EACVI/ASE EXPERT CONSENSUS STATEMENT

Expert Consensus for Multi-Modality Imaging Evaluation of Cardiovascular Complications of Radiotherapy in Adults: A Report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography

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Cardiac toxicity is one of the most concerning side effects of anti-cancer therapy. The gain in life expectancy obtained with anti-cancer therapy can be compromised by increased morbidity and mortality associated with its cardiac complications. While radiosensitivity of the heart was initially recognized only in the early 1970s, the heart is regarded in the current era as one of the most critical dose-limiting organs in radiotherapy. Several clinical studies have identified adverse clinical consequences of radiation-induced heart disease (RIHD) on the outcome of long-term cancer survivors. A comprehensive review of potential cardiac complications related to radiotherapy is warranted. An evidence-based review of several imaging approaches used to detect, evaluate, and monitor RIHD is discussed. Recommendations for the early identification and monitoring of cardiovascular complications of radiotherapy by cardiac imaging are also proposed. (J Am Soc Echocardiogr 2013;26:1013-32.)

Keywords: Radiotherapy, Echocardiography, Cardiac magnetic resonance, Nuclear cardiology, Cardiac computed tomography, Heart disease

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Conflict of interest: None declared.

Funding: No financial assistance was received to support this study.

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0894-7317/$36.00

http://dx.doi.org/10.1016/j.echo.2013.07.005

TABLE OF CONTENTS

INTRODUCTION

The two major contributors to radiation exposure in the population are ubiquitous background radiation and medical exposure.[1] A high-dose radiation exposure on the thorax is mainly used in the context of adjuvant radiotherapy after conservative or radical breast surgery, adjuvant or exclusive radiotherapy of lung and oesophageal cancer, and as a complement to systemic treatment in lymphoma. Irradiation of the heart increases the risk of the so-called 'radiation-induced' heart disease (RIHD).[2] RIHD is generated by total cumulative dosage of radiotherapy potentiated by the adjunctive chemotherapy. The total cumulative dosage of radiotherapy is a function of the number of treatments and the dose of irradiation.[3] The manifestations of RIHD may acutely develop but most often become clinically apparent several years after irradiation. RIHD holds a wide range of deleterious effects on the heart including pericarditis, coronary artery disease (CAD), myocardial infarction, valvular heart disease, rhythm abnormalities, and non-ischaemic myocardial and conduction system damages. The number of patients at risk of developing RIHD is likely to increase as ~40% of cancer survivors are at least 10 years past their radiotherapy treatment.[4] The development of RIHD may be accelerated by the contribution of shared common risk factors of cardiovascular disease and cancer such as obesity, inactivity, and substance abuse (i.e. tobacco and alcohol). Several clinical trials and epidemiologic studies have revealed the adverse impact of RIHD on the outcome of long-term cancer survivors.[2,3] Appropriate recognition of potential cardiac complications related to radiotherapy is warranted in our day-to-day clinical practice. Several imaging approaches can be used to detect, evaluate, and monitor RIHD. This document represents a consensus summary by experts of an extensive review of the literature regarding the role of cardiac imaging in the detection and serial monitoring of RIHD.

RADIATION EFFECTS ON THE HEART

Prevalence

Evidence of the dose-dependent increase in cardiovascular disease after chest radiotherapy has been documented in several studies, especially in the field of breast cancer and lymphoma (Table 1).[5-15] The estimated aggregate incidence of RIHD is 10–30% by 5–10 years post-treatment.[9] Among these patients who have received radiation, cardiovascular disease is the most common non-malignant cause of death. Comparing the long-term benefits and risks, the positive effect of adjuvant radiotherapy may thus be partially offset by cardiac complications. However, the precise prevalence of RIHD is difficult to determine because currently available data mainly come from single-centre studies, often retrospective, in which old radiotherapy techniques were used, patients with a prior history of CAD were excluded, and baseline pre-radiotherapy imaging was lacking. The prevalence of RIHD in the setting of modern protocols of delivering adjuvant radiotherapy, reduction in doses, and field radiation size is still poorly defined.

Table 1 Relative risks of RIHD in cancer survivors

Types	Hodgkin's disease relative risk	Breast cancer relative risk
RIHD	>6.3	2–5.9
Ischaemic heart disease	4.2–6.7	1–2.3
Cardiac death	2.2–12.7	0.9–2

The reported relative risk of RIHD is proportional to radiation dose and time to exposure.

Population Risk Factors

Despite considerable uncertainty, we are increasing our understanding of the factors that may influence the long-term risk of RIHD (Table 2). However, risk factors modulating the acute effects of cardiac radiation are hardly known.[3] It appears that the cumulative dose and its fractioning determine acute and chronic cardiac effects of radiation therapy. In the past, pericarditis used to be the most common side effect in patients receiving traditional radiotherapy for Hodgkin's disease.[9] Dose restriction to 30 Gy with lower daily fraction, different weighting of radiation fields, and blocking of the sub-carinal region have been reported to reduce the incidence of pericarditis from 20 to 2.5%. While, in doses >30 Gy, the risk of RIHD becomes apparent, the nature and magnitude of lower doses is not well characterized nor is it clear whether there is a threshold dose below which there is no risk.[3,7] Radiation increases the risk of cardiotoxic effects of certain chemotherapeutic agents, such as anthracyclines.[13] This interaction appears to be dependent on the total cumulative dose of anthracyclines.[14] Other patients and disease-related factors may potentially influence cardiac risk after ionizing radiation. Age at irradiation for breast cancer has been shown to influence the risk; patients younger than 35 have a relative risk of 6.5 than the general population of RIHD.[15] Similar observations have been made in the case of Hodgkin's lymphoma.[2,7] Smoking also increases the relative risk. Other risk factors such as diabetes, hypertension, overweight, and hypercholesterolaemia influence the overall risk.[16] However, in some studies, no increase in cardiac risk, especially of myocardial infarction, has been observed after adjusting for pre-existing cardiovascular risk factors.[17]

Pathophysiology

It is known that irradiation of a thoracic region encompassing the heart might be at the origin of acute and chronic RIHD.[1] Current knowledge about acute radiation effects mainly derives from animal experiments, which do not necessarily reflect contemporary radiotherapy treatment strategies, neither in dosage nor in timing of irradiation.[17] Furthermore, the processes from the acute injury to progressive