis will resolve geographically at different rates and times, with the entire course of the pandemic likely lasting into 2021. The unprecedented impact the pandemic has had overall on the field of medicine has also considerably affected the practice of cardio-oncology. Because there has been widespread cancellation and postponement of nonurgent consultations, diagnostic tests, and procedures for numerous indications, cancer patients may be competing for a period of time with other patients for access to healthcare resources. The pandemic has also complicated cardio-oncology education for trainees, a field that has already generated much discussion and debate on an optimal training curriculum needed to

achieve competence (92,93). From a research standpoint, the suspension of laboratories and research programs, and decreasing clinical volume and revenue may potentially affect programmatic stability; efforts and research funding should be directed to understand the impact of COVID-19 on the cardio-oncology population (94). This may occur through registries and quality improvement initiatives to evaluate how the pandemic has affected systems of care in both the cardiac and cancer realms.

However, the pandemic has also been a catalyst to increase remote learning and care. From a training standpoint, fellowship programs have made the transition to virtual didactics and meetings (95); although a certain element of depersonalization may permeate throughout these interactions, educational resources and lectures (ie, grand rounds) that were previously institutionally exclusive now have the ability to be viewed anywhere in the world. This can potentially disseminate ideas, education, and research collaborations in a more rapid fashion. Virtual platforms can also be held in a multidisciplinary fashion to discuss cardio-oncology patient care, and trainees overall can be involved in the telehealth aspect of cardio-oncology care. It is possible that telemedicine will play a much more dominant role in outpatient care in the post-COVID-19 era and will be pertinent to the delivery of medical care as a whole.

Collaboration between the oncology and cardiology communities will continue to be of utmost importance in taking care of cardio-oncology patients, now even more than ever, during this COVID-19 pandemic. Although this era poses difficulty to the care of these complex patients, it has also challenged practitioners to develop unique and efficient ways to communicate, work together, and approach patient care. Most certainly, the cardio-oncology community will carry these skills into the future and continue to build on this experience to even further strengthen the care of patients in this growing field.

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Author contributions: Lauren A Baldassarre, M.D. (Conceptualization; Supervision; Visualization; Writing –original draft; Writing – review and editing). Eric H Yang, M.D. (Conceptualization; Supervision; Visualization; Writing – original draft; Writing – review and editing). Richard K Cheng, M.D. MSc (Conceptualization; Visualization; Writing – original draft; Writing – review and editing). Jeanne DeCara, M.D. (Writing – original draft; Writing – review and editing). Susan Dent, M.D. (Supervision; Writing – original draft; Writing – review and editing). Jennifer E Liu, M.D. (Writing – original draft; Writing – review and editing). Lawrence G Rudski, M.D. (Writing – original draft; Writing – review and editing). Jordan B Strom, M.D. M.Sc (Visualization; Writing – original draft; Writing – review and editing). Paaladinesh Thavendiranathan, M.D. S.M. (Conceptualization; Supervision; Writing – original draft; Writing review and editing). Ana Barac, M.D. Ph.D. (Conceptualization; Supervision; Writing—original draft; Writing—review and editing). Vlad G. Zaha, M.D. Ph.D. (Writing – original draft; Writing – review and editing). Chiara Bucciarelli-Ducci, M.D. Ph.D. (Writing – original draft; Writing – review and editing). Samer Ellahham, M.D. (Writing – original draft; Writing – review and editing). Anita Deswal, M.D. M.P.H. (Writing – original draft; Writing – review and editing). Carrie Lenneman, M.D. M.S.C.I. (Writing – original draft; Writing – review and editing). Hector R Villarraga, M.D. (Writing – original draft; Writing – review and editing). Anne H Blaes, M.D. M.S. (Writing – original draft; Writing – review and editing). Roohi Ismail-Khan, M.D. M.Sc. (Writing – original draft; Writing – review and editing). Bonnie Ky, M.D. M.S.C.E. (Conceptualization; Supervision; Writing – original draft; Writing – review and editing). Monika J Leja, M.D. (Conceptualization; Supervision; Visualization; Writing – original draft; Writing – review and editing). Marielle Scherrer-Crosbie, M.D. Ph.D. (Conceptualization; Investigation; Supervision; Visualization; Writing – original draft; Writing – review and editing).

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