Chapter 10

Radiation-Related Heart Disease: Up-to-Date Developments

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Abstract

Approximately 25–30% of patients with cancer undergo thoracic radiation therapy (RT). RT might inadvertently induce heart injury and result in various forms of radiation-related heart disease (RRHD). The main endpoints of RRHD include cardiac death from RT, clinical heart disease (congestive heart disease, ischemic heart disease, and myocardial infarction), and subclinical heart disease (cardiac perfusion defects). Advanced RT techniques, such as breath control, intensity-modulated RT, and image-guided RT, as well as limited target volume definition might spare or avoid cardiac doses and/or volume, which may translate into decreased incidence of RRHD. The total delivered radiation dose to cardiac implantable electronic devices was strongly recommended not to exceed 2 Gy. The treatment strategies of RRHD were based on the various recommended consensus of related heart diseases in cardiology. However, the standardized definitions of the cardiac structures, dose-volume limits during radiation planning design, the optimal dose-volume parameters, and the dose-volume effects of various cardiac substructures warrant further investigation. The recognition, prediction, prevention, and management of RRHD require close collaboration between oncologists and cardiologists.

Keywords: radiation therapy, heart disease, prevention, treatment

1. Introduction

Cancer is a leading cause of death in both developed and less developed countries worldwide, and its health burden is expected to increase rapidly [1]. In 2012, an estimated 14.1 million new cancer cases and 8.2 million deaths occurred worldwide [1]. Currently, approximately 57% of cancer cases and 65% of cancer deaths occur in less developed countries [1]. Worldwide, the new cases or deaths from lung and breast cancer were at the top of the list [1]. In China, in 2015, an estimated 4,292,000 new cancer cases and 2,814,000 cancer deaths

occurred [2]. Lung cancer is the most common incident cancer and the leading cause of cancer death in China, and esophageal cancer is also commonly diagnosed. Worldwide, lung, esophageal, and breast cancer account for approximately 27% of new cancer cases which means that more than 20% of patients will receive thoracic radiation therapy (RT). Many studies have proven that local RT improves local control and prolongs overall survival [3–11]. However, thoracic RT might inadvertently result in various forms of cardiac toxicity and manifest as clinical and subclinical cardiac disease, termed radiation-related heart disease (RRHD) [12, 13]. In this chapter, we will present the epidemiological data and discuss the possible pathophysiological mechanisms in brief. We will also address the cardiac avoidance techniques and the dose-volume-effect relationship. Although many cytotoxic and molecularly targeted drugs also result in various cardiac toxicities [14], consideration of these is outside the scope of this chapter.

2. Epidemiological data for radiation-related heart disease

Following the use of mantle field radiation for Hodgkin lymphoma in the 1960s, RRHD was recognized because substantial cardiac damage was observed to occur after the whole heart received doses of radiation higher than 30 Gy [12]. Traditionally, RRHD mainly included radiation-related pericarditis, pericardial and myocardial fibrosis, and coronary artery disease, as well as conduction system abnormalities. However, with improvements in RT techniques and refinements in RT delivery, radiation doses to the heart have decreased in the past three decades. For example, in lung and esophageal cancer, the mean heart dose might be >20 Gy [15], while in postoperative RT for breast cancer, it might be <10 Gy [16, 17]. As a reference point, the survivors of the atomic bombings of Japan received up to 4 Gy [18]. The endpoints of RRHD could be categorized as radiation-induced death from heart disease (mortality), clinical manifestations (clinical disease), and imaging or laboratory abnormalities (subclinical disease) [14] as shown in **Figure 1**.

Breast cancer is a curable disease. Therefore, minimization of anticancer therapy-induced toxicity is an important concern during treatment decision-making. In a study of breast cancer, mortality due to heart disease was increased by 27% (2p = 0.0001) in women who received surgery plus RT compared to the rate in those who did not receive postoperative RT. The proportional excess of vascular deaths was similar in the first decade and the period thereafter (ratio 1·32 vs. 1·27). However, the absolute rates were about three times higher in the second decade and the latter period for the patients with left-sided breast cancer [5]. Exposure to cardiac radiation in the treatment of breast cancer will increase the subsequent rate of ischemic heart disease for more than 10 years after completion of the therapy. In addition, women with cardiac risk factors experience greater increases in risk after thoracic RT. Darby et al. quantified the dose effect of ischemic heart disease in patients with breast cancer who received adjuvant thoracic RT. They found that the rate of major coronary events increased by 7.4% per Gy without an apparent threshold, and the major coronary events included myocardial infarction, coronary revascularization, and death from ischemic heart disease [13, 19]. Even in the era of modern RT, in comparison with patients with right-sided breast cancer, those with left-sided breast cancer experienced a small increase in the risk of percutaneous coronary

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intervention (PCI) following RT, and the 10-year cumulative incidences in patients with left-sided and right-sided disease were 5.5 and 4.5%, respectively [20].

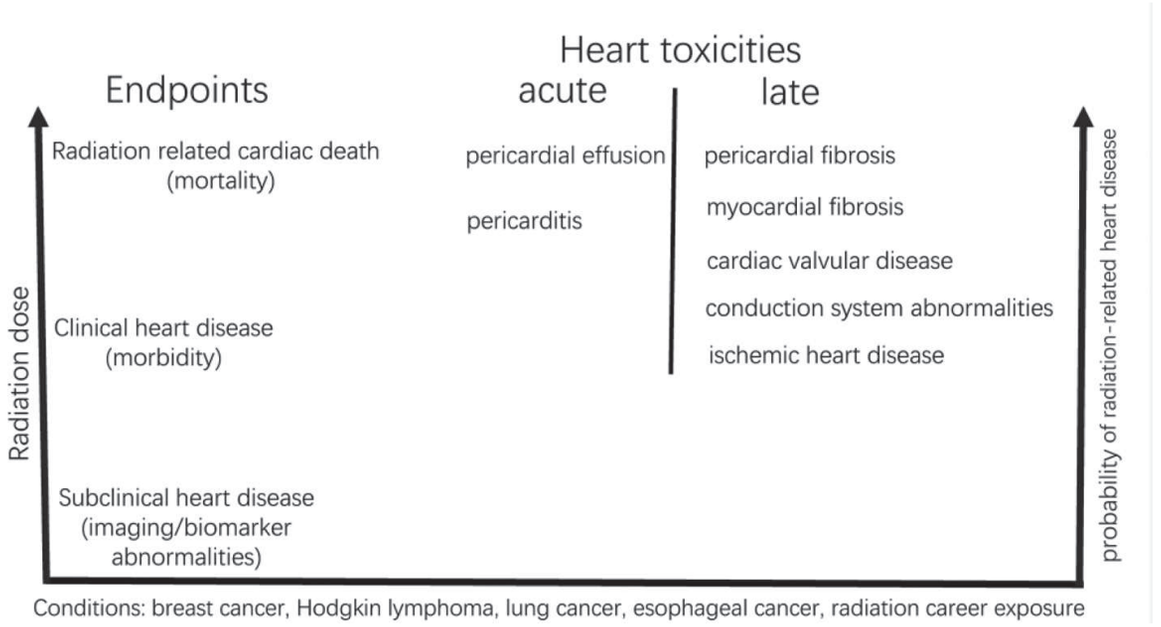

Figure 1. Radiation-related heart disease usually occurs with a certain latency from a few hours to several decades after the heart and its substructures receive direct or indirect irradiation. The endpoints of RRHD included its mortality and morbidity. According the occurrence timing of cardiac radiation response, RRHD includes acute and late cardiac toxicities. Generally, the probability of RRHD is positively related to the radiation dose that the heart received.

Hodgkin lymphoma usually occurs in young patients and is also one of the most curable cancers. Cytotoxic treatment with anthracyclines and vinca alkaloids and RT are the cornerstone choices for therapy of this cancer, and both are associated with the risk of cardiovascular disease. The cardiovascular risks after chemotherapy and RT have been well established [21, 22]. According to data from old cohort studies, Hodgkin lymphoma was usually treated with radiation doses of 35–45 Gy using extended field treatment such as mantle field radiation. The cumulative risks of heart disease among survivors of adult Hodgkin lymphoma are approximately 5–10% at 15 years, 16% at 20 years, and 34% at 30 years, and coronary artery disease, as the most common form, accounts for approximately 40–50% of adverse cardiac events [23]. A recent systemic analysis showed that among 6039 patients with a median length of follow-up of 9 years, 703 patients were recorded to have 1238 first cardiovascular events, which mostly included ischemic heart disease (19%), congestive heart failure (12%), arrhythmia (16%), and valvular disease (11%). The predictors of cardiovascular disease were the mean heart radiation dose per 1 Gy increase (HR 1015) and the dose of anthracyclines per 50 mg/m^2 increase in cumulative dose (HR 1077) [24]. In a Dutch study conducted to examine the relative and absolute excess risk of cardiovascular disease incidence, 1713 cardiovascular events were detected in 797 patients after a median follow-up of 20 years. Furthermore, 20% of patients with a cardiovascular disease developed multiple events. Mediastinal RT, anthracycline-containing chemotherapy, and smoking are appeared to be additive factors [25]. In addition, the data

from both individuals exposed to radiation during a medical career [26, 27] and survivors of the atomic bombings in Japan [28] proved that radiation was the source of the risk for RRHD.

Cardiac valvular disease is less common, typically has a late onset (10 years after RT), and is related to higher doses (30 Gy) or young age at treatment. Treatment of a large cardiac volume with high doses can produce acute pericarditis, although this is uncommon. At times, this may lead to chronic or delayed reemergence of pericarditis with effusion.

Furthermore, due to the wide use of advanced imaging techniques, more subclinical manifestations are detected. With repeat nuclear imaging to assess changes in regional and global cardiac function after RT for left-sided breast cancer, a prospective clinical study found that volume-dependent perfusion defects occurred in approximately 40% of patients within the first 2 years after RT for left-sided breast cancer, and these perfusion defects were associated with cardiac wall motion abnormalities [29]. In addition, new perfusion defects usually occurred in the anterior left ventricle within 6 months after radiation [30]. The data from the Surveillance, Epidemiology, and End Results Medicare database showed that patients with left-sided breast cancer who had a history of cardiac disease had an increased risk of PCI after thoracic RT, and there was a lower survival rate in those who received PCI. The 10-year cumulative PCI incidence was 5.5% [95% confidence interval (CI) 4.9–6.2%] and 4.5% (95% CI 4.0–5.0%) for patients with left- and right-sided cancer, respectively [20].

For curable cancer types, such as breast cancer and Hodgkin lymphoma, both the radiation dose to the heart and its substructures and the risks and benefits of different regimens for individual patients should be well balanced during treatment decision-making.

3. Pathophysiological mechanisms of RRHD

The detailed pathogenesis of RRHD has been well reviewed [12, 31]. Overall, the endothelial system of blood vessels, particularly the arteries seem to be the critical target structures. After radiation, early functional alterations might include the pro-inflammatory responses and other changes, followed by slow progression [31, 32]. Although experimental animal models will help to elucidate the possible cellular and molecular mechanisms of RRHD, the results from various animals might be species-specific, and caution should be used in extrapolating to humans. In cancer patients, radiation induces macro- and microvascular injury. The former accelerates age-related atherosclerosis and leads to coronary artery disease after several years or decades due to reduced blood flow to the radiated myocardial territory. On the other hand, the latter reduces capillary density and results in decreased vascular reverse, which usually occurs within several months after RT and has only subclinical manifestations [12].

4. Dose-volume effect of RRHD

The dose-volume effect of RRHD is highly dependent on the definition of its endpoints. According to the length of its latency, RRHD could be divided into acute injury, which often manifests within a few months and is usually transient, and chronic toxicities, which often

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manifest as congestive heart failure and ischemic heart disease, among others, and occur with a long latency [33]. RRHD can have subclinical manifestations, such as localized cardiac imaging abnormalities on nuclear magnetic resonance imaging or regional wall motion abnormalities on cardiac ultrasonic examination, but manifestations could also be clinical, such as coronary artery disease or myocardial infarction [33].

The accurate definition of the heart and its substructures is critical to the estimation of the radiation dose-volume effect on RRHD. However, the imprecise definition of the heart in treatment planning computed tomography (CT) imaging poses a great challenge [33]. Feng et al. [34] developed a heart atlas to study cardiac exposure to radiation in the treatment of breast cancer. Using this consistent atlas for cardiac structure delineation, we could quantify the causative effects of RT on cardiac morbidity and mortality and study the dose-volume constraints on the heart and its substructures [34] (**Figure 2**).

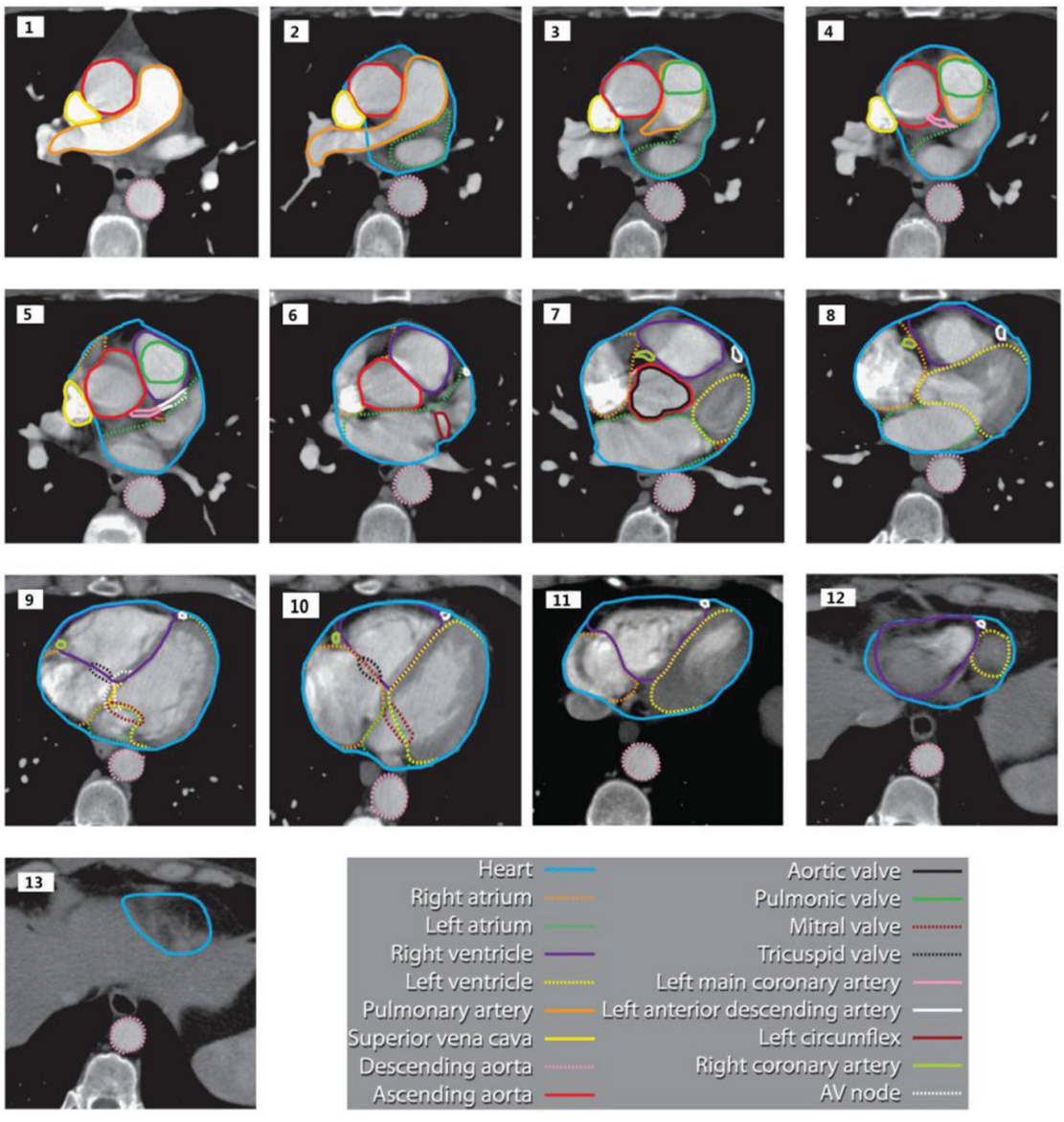

Figure 2. Cardiac atlas is illustrated in the CT images with intravenous contrast [34] (with permission).

In all of the published studies about the dose-volume response relationships of RRHD, mortality from pericarditis, ischemic heart disease, and decreased myocardial perfusion were three main clinical endpoints [33]. Gagliardi et al. [33] (**Figure 3**) summarized the dose-volume predictors and normal tissue complication probabilities of pericarditis/pericardial effusion, and the results showed that the mean doses to the pericardium (>30 Gy or >26.1 Gy) or mediastinum (>41 Gy) might be the predictors of radiation-induced pericarditis or pericardial effusion. The incidence of pericarditis was 7% (14/198) with a radiation dose of ≤6 Gy; 12% (5/42) with a dose of 6–15 Gy; 19% (23/123) with a dose of 15–30 Gy; and 50% (7/14) with a dose of >30 Gy. Regarding cardiac mortality from ischemic heart disease or myocardial infarction, radiation dose to the mediastinum >30 Gy; 35% of heart volume receiving a radiation dose > 38 Gy; mean dose to the whole heart volume > 2.5 Gy; and radiation to the internal mammary chain would be the predictive parameters [33]. When taking cardiac perfusion defects as the clinical endpoints, volume of the left ventricle receiving doses higher than 23 (V_{23Gy}) or 33 Gy (V_{33Gy}) could predict myocardial perfusion defects [35].

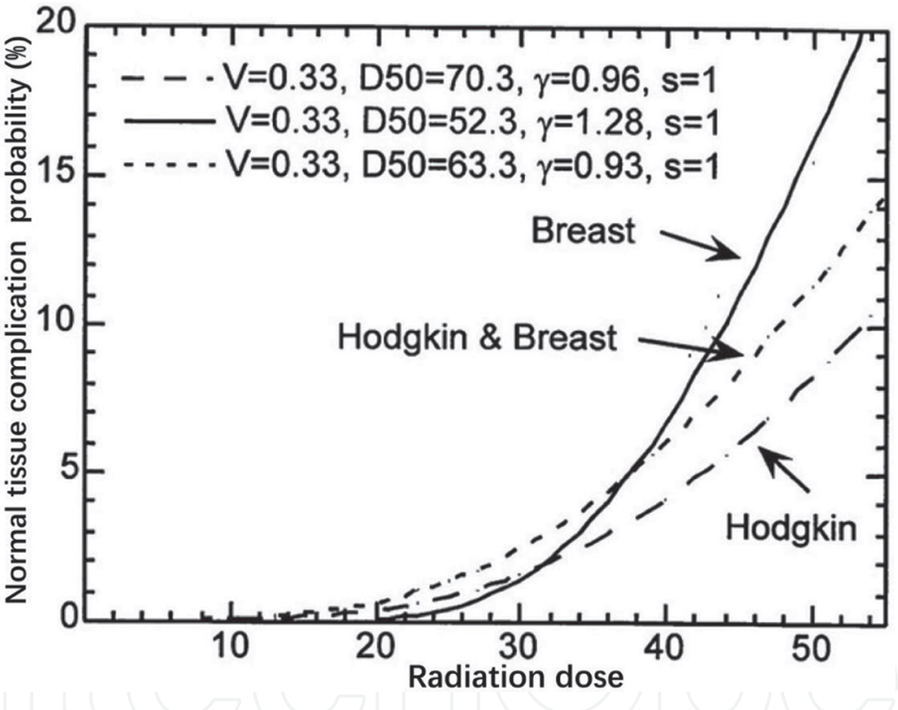

Figure 3. Dose-response curves of radiation-induced cardiac mortality. These data were estimated based on the breast cancer and Hodgkin lymphoma data sets [33] (with permission).

5. Cardiac dose sparing and avoidance techniques

For curable cancers, such as breast cancer and Hodgkin lymphoma, cardiac dose protection and/or avoidance techniques might be beneficial in minimizing RRHD. For breast cancer, several techniques have been utilized clinically. These techniques include the following: (1) RT delivery with breath control or holding techniques, (2) prone patient positioning, (3) new RT techniques such as intensity-modulated RT (IMRT), proton therapy, or partial breast irradiation techniques, and (4) single-fraction, intraoperative radiation [36] (**Figure 4**).

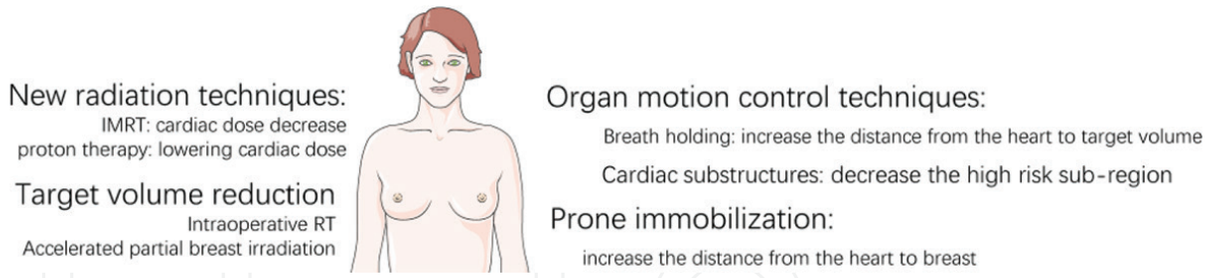

Figure 4. Cardiac sparing techniques is available nowadays. These techniques included radiation techniques improvement and patient or organ motion management.

With breath holding within inspiration, the distance from the chest wall to the heart will increase and the cardiac volume in the field will decrease, the mean or maximal dose to the heart or left anterior descending artery will be reduced [36], and the probability of cardiac mortality will also be reduced (4.8 vs. 0.1%) [37]. In the delivery of RT, patients are immobilized in the prone position so that the breast falls away from the chest wall and the distance from the heart to the RT beam increases. A few studies showed that with this technique, 75–85% of left-sided breast cancer patients had reduced cardiac volume in the field [38] and the mean cardiac dose decreased [39]. Although the main concerns of the prone position include its reproducibility and the potential increase in radiation to other normal tissues due to the poor setup, recent data showed that this technique could be well reproducible with daily cone-beam CT [40, 41].

For breast cancer patients, IMRT has been proven to have a cardiac dose sparing effect without compromising the dose homogeneity in the breast, especially for those with left-sided lesions [36, 42]. With the IMRT technique, the cardiac dose decreased with improved dose homogeneity in the breast [43]. A series of studies showed that, compared with breath holding in three-dimensional conformal RT and prone position techniques, IMRT has similar benefits and is more reproducible. The advantages of IMRT technique included the improvement of radiation dose homogeneity in target volume, the reduction of high cardiac dose volumes, and the decrease of normal tissue complication probability. In addition, IMRT technique showed its advantages in sparing the high-risk cardiac subregions such as the anterior part of the heart, the coronary arteries, and the left ventricle [16, 17, 44].

Partial breast irradiation, as an alternative method to reduce the cardiac dose, could decrease the irradiated breast volume and increase the distance from the target volume to the heart. Hypofractionation is required by partial breast irradiation, and two recent reviews suggest that hypofractionation has not resulted in increased cardiac morbidity [45, 46]. Dosimetric studies showed that interstitial brachytherapy could reduce cardiac doses with image-guided RT techniques [47, 48]. The mean cardiac dose decreased to 21% of the prescription dose in patients with left-sided breast cancer [48] and the cardiac volume receiving low doses (5 and 10 Gy) decreased significantly. In addition, the advantages of proton therapy including the rapid dose falloff and the Bragg peak make it possible to spare the radiation dose to the surrounding tissues including the heart. Several dosimetric studies showed that

proton RT could reduce the maximal dose, V_{20Gy}, V_{5Gy}, etc [49–52]. However, because of the limited availability and high cost, at present, this technique is not advocated for cardiac dose sparing [36].

For Hodgkin lymphoma, the RT field has changed over the past decades. Previously, the majority of patients received mantle field radiation with/without upper abdomen field radiation, and a large volume of the heart had a prescribed dose irradiation. According to the anatomical sites of disease presence, the caudal border of the mantle field individually varied from the bottom border at the 8th–9th thoracic vertebrae (T8–T9) [53] to T10–T11 [54, 55], and the higher caudal border might spare most of the irradiated heart volume [53]. With advanced imaging modalities such as positron emission tomography–CT and improved RT delivery techniques such as IMRT, image-guided RT, and breath control techniques, among others, the previously applied extended field and involved field techniques have now been replaced by techniques using limited target volumes, such as involved node RT (INRT) and involved site RT (ISRT) [56]. With the optimal imaging during the course of treatment, both the INRT and ISRT techniques reduce the treated volume to a safe minimum [56]. In addition, with refinements of Hodgkin lymphoma, the prescription dose decreased to 20–36 Gy [57]. Due to more limited target volume and lower prescribed radiation doses, greater amounts of normal healthy tissues such as lung and heart could be spared.

Theoretically, for RT of non-small cell lung cancer, dose escalation to 74 Gy would be better than the standardized 60 Gy dose. However, the results of a randomized phase 3 study (RTOG 0617) showed that a higher dose did not translate to a better outcome and might even be potentially harmful [58]. One reasonable explanation is that patients receiving doses of 74 Gy usually had worse dose-volume effects on the heart. The dose volume parameters including V_{5Gy} and V_{30Gy} of the heart were the important predictors of patient survival [58]. The dose-volume effects on the heart substructures such as the pericardium, atria, and ventricles will be investigated and their dose-volume limitations will be included in future lung cancer trials. In addition, for early and locally advanced non-small cell lung cancer, proton RT will potentially be used for cardiac sparing [59].

6. Radiation for patients with cardiac implantable electronic devices

The numbers of patients with both cardiac implantable electronic devices (CIEDs) including pacemakers (PMs) and implantable cardiac defibrillators and cancer are expected to rise, and patients in these situations require RT. The potential interactions between high doses of radiation and the function, longevity, and integrity of the CIEDs, as well as the harm to the patients, remain unclear. The results of a recent review [60, 61] showed that the risk of device failure increases with increasing radiation doses, without a clear cutoff point. For patients with pacemakers, the delivered total radiation dose to the device was strongly recommended not to exceed 2 Gy and the dose in patients with implantable cardiac defibrillators should be

within 1 Gy. The radiation energy should be less than 6 MV. Because of the potential dangers of device malfunction, the radiation oncologist should have all the measures designed to minimize the risk to patients. Furthermore, it is necessary for the cardiologist, oncologist, radiotherapist, and physicist to collaborate closely.

7. Treatment strategies of RRHD

Generally, the treatment strategies of various RRHDs are similar to those in normal population [62–64]. For example, radiation-induced left ventricular dysfunction or heart failure could be treated according to the recommended guidelines of heart failure [65]. And for those with anticancer drug-induced hypertension, antihypertensive agents should be individualized to the clinical circumstances of the patients [66]. Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers are usually considered for patients with proteinuria, metabolic syndrome, or high risk of chronic kidney disease [66]. Treatment with nondihydropyridine calcium channel blockers should be avoided in patients receiving cytochrome P450 inhibitors, while dihydropyridine calcium channel blockers are preferred in elderly patients [67, 68]. Low-molecular weight heparin for a minimum of 3–6 months is the recommended treatment for patients with newly diagnosed venous thromboembolism [69].

8. Unanswered questions regarding RRHD

Variability in certain risk factors may influence the development of a radiation-associated heart disease. These factors included patients themselves, RT techniques, the evaluable endpoints, and social-psychological variables [19]. The patient-related factors include age, personal alcohol and tobacco history, systemic anticancer drugs with potential cardiac toxicities such as anthracyclines, trastuzumab, taxanes, tamoxifen, and letrozole, among others, individual sensitivity to late heart morbidity, and hereditary heart disease [19]. The definitions of the heart and its substructures are shown in **Table 1**, and the standardized delineation consensus and atlas should be consulted by radiation oncologists. For the heart and cardiac substructures, further investigation should be conducted regarding which dose-volume limitations were used during the design of radiation planning and what optimal dosimetric parameters were reported to be necessary, such as maximal or mean heart dose, V_{5Gy}, V_{10Gy}, V_{20Gy}, etc. The clinical endpoints included cardiac mortality and radiation-associated clinical and subclinical heart diseases [33]. The optimal RT delivery techniques and reliable methods to evaluate these endpoints will require further studies. The designation of RRHD might unavoidably increase the psychological burden of patients. In addition, to find those patients who may develop late RRHD, health economic evaluations should be critically performed prior to the initiation of screening programs [19].

Substructure	Definition	Note
Heart [16, 34, 70]	Cranial: The whole heart starts just inferior to the left pulmonary artery Caudal: The heart blends with the diaphragm	If contrast is administered, the superior vena cava (SVC) can generally be separately contoured from the whole heart. In a noncontrast scan, the SVC can be included for simplification and consistency
Pericardium [34]	The whole heart	Cardiac vessels run in the fatty tissue within the pericardium and should be included in the contours
Left atrium [34]	Begins just inferior to the left pulmonary artery	–
Left ventricle [16, 34]	The visible heart according to both CT images and heart anatomy	Typically, anterior and to the left of the left atrium
Right atrium [34]	No	Starts to the right of the aortic root superiorly
Right ventricle [34]	No	Lies directly beneath the sternum and connects to the pulmonary trunk
Left main coronary artery [34, 70]	Defined from its origin in the aortic sinus to the first branches	Originates from the left side of the ascending aorta, inferior to the right pulmonary artery
Right coronary artery [34, 70]		Originates from the right side of the ascending aorta
Left anterior descending artery [34, 70]	Defined from where they branched at the left or right main coronary artery to the caudal edge of the endocardial surface of the left ventricle	Originates from the left coronary artery and runs in the interventricular groove between the right and left ventricles
Left circumflex artery [34, 70]		Originates from the left coronary artery and runs between the left atrium and ventricle
Right marginal artery [70]		–
Aortic valve [34]	No	Found within the ascending aorta and seen in cross section on axial CT
Pulmonic valve [34]	No	Found within the pulmonary trunk and seen in cross section on axial CT
Tricuspid valve [34]	No	Located between the right atrium and ventricle. It is difficult to see, but it is defined as the area where the blood pool between the atrium and ventricle is shared
Mitral valve [34]	No	Located between the left atrium and ventricle. It is difficult to see, but it is defined as the area where the blood pool between the atrium and ventricle is shared
Atrioventricular node [34]	No	Cannot be seen on CT. It is located on the basal portion of the interventricular septum and extends between the right atrium and ventricle
Anterior myocardial territory [16, 17, 70]	Comprises the myocardium from the anterior surface of the heart up to 1.0 cm posteriorly and the main branches of the coronary arteries at the anterior portion of the heart	It is an imaged subregion in the anterior port of the heart as a high-risk region for breast cancer radiation therapy

Table 1. Recommended delineations of the heart and substructures.

9. Conclusion

As a significant radiation-induced toxicity, RRHD should not be neglected during clinical decision-making, especially for patients who could be cured by modern anticancer modalities. RRHD includes radiation-induced death from heart diseases, as well as clinical and subclinical heart disease. Advanced RT techniques including breath control, IMRT, and imaging-guided RT might be used to avoid or spare cardiac doses and/or volume, which might translate into decreased incidence of RRHD. Furthermore, the significance and implications of RRHD differ depending on the clinical scenario; therefore, a consensus has not yet been reached regarding the recommended dose-volume limits. It is prudent to minimize the cardiac dose/volume and optimize the patient cardiovascular risk profiles. The recognition, prevention and prediction, and treatment of RRHD should be within the domain of oncocardiology, which requires close collaboration between oncologists and cardiologists [14, 63].

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