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Consensus

Risk Management for Radiation-Induced Cardiovascular Disease (RICVD): The 2022 Consensus Statement of the Taiwan Society for Therapeutic Radiology and Oncology (TASTRO) and Taiwan Society of Cardiology (TSOC)

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Advances in cancer management have significantly improved survival in patients with cancers. Cardiovascular complications of cancer treatment are becoming significant competing causes of death in these patients. Radiotherapy is an indispensable component of cancer treatment, and irradiation of the heart and vasculature during cancer radiotherapy is now recognized as a new risk factor for cardiovascular diseases. It is important to involve multidisciplinary expertise and provide practical recommendations to promote awareness, recognize risks, and provide adequate interventions without jeopardizing cancer control. In this consensus paper, experts from the Taiwan Society for Therapeutic Radiology and Oncology and Taiwan Society of Cardiology provide a focused update on the clinical practice for risk stratification and management of radiation-induced cardiovascular disease (RICVD). We believe that implementing RICVD care under a collaborative cardio-oncology program will significantly improve cancer treatment outcomes and will facilitate high quality clinical investigations.

Key Words: Cancer survivorship • Cardio-oncology • Cardiosparing radiotherapy • Radiation-induced cardiovascular diseases

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INTRODUCTION

Cancer has been the leading cause of death in Taiwan for the past four decades. While the annual incidence of all cancers increased from 284 to 492 per 100,000 persons between 1998 and 2018, cancer mortality also increased from 134 to 213 per 100,000 persons. Owing to convenient access to quality cancer care in Taiwan, the slope of cancer-related death has gradually slowed, and for the first time, negative growth was recorded in 2020. Cancer treatment includes surgery, systemic therapy, radiotherapy, and combination of therapies. In the past two decades, there have been great technical improvement in every component. As cancer patients live longer and better after an initial cancer diagnosis, cancer therapy-related health sequelae have become an increasing major concern.

Among these concerns, cardiovascular diseases (CVDs) are the major competing causes of death. In breast cancer survivors, longitudinal studies have revealed that CVD-related mortality continues to rise after a breast cancer diagnosis. Moreover, CVD has been reported to be the dominant cause of death, accounting for 19% of all-cause mortality in women who survived more than 10 years after the initial breast cancer diagnosis.[1] This is because curative anti-cancer treatment inevitably affects the cardiovascular system. Cells in the cardiovascular systems are damaged when exposed to chemotherapeutics, biologically targeted agents, or ionizing radiation. Responses to this damage frequently lead to cardiovascular cell loss and the accumulation of senescent, proinflammatory cells, which in turn activate chronic inflammation, endothelial dysfunction, atherogenesis and tissue fibrosis.[2] These factors result in less functional reserve and vulnerability to CVD and related morbidity.

Most of our understanding of cancer therapy-related CVDs (CTRCVDs) comes from doxorubicin induced cardiotoxicity.[3,4] The disease presents as refractory heart failure in patients who have documented exposure, and the most important risk factor is an accumulated dose of doxorubicin higher than 400 mg/m^2. The onset of CTRCVD may take many years after cancer treatment to become discernible, and the causal role of topoisomerase II β-dependent DNA damage in the pathogenesis indicates a possible genetic basis for individualized vulnerability.[5] As CTRCVD is usually irreversible upon symptomatic presentation, the key to its management focuses on clinically actionable risk factors, which are usually the cancer therapy itself.

Radiation induced cardiovascular disease (RICVD) is no exception. The number of radiotherapy-treated cancer survivors more than doubled from 1.48 to 3.05 million between 2000 and 2016 in the United States.[6] This trend is projected to continue in the next 20 years, with the growth momentum coming from patients with breast cancer, lung cancer and lymphoma. A growing body of evidence has established the causative role of thoracic irradiation in increased the risk of CVD. Since survivors with a history of thoracic irradiation will increase, it is of paramount importance to promote awareness in these patients and cancer/cardiology professionals. In order to update practice guidelines of the 2019 Taiwan Society of Cardiology for the prevention and management of heart failure[7] and to identify the important cardio-oncology issues, experts from the Taiwan Society for Therapeutic Radiology and Oncology and Taiwan Society of Cardiology organized a joint task force to address this important field. In this paper, we provide a focused update on the team structure of a cardio-oncology unit, definition of cardiotoxicity, risk stratification, and cardioprotective strategies.

TEAM STRUCTURE OF A CARDIO-ONCOLOGY UNIT

All patients with cancers should be evaluated for possible cardio-oncology consultation before initiating anti-cancer treatment. It is the expert consensus that high risk patients require co-supervision with cardiologists (preferably with expertise in cardio-oncology) during and after cancer treatment. In order to meet the unmet needs of cardio-oncology services, we recommend establishing a cardio-oncology unit in hospitals to provide cancer treatment.[8]

The basic functions of a cardio-oncology unit are to evaluate baseline CVD risk, to monitor and to manage cardiovascular manifestations during and after cancer treatment, to tailor oncological treatments according to the presence of cardiovascular risks or symptomatic dysfunction, and to maintain standard quality of care delivery. A cardio-oncology team is commonly part of the ex-

isting cardiology service and share key infrastructure and human resources. It is recommended to involve one or more cardiologists with expertise in this field, primary treating oncologists, radiation oncologists, pharmacists, and case managers. The experts usually interact in regular meetings, in addition to clinical referrals and consultations.[9] An outpatient clinic, electrocardiography facility, echocardiography laboratory, and diagnostic laboratory that routinely evaluates cardiac biomarkers are considered basic elements for a cardio-oncology service to offer standard quality of accessible cardio-oncology care as part of integrated cancer care (Figure 1).

Depending on the volume and characteristics of oncology services, it is reasonable to establish a referral system so that cardio-oncology centers can set up resources to provide for in-patient/emergency consultation, advanced cardiovascular imaging [including strain imaging, cardiac magnetic resonance imaging (MRI), and positron emission tomography (PET)] and/or interventions (including myocardial biopsy, catheter ablation, cardiac surgery, and device therapies) for complicated cases such as primary or metastatic cardiac tumors.[10,11] It is also encouraged to direct clinical trials/registries in facilities that host a cardio-oncology center. With these resources, cardio-oncology centers are charged with the additional responsibility of training, maintaining databases, and conducting research.

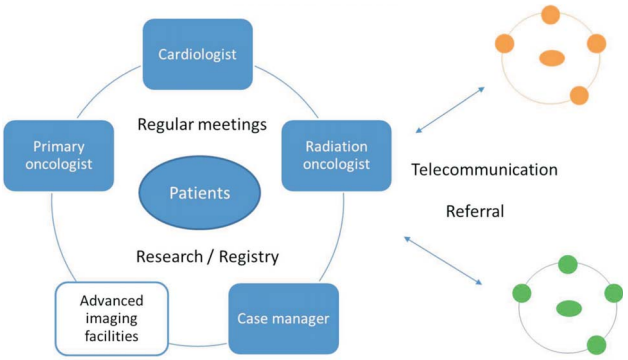

Figure 1. *Structure of a Cardio-Oncology Unit Network. A Cardio-Oncology Unit Network is composed of hospitals that host either a basic cardio-oncology unit or a comprehensive one. A cardio-oncology center (the blue circle) has advanced cardiac imaging facilities and is charged with responsibility for research and registry. A basic cardio-oncology unit (the orange and green circles) hosts cardiology and oncology experts that meet regularly to serve patients. A cardio-oncology center receives referral when advanced imaging facilities or complicated case management is needed. Telecommunication is an essential component for the interaction within the network.*

DEFINITION OF RADIOTHERAPY-INDUCED CARDIOVASCULAR DYSFUNCTION

The definitions of cardiotoxicity secondary to cancer therapies vary widely among international guidelines and clinical trials.[8,12-19] The spectrum of RICVD is versatile, ranging from asymptomatic diastolic dysfunction, heart failure with preserved or reduced ejection fraction (HFpEF, HFrEF), coronary artery disease, acute myocardial infarction, valvular heart diseases, constrictive pericarditis, arrhythmias, carotid artery disease, peripheral vascular disease, and sudden cardiac death. Moreover, the detrimental effects of ionizing radiation on the cardiovascular system appear to be stochastic with linear dose dependence. Except for acute radiation pericarditis, it is generally believed that the pathogenesis of RICVD, as with other CTRCVDs, sequentially goes through early stages of biochemical, mechanical, or mixed dysfunction before symptomatic heart failure ensues.[20] Since time significantly confounds the causal relationship between radiotherapy and CVD events, it is reasonable to consider radiotherapy as a risk factor rather than a trigger of CVD in the heart/vasculature located within the radiation field. Because RICVD, as with all other CTRCVDs, is less responsive to standard therapies once it becomes symptomatic, it is imperative to detect cardiovascular dysfunction early before the point of no return. Considering all these factors, we propose that RICVD should be defined as any cardiovascular dysfunction that occurs in the irradiated field during or after radiotherapy treatment sessions.

The definition of “dysfunction” for RICVD? It relies on laboratory and imaging biomarkers, in addition to clinically detectable cardiovascular symptoms. One of the most widely adopted definitions was reported in the 2016 European Society of Cardiology (ESC) Cardio-Oncology position statement, which defined CTRCVD as any reduction in left ventricular ejection fraction (LVEF) to $\leq$ 50% or a > 10% reduction from baseline that falls below the low normal limit.[21] Using this definition, the detection of cardiotoxicity is feasible and practical at every basic cardio-oncology unit before symptoms inter-

fere with daily activities. This also implies an important opportunity to initiate cardioprotective therapies and avoid symptomatic heart failure owing to RICVD.

However, it has been argued that up to 42% of the reversible CTRCVD/RICVD cannot be detected using the ESC definition,[22] and that more sensitive tools are needed to detect subclinical and reversible cardiotoxicity. Among the advanced cardiovascular imaging techniques, there is an increasing interest in defining RICVD according to a decrease in global longitudinal strain (GLS) of the left ventricle. GLS is derived from speckle tracking of left ventricular apical images and is analyzed offline using image processing software. It describes longitudinal shortening of left ventricular myocardium as a percentage of the diastolic dimension. GLS is a relatively load-independent indicator of left ventricular contractility and is a sensitive tool to detect subclinical left ventricular dysfunction.[23,24] Mediastinal radiotherapy has been reported to result in reversible GLS change below -16% during the course of lymphoma treatment.[25] By incorporating GLS into protocol cardio-oncology evaluations, early initiation/escalation of cardiovascular optimization treatment during cancer therapy may reverse CTRCVD and allow for the completion of cancer therapy without interruption.[26] The use of this technology in routine cardio-oncology evaluation deserves further attention.

In addition to contractile parameters, tissue fibrosis and diastolic dysfunction are significant contributors to the pathophysiology of RICVD. Echocardiography is the first-line tool for the relevant evaluations. Decreased E/A ratio has been found in patients receiving mediastinal irradiation and it has been shown to predict unfavorable cardiovascular outcome.[27] However, the highly variable loading conditions in cancer patients make it challenging to interpret serial E/A measurements. Recently, the introduction of tissue Doppler imaging and the application of contrast enhanced cardiac MRI have partially improved the assessment of diastolic dysfunction in RICVD. Due to limited MRI scanner capacity in general, it is not feasible to routinely schedule cardiac MRI for cardio-oncological evaluations at every hospital. However, in patients with technical challenges for standard quality echocardiographic assessments or in those with complex heart disease history, cardiac MRI provides an excellent alternative to evaluate cardiac structure and function. As it provides rich information on tissue characteristics and microvascular dysfunction, cardiac MRI is especially useful to detect the presence of asymmetric interstitial fibrosis and myocardial edema, which are all hallmarks of RICVD.

The role of cardiac computed tomography (CT) in RICVD risk stratification has been overlooked in the past. However, cardiac CT and the resultant coronary calcium analysis is a valuable risk stratification tool as indicated in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines on the primary prevention of coronary artery disease in asymptomatic populations.[28] Of note, an elevated coronary calcium score helps to identify high risk subjects when the 10-year atherosclerotic cardiovascular disease (ASCVD) risk score falls in the intermediate category.[29] This is especially relevant to RICVD because when considering risks from cancer treatment and radiotherapy, a significant proportion of cardio-oncology patients may fall in this category. Furthermore, coronary calcium score calculated from a non-contrast simulation CT scan, which is a routine image for radiotherapy treatment planning, has been highly correlated to coronary calcium score obtained from a dedicated cardiac CT scan.[30] A study of Taiwanese breast cancer patients reported that adjuvant radiotherapy was associated with increased coronary calcium burden in a dose-dependent manner.[31] The value of this approach was also demonstrated in a small breast cancer series, in which coronary calcium analysis from simulation CT identified 44% women scheduled for breast irradiation at high CVD risk and who never received the recommended treatment.[32] Therefore, radiation oncologists in a cardio-oncology unit may play an active role by reporting abnormal coronary calcium findings and by providing cardio-oncology referral.

The role of nuclear imaging in cardio-oncology practice is yet to be clearly defined. While single-photon emission computed tomography (SPECT) images have been used to investigate perfusion defects associated with radiotherapy in clinical study settings, fluorodeoxyglucose-positron emission tomography (FDG-PET) provides semi-quantitative functional evaluations of myocardial metabolism. Moreover, serially increased FDG uptake has been associated with a decline in LVEF in patients receiving doxorubicin-containing chemotherapy.[33] Although topographically increased cardiac FDG uptake in the irradiated myocardium has been shown,[34] and its

correlation with localized myocardial perfusion defects and cardiac mortality has been demonstrated,[35,36] the diagnostic efficacy of FDG-PET for RICVD has yet to be established. As PET/PETCT has been increasingly used for cancer staging and follow-up, a more practical approach to incorporate PETCT in cardio-oncology care will start from the systemic retrieval of information for cardio-oncology interpretation from cancer diagnostic scans. In addition to myocardial evaluation, arterial FDG uptake has also been associated with the risk of subsequent cardiovascular events.[37] This may also be valuable information from a cardio-oncology point of view to maximize the value of PET images obtained during routine cancer workup and follow-up.

Serial multigated acquisition SPECT scans (MUGA), another nuclear cardiology imaging modality, was used to evaluate ejection fraction. However, because of the relatively limited information, inherent test-to-test variation, and concerns over significant radiation exposure (7.8 mSv per study), the use of MUGA scans has significantly decreased in the past decade in oncological patients.[38]

An apparent limitation with imaging biomarkers for RICVD is the limited service capacity compared to the rapidly increasing need for cardio-oncology services. Therefore, it is important to consider the role of serum biomarkers as a useful screening test to prioritize patients for imaging studies. Currently, troponins and brain natriuretic peptides are among the best characterized serum biomarkers for CTRCVD. A clinical variable network analysis of the Cleveland Clinic cardio-oncology cohort indicated that elevated troponin T (> 0.05 μg/L) and NT-proBNP (> 900 pg/mL) were both strong predictors of cardiac mortality in cancer patients.[39] While troponins measure acute cardiac cytotoxic injury and natriuretic peptides measure cardiac response to excessive strain, both biomarkers are known to indicate the risk of cardiovascular morbidity in asymptomatic population.[40] It is not surprising that the cutoff of both biomarkers varies among studies. Currently the consensus when interpreting these biomarkers is to compare values to baseline, and a persistent increase during or after cancer therapy is considered abnormal.[41]

In summary, in routine cardio-oncology services, the clinical definition of cardiotoxicity relies on echocardiographic and serum biomarkers. While echocardiographic measurements have better diagnostic efficacy, serum biomarkers allow for convenient and high-volume screening for early biochemical/mixed cardiovascular dysfunction. It is encouraging that the same markers can be used in serial evaluations. When evaluating RICVD, special attention should be paid to diastolic dysfunction and myocardial fibrosis. In cases that are not amenable for such evaluations, referral to a cardio-oncology center for advanced cardiovascular imaging including FDG-PET and MRI is encouraged for comprehensive workup and follow-up.

RISK STRATIFICATION

The risk of RICVD can be categorized into two domains: the patient factors, and treatment factors (Table 1). In general, the impacts of cancer therapies on CVD risk are usually independent of traditional risk factors, however the risk may accumulate in patients receiving multimodality treatment.[42,43] A landmark retrospective study on RICVD caused by whole breast irradiation in a Danish and Swedish population between 1958-2001 found that the impact of left-sided radiotherapy was equivalent to traditional risk factors including hypertension, age, and smoking.[44] Similar findings have been confirmed in multiple cohorts of patients with lung cancer, esophageal cancer, and mediastinal lymphoma.[36,45,46] Therefore, it is important to consider baseline risks prior to initiating radiotherapy to the heart to avoid therapy-related exhaustion of cardiovascular reserve in the long term. This is especially relevant in the era of the coronavirus infectious disease (COVID) pandemic, as patients with a history of thoracic radiotherapy may have a reduced functional reserve and therefore be more vulnerable to severe diseases.

For patient factor, a previous history of cancer treatment and the location of the disease are important determinants of RICVD, as these factors will likely determine if the patient will receive potentially toxic treatments to the cardiovascular system. Pre-existing risk factors and CVD history should be comprehensively evaluated as in a routine cardiology clinic. Quantitative global risk assessment tools such as 10-year ASCVD risk score and Framingham risk score[28,47] provide quantitative estimates of the underlying risk and have been proven to

Table 1. Cardio-oncology risk factors for RICVD

	Patient factors	Treatment factors
Risk factors	* 10 y ASCVD score > 7.5% * History of symptomatic heart disease * Abnormal cardiac biomarkers * Abnormal echocardiography * Prior cancer therapy	* Doxorubicin > 250 mg/m^2 or Epirubicin > 600 mg/m^2 * Thoracic RT > 30 Gy when heart is in the field * Any thoracic RT plus one of the followings: = any anthracyclins = anti-HER2 agents = anti-VEGF agents = proteosomal inhibitors = Bcr-Abl tyrosine-kinase inhibitors = immune checkpoint inhibitors

Risk factors are categorized into patient factors and treatment factors.
Bcr-Abl, a chimeric oncogene as a result of the fusion between Abelson tyrosine kinase gene at chromosome 9 and the break point cluster (Bcr) gene at chromosome 22; HER2, human epidermal growth factor receptor 2; RT, radiotherapy; VEGF, vascular endothelial growth factor; 10 y ASCVD, 10-year atherosclerotic cardiovascular disease risk score.

predict cardiac hard endpoints in primary prevention settings. Since the outcomes of ASCVD data encompass coronary heart disease, cerebrovascular disease, peripheral artery disease, and aortic aneurysm, it appears to be a suitable tool to evaluate the risk of RICVD when any of the cardiovascular system components is in the irradiation field. Although prospective studies are lacking, our expert panel recommends that a 10-year ASCVD score $\geq$ 7.5% (intermediate risk category), which indicates possible pharmacological treatment in the ACC/AHA guidelines, can be considered as a risk for RICVD.

For the treatment factors, it is important to clarify a history of cardiotoxic agents, including doxorubicin exposure and prior thoracic radiotherapy. The list of cardiotoxic anti-cancer therapies is rapidly expanding. Novel microtubule-targeting agents, antibodies or small molecules that target HER2/Neu, vascular endothelial growth factor (VEGF), proteasome, multiple tyrosine kinases including VEGF receptors, Bcr-Abl, Bruton kinase, and fibroblast growth factor receptors are all known to cause endothelial dysfunction, hypertension, prolonged repolarization, and adverse cardiac remodeling.[12] Furthermore, acute myocarditis resulting from cancer immunotherapy is an increasing concern due to the rapidly expanding use of these agents globally.[48] In addition to the potential cardiovascular toxicity of these agents, their concurrent/sequential combination with thoracic radiotherapy deserves additional consideration. Before clinical evidence of these concerns is available, such combinations should be regarded as a risk for RICVD, as suggested in European and American cardio-oncology guidelines.[48,49]

CARDIOPROTECTION STRATEGIES

For patients with more than one risk for RICVD, cardioprotection should be provided by cardio-oncology services in a risk-adapted manner. The immediate goal is to avoid interruption of oncological treatment due to cardiovascular complications. The long-term goal is to minimize cardiovascular morbidity and mortality as a result of radiotherapy.

In a cardio-oncology clinic, patients should be provided with adequate treatment for the traditional cardiovascular risk factors. This may include stopping smoking, optimal medications for hypertension, diabetes, and dyslipidemia, as well as body weight control. Although the early administration of optimal cardiac drug therapies can reverse subclinical cardiac damage and avoids interrupting scheduled anti-cancer treatment,[20] the benefits of specific cardioprotective agents such as angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, statins, and even sodium-glucose cotransporter 2 inhibitors for RICVD have only been studied in some single institute small series with equivocal short-term results.[50-53] As a result, it is uncertain whether pharmacologic cardioprotection should be offered to cancer patients to prevent RICVD if there is no evidence of existing cardiovascular dysfunction. Careful discussion of the risks and benefits should be provided if such an approach is considered.

In contrast, evidence from population studies suggests that the dose of cardiac radiation is a major modifiable risk factor for RICVD.[44,54] Currently, the best car-

dioprotective strategy for RICVD is to lower the cardiac radiation exposure as low as reasonably achievable while keeping the radiation dose within disease-specific guidelines. For this purpose, it is recommended to commence radiotherapy treatment planning based on simulation CT scans. The use of intravenous contrast and dynamic scans may better depict coronary vasculature and valve structure, and it can be considered at the discretion of the treating radiation oncologist. It is also recommended to contour the major substructures of the heart on the planning CT, including the whole heart, the four heart chambers, and three major coronary branches.[55,56] In cases when an enhanced CT is not indicated, it is encouraged to contour the left ventricle and left anterior descending artery regions.[57]

Most available data agree that mean heart dose is a reasonable predictor of cardiovascular complications. In addition, the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) review summarized the available radiation dose/volume and outcome data, and showed that cardiac V_{25} > 10% is a critical predictor of long-term cardiac mortality.[58] Additional dosimetric parameters, such as V_5 of the left ventricle and D_{mean} of the left anterior descending artery, may also effectively predict adverse cardiovascular outcome.[59] Currently cardiac radiotherapy constraints are disease specific, and it is predicted to rapidly evolve as awareness of RICVD improves and relevant data accumulates over time.

Cardiosparing radiotherapy techniques can be achieved through improvements in two major categories: target volume definition and radiation physics. It is very important to re-emphasize that the intent of oncological treatment needs to be respected when considering for cardiosparing techniques. For curative treatments, cardiosparing radiotherapy should only be considered without compromising oncological outcomes.

There is a significant body of evidence showing the benefits of cardiosparing treatment by refining the radiation target volumes. Moving the heart away from the radiation target volume by deep inspiration breath hold (DIBH) is one of the most widely studied approaches.[60-64] DIBH involves delivering radiation only when the patient holds their breath on a deep inspiration. The maneuver effectively displaces the heart downwards and expands the lungs. In several breast cancer studies, DIBH effectively and reproducibly reduced the volume of the heart that was irradiated by more than 20 Gy.[52,65] Devices to monitor the position of the diaphragm or the movement of the chest wall have been developed to improve consistency of the depth of breath hold. With such devices and trained personnel, excellent control of intra-fractional dose heterogeneity can be achieved in a real world setting.[66-68] This is one of the preferred cardiosparing radiotherapy approaches for breast cancer reported by international radiation oncology societies, including the Germen Society of Radiation Oncologists.[69] It is recommended that cardiosparing with DIBH can be considered when the target volume anatomically overlaps with the heart in the radiation field.

Breast displacement, either achieved by a prone position,[70-72] a left decubitus position,[73,74] or by thermoplastic personalized breast holders,[75] may serve a similar purpose. Although these techniques are limited to whole breast radiotherapy, the ease of operation makes them reasonable alternatives if respiratory gating is resourcefully or technically challenging.

Size reduction of the target volume is a novel approach for cardiosparing radiotherapy. An increasing amount of data from clinical trials suggest that it is a feasible approach to curatively control early cancers if sufficient radiation energy is delivered as adjuvant treatment in breast and lung cancers.[76,77] The radiation energy can be in the form of a larger fraction size for tissue ablation. It can also be delivered in the form of brachytherapy intra-operatively[78] or immediately after surgery.[79] As the radiation dose sharply drops off in a typical brachytherapy treatment plan, it is especially suitable when the planned target volume is anatomically adjacent to the heart, the coronaries, and the great vessels. The dosimetric benefit has been demonstrated in breast and esophageal cancers.[80] However, the clinical benefit in terms of cardiac injury has yet to be proven.

The most significant progress in radiation physics is the clinical utility of particle therapies. Proton beam therapy (PBT), which is an increasingly accessible clinical particle therapy in Taiwan and throughout the world, has demonstrated unparalleled dosimetric strength compared to the currently technologies. The physical characteristics of a proton beam allows position-specific deposition of the radiation dose within the target volume. This results in virtually no radiation exposure beyond the tail end of the beam. Significant cardiac avoidance

has been achieved with PBT in craniospinal irradiation for pediatric central nervous system tumors, breast cancers, lung cancers, esophageal cancers, lymphoma, and thymic carcinoma.[81-85] Although the technology is relatively new clinically, early results froma phase II study have already shown its cardiovascular benefits in decreasing heart failure and mini stroke in patients with lung cancers.[86] Given its advantages with regards to physics, it is reasonable to expect its cardiosparing outcomes for RICVD, and therefore that it may be a reasonable option for cardiosparing radiotherapy.

Other modern radiation techniques include multiple field intensity-modulated radiotherapy (IMRT) and volume-modulated arc therapy (VMAT). The basic principles for these advanced techniques are to deliver the radiation dose to the target tumor volume from multiple angles via a complex radiation field in the same treatment session. Although these techniques effectively reduce the volume receiving a high radiation dose, they generally lead to an increase in the volume of the tissues exposed to a lower radiation dose.[87,88] Furthermore, the position sensitivity of these advanced radiotherapy techniques can lead to inaccurate dose estimation in spontaneously breathing subjects. Currently, clinical evidence to support the universal superiority of IMRT/VMAT in the setting of cardiac protection is lacking. Therefore, whether to use these techniques is a highly individualized decision made by the treating radiation oncologist.

CONCLUSIONS

RICVD is a major risk factor for non-cancer deaths in patients with thoracic cancers. The landscape of cancer radiotherapy is rapidly evolving, driven by both clinical needs and technology innovation. In this context, it is especially challenging to obtain high quality clinical evidence for RICVD, as the disease onset may vary from weeks to decades and the disease prevalence has yet to be defined. In response to the urgent need, the recommended cardio-oncology workflow is summarized in Figure 2. This expert consensus is meant to promote public

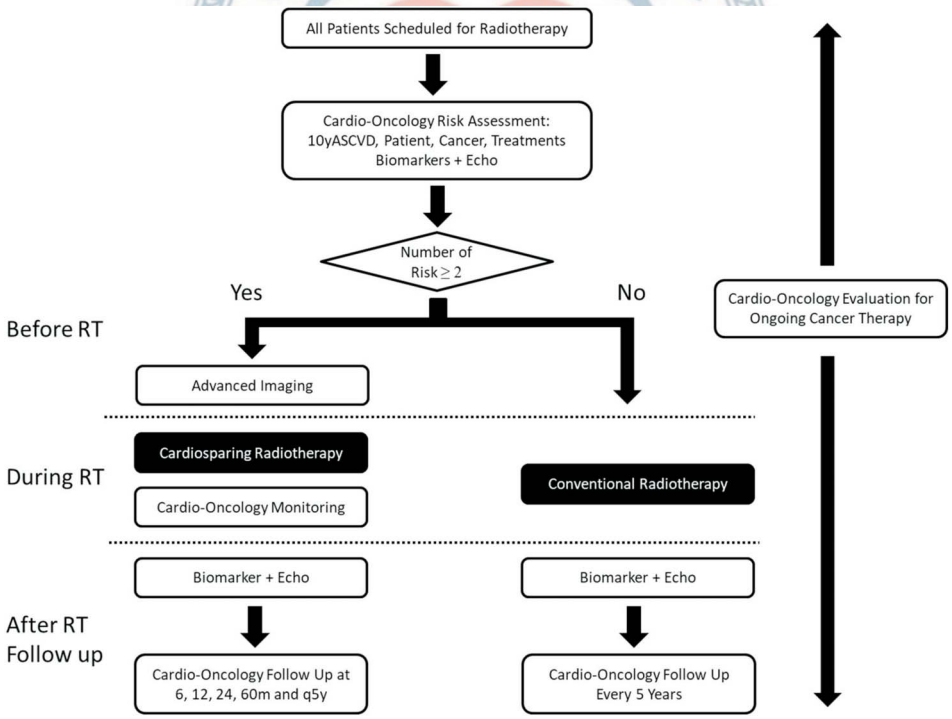

Figure 2. *The cardio-oncology workflow for radiation-induced cardiovascular disease (RICVD). All patients scheduled for radiotherapy is recommended to be evaluated for cardio-oncology risk (Table 1). For patients with ≥ 2 risk factors, advanced cardiac imaging is recommended. For these high risk patients, cardiosparing radiotherapy and cardiac monitoring during radiotherapy can be considered to minimize the RICVD risk. After completion of radiotherapy, a post-treatment cardio-oncology evaluation is recommended. Frequent follow up within 5 years of radiotherapy can be considered for high risk patients. Then all patients are recommended to be followed up every 5 years. For patients receiving multidisciplinary treatment, the integrative cardio-oncology plan should consider and integrate all the treatment-specific recommendations from updated cardio-oncology guideline.*

awareness, unify risk assessment, and promote the implementation of cardioprotective strategies during and after radiotherapy. This consensus marks the beginning of interdisciplinary collaboration, and the results are expected to serve as the basis for high quality clinical investigations, including but not limited to discovery of genomically informed RICVD risk, novel cardiac dysfunction biomarkers, cardioprotective radiotherapy techniques, evidence for pharmaceutical interventions, pattern of care for non-curative settings, and of paramount significance, health economic analysis. Furthermore, this framework can be expanded to explore CVD prevention in cancer patients receiving novel systemic therapies. Cardio-oncology services are expected to be incorporated as standard after the COVID pandemic, and to benefit all cancer patients and cancer survivors.

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DECLARATION OF CONFLICT OF INTERESTS

Long-Sheng Lu had liscensed his relevant patent to Bosomeer Biotechnology Inc.

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