



## Radiation-Induced Heart Disease: from Diagnosis to Prevention

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### ABSTRACT

Radiotherapy has become an important component of multimodal treatment of malignancy. After 50 years, there was a drastic increase in outcomes of patients with malignancy. However, improvement of the survival is also accompanied by some inevitable complications on cardiovascular systems which are often called radiation-induced heart disease (RIHD). RIHD comprises a spectrum of heart disease including pericardial disease, coronary artery disease, valvular heart disease, conduction system abnormalities, cardiomyopathy, and medium or large vessel vasculopathy. The underlying mechanisms include direct effects on function and structure of the heart, or accelerate development of cardiovascular disease, especially with the presence of previous cardiovascular risk factors. Recent studies have identified non-invasive methods for evaluation of RIHD. Furthermore, potential options preventing or at least attenuating RIHD have been developed. This review provides an overview of pathogenesis, clinical manifestation, diagnosis, management, and prevention of RIHD.

### INTISARI

Radioterapi telah menjadi komponen penting dalam manajemen multimodal keganasan. Selama 50 tahun, terjadi peningkatan luaran secara drastis pada pasien dengan keganasan. Namun demikian, perbaikan ketahanan hidup juga diiringi dengan peningkatan komplikasi yang tidak dapat dihindarkan pada sistem kardiovaskular yang sering disebut radiation-induced heart disease (RIHD). RIHD meliputi spektrum penyakit jantung termasuk penyakit perikardial, penyakit arteri koroner, penyakit katup, gangguan konduksi, kardiomiopati, dan vaskulopati pembuluh darah besar atau sedang. Mekanisme yang mendasari termasuk efek langsung kepada fungsi maupun struktur jantung, atau percepatan perkembangan penyakit kardiovaskular, terutama adanya faktor risiko kardiovaskular sebelumnya. Penelitian terbaru telah mengidentifikasi metode non-invasif untuk mengevaluasi RIHD. Selanjutnya, pilihan potensial mencegah atau menurunkan kejadian RIHD telah dikembangkan. Oleh karena itu, tinjauan pustaka ini memberikan gambaran manifestasi klinis, patogenesis, diagnosis, manajemen, dan pencegahan RIHD.

### Introduction

Radiotherapy is thought to have benefits as management in more than 50% of cancer cases, this include as curative therapy in 3.5 million patients and palliative therapy in 3.5 million other patients.<sup>1</sup> Radiotherapy improves survival of patients with malignancy, but it also involves some inevitable complications of radiation. Complication on the heart region is one of the most common side effects and has an effect on early morbidity and mortality in cancer

survivors.<sup>2</sup> The set of this heart disease is called radiation-induced heart disease (RIHD).<sup>3</sup> The number of patients at risk of developing RIHD increases to 40% in survivors of cancer after at least 10 years post radiotherapy and will increase over time.<sup>4,5</sup> RIHD is a result from cumulative total radiotherapy doses and potentiated by adjuvant chemotherapy.<sup>3</sup> The underlying mechanisms include direct effects on function and structure of the heart, or accelerate development of cardiovascular disease,

especially with the presence of previous cardiovascular risk factors.<sup>6</sup>

The RIHD comprises a spectrum of heart disease including pericardial disease, coronary artery disease, valvular heart disease, conduction system abnormalities, cardiomyopathy, and medium or large vessel vasculopathy.<sup>7</sup> Over the decade, there has been progress on radiation technique and decrease the risk and death caused by RIDH.<sup>8,9</sup> However, there is no specific treatment has been established for RIDH and mostly using standard treatment for heart disease caused by non-radiation. Instead, there has been many studies on pharmacological and non-pharmacological in order to attenuate risk of RIHD.<sup>3,10</sup>

## Discussion

Radiation therapy uses radiation energy from X-rays, gamma rays, or particle changes that induce the breakdown of DNA double-stranded cells in malignant cells, thereby causing apoptosis or preventing cell division.<sup>7</sup> Radiation therapy is given by fractionation based on radiobiological differences in cancer cells and various normal tissue cells. In normal cells proliferation is relatively slower than cancer cells so that it has time to repair the damage before it replicates.<sup>11</sup> Daily low dose of 2 Gy fraction given five times per week gives a better outcome than large doses directly.<sup>12</sup>

In 1895, radiotherapy was first conducted by Emil Grubbé in breast cancer patients.<sup>13</sup> After 50 years; there was a drastic increase in outcomes of patients with malignancy. It is related to technological advances in the field of radiotherapy aimed at providing even more accurate results. Many techniques have been developed, such as 3D conformal radiotherapy, intensity modulated radiation therapy, image-guided radiotherapy, and stereotactic body radiation therapy.<sup>7</sup>

### Pathogenesis

The mechanism of RIDH from acute injury to progressive heart disease, and its relationship with short-term and long-term effects is not fully understood.<sup>3</sup> Nevertheless, many studies has been conducted to understand the process and control mechanism of RIHD. The primary mechanism behind radiation that induces damage is seen in endothelial dysfunction. Edema of endothelial cells, increase permeability, interstitial fibrin deposition, and development of platelet thrombus which causes fibrosis.<sup>14</sup> Significant increases in superoxide and peroxide explain other mechanisms of endothelial dysfunction through the reactive oxygen species (ROS) pathway, and also through cell apoptosis through endoplasmic reticulum and mitochondria pathway.<sup>14-16</sup> Recent study has found that micro-RNA also play an important role on promoting cell proliferation and anti-apoptosis.<sup>17</sup> Fibrosis of the myocardium decreases elasticity and distensibility, which causes decrement in ejection fraction and heart failure.<sup>18</sup>

The secondary mechanism is through systemic inflammation by increasing proinflammatory cytokines IL-6, c-reactive protein (CRP), tumor necrosis factor (TNF) -

$\alpha$ , and interferon- $\gamma$ , and increasing anti-inflammatory cytokines IL-10.<sup>19</sup> Another mechanism is macrovascular damage through accelerated atherosclerosis due to radiation in moderate and large coronary arteries resulting in endothelial dysfunction and coronary heart disease. Sub-endothelial fibrosis also contributes to vascular injury in small coronary arteries. Microvascular damage and neovascularization of the pericardium, venous and lymphatic fibrosis, result in the accumulation of fibrin-rich exudates in the pericardium which causes pericardial tamponade. This is also the result of the conduction pathway that causes arrhythmia.<sup>20</sup>

## Diagnosis

### Pericardial disease

After 1970s, there was lower incidence of acute pericarditis due to lower doses and modern techniques.<sup>3</sup> However, 7-20% of patients will still develop chronic pericarditis after 10 or more years after radiotherapy.<sup>21</sup> Signs and symptoms of pericarditis include dyspnea, chest pain, fever, pleural effusion, increased of jugular venous pressure and paradoxical pulse. Constructive pericarditis is a late complication of pericardial disease and usually causes symptoms of congestive heart failure.<sup>22</sup>

Constructive pericarditis can be detected using non-invasive imaging, such as echocardiography, Computed Tomography (CT), and Magnetic Resonance Imaging (MRI). In general, pericarditis on CT shown as pericardium thickening  $\geq 4$  mm, tubular ventricles, dilated inferior vena cava, pericardial and pleura effusion. MRI is the preferred imaging modality for pericardium anatomy.<sup>7</sup>

### Coronary artery disease

The incidence of coronary artery disease (CAD) is 10% after 20 years after radiotherapy, median time to develop is 9 years, with all patients have at least 1 conventional cardiovascular risk factor.<sup>23</sup> Clinical manifestations of CAD due to radiotherapy compared to the non-radiation population are not much different. Ischemia can be silent, causing symptoms of angina, or sudden death. The incidence of silent myocardial infarction is found to be higher on post-radiotherapy than the general population, possibly due to damage to nerve endings in the radiation field.<sup>24</sup>

Electrocardiography and cardiac markers (troponin and Creatinine Kinase Myocardial Band [CKMB]) are very helpful in diagnose CAD. The assessment of non-invasive ischemia with technetium-99 m tetrofosmin has been validated in patients suspected of having CAD due to radiation. However, the gold standard of diagnosis and localization of CAD is coronary angiography.<sup>8</sup>

### Valvular heart disease

Valvular heart disease can be experienced by up to 81% of patients with RIHD, with aortic and mitral valves affected more often than tricuspid and pulmonary valves.<sup>25</sup> Sign and symptom of valvular heart disease due to radiation can vary from asymptomatic with mild thickening to

severe thickening which causes significant hemodynamic disorders with stenosis or insufficiency manifestations.<sup>26</sup>

Echocardiography has high sensitivity on detecting degree of valvular heart disease. Mild regurgitation of left sided valve is most common finding after 10 years radiation. Echocardiography is a diagnostic option for valvular heart disease and 3-Dimension echocardiography is useful, especially for the evaluation of mitral valve commissures.<sup>10</sup>

#### *Conduction system abnormalities*

Conduction abnormalities do not manifest immediately after radiotherapy, but many years afterwards, making it difficult to find cause-effect relationships and determine their incidence. However, several criteria were proposed to establish the relationship between radiotherapy and conduction abnormalities, which are total radiation dose >40 Gy; 10 years after therapy; abnormal ECG changes, such as bundle branch blocks; history of pericardium involvement; and associated lesions on the chest and mediastinal.<sup>23</sup>

Right bundle branch block is the most common conduction abnormalities. This is because the right bundle is proximal to the endocardium in the right heart.<sup>29</sup> Other conduction abnormalities can be found are corrected QT interval prolongation, atrioventricular block, premature ventricular contractions, supraventricular tachycardia, and ventricular tachycardia.<sup>24,27</sup> Syncope is the most frequent clinical appearance in patients with symptomatic conduction abnormalities at 12-year intervals after radiotherapy.<sup>8</sup>

#### *Cardiomyopathy*

Cardiomyopathy can be caused by direct radiation or the consequences of coronary disease and/or valvulopathy. It is estimated that less than 10% of patients on radiotherapy experience cardiomyopathy, however the prevalence will increase to 40-70% after 8 years.<sup>7,28</sup> In one study showing high doses radiotherapy alone can cause restrictive cardiomyopathy, whereas if given together with cardiotoxic chemotherapy agent such as anthracycline it results in dilated cardiomyopathy.<sup>29</sup> Congestive heart failure is a symptomatic clinical feature of cardiomyopathy in the form of peripheral edema, jugular venous distension, and gallop rhythm.<sup>30</sup>

Echocardiography is the preferred method for detecting myocardial dysfunction before, during, and after radiotherapy. Cardiac dysfunction associated with cancer treatment is defined as decrement in left ventricular ejection fraction (LVEF) >10% to the normal limit. The decrement must be confirmed by repeating examination within 2-3 weeks after the initial decrease in LVEF. The use of echocardiography can also detect cardiac abnormalities, and features of cardiomyopathy.<sup>10</sup>

#### *Vasculopathy*

Vascular injuries can involve various arteries exposed to radiation fields. Supra aortic arch vasculopathy increases the risk of cerebrovascular disease due to carotid stenosis

and occlusion. The incidence of carotid stenosis is 30-50% and the presence of cardiovascular risk factors increases the risk.<sup>31</sup>

Ultrasonography is the standard screening approach, while still considering MRI or CT angiography if ultrasonography is not conclusive. Screening is done in patients with signs and symptoms suggestive of stroke or TIA (transient ischemic attack); carotid bruits; other vascular diseases; the presence of one or more cardiovascular risk factors. The examination is repeated every year.<sup>7</sup>

#### *Management*

In general, management of heart disease due to radiation is almost the same as non-radiation population, which emphasizing on symptoms management. In patients with cardiomyopathy, angiotensin converting enzyme inhibitor (ACE-1) or angiotensin receptor blocker (ARB) and beta blockers are recommended, also mineralocorticoid receptor antagonists if symptoms are persistent.<sup>32</sup> Patients with end-stage heart failure, orthotopic heart transplantation or ventricular assistive devices are technically feasible.<sup>33</sup> Pericarditis is treated with non-steroidal anti-inflammatory drugs, diuretics, and low-sodium diets. Pericardiocentesis can be performed if effusion symptomatic or unstable hemodynamic.<sup>23</sup>

Management of coronary artery disease due to radiation is the same as non-radiation populations, but percutaneous coronary intervention is preferred over coronary artery bypass grafting due to fibrosis caused by radiation in the surrounding structures making surgical procedures difficult.<sup>34,35</sup> Valve replacement is preferred over valve repair, with transcatheter aortic valve replacement is the preferred method of aortic valve replacement.<sup>23,36</sup> Whereas management of carotid stenosis due to radiotherapy remains a challenge. Carotid endarterectomy has a high risk of wound complications, cranial nerve injuries, and neurological disorders. In addition, the use of stents has the same risks as surgery.<sup>37</sup>

#### *Screening and Prevention*

In general, patients at high risk for cardiotoxicity are patients who are given anterior and/or left chest irradiation location with at least 1 risk factor for RIHD that shown in Table 1.<sup>38</sup> The main prevention of the effects of radiotherapy on the heart is radiotherapy delivery with adequate dose and volume by minimizing radiation towards the heart. The use of latest radiotherapy techniques is the best solution in reducing the risk, i.e. CT planning, radiation shielding block, deep-inspiration breath-hold or respiratory gating techniques that provide heart protection from tangential fields and reduce radiation to risky organs without reducing the target volume, and multiple or rotational radiation sources.<sup>3,10</sup>

**Table 1.**  
Risk factor of RIHD<sup>38</sup>

Anterior or left chest irradiation location
High cumulative dose of radiation (>30 Gy)
Younger patient (<50 years)
High dose of radiation fractions (>2 Gy/day)
Presence and extent of tumor in or next to the heart
Lack of shielding
Concomitant chemotherapy (the anthracyclines considerably increase the risk)
Cardiovascular risk factors (i.e. diabetes mellitus, smoking, overweight, ≥moderate hypertension, hypercholesterolemia)
Pre-existing cardiovascular disease

Patients who are given chemotherapy together with radiotherapy need to be considered given cardioprotective agent. In circumstance where patient receives chemotherapy of either anthracycline or trastuzumab can be given ACE-I or ARB, betablockers, or statin.<sup>10</sup> Furthermore, lifestyle improvement, including healthy diet, smoking cessation, regular exercise, and weight control should be recommended to the patient. Aerobic exercise is non-pharmacological strategy to prevent and improve the effect of treatment for cardiotoxicity.<sup>38</sup>

To minimize the burden of RIDH, history taking and physical examination to assess the signs and symptoms is analyzed annually. For asymptomatic patients, echocardiography screening is performed 10 years after radiotherapy, whereas in high-risk patients is 5 years after radiotherapy. Reassessments are conducted every 5 years.<sup>7</sup>

**Conclusion**

Radiation induced heart disease (RIHD) is growing problem due to increased survival in cancer patients. Although lowering dose and use of radiotherapy protectors can reduce the incidence of this disease, morbidity due to heart disease is still a substantial issue. Increased prevalence over time provides an illustration that RIHD evaluation and screening of cancer survivors is essential. RIHD screening strategies are still being developed, especially using non-invasive imaging in asymptomatic patients. However, history taking and clinical examination of patients after receiving radiotherapy are the basis for screening. As a conclusion, screening and early findings of patients with RIHD will increase survival by providing adequate therapy.

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