Nuclear medicine imaging methods of radiation-induced cardiotoxicity

Elisabeth-Anne Sophie Polomski, MD,* Maria Louisa Antoni, MD, PhD,*
Johan Wouter Jukema, MD, PhD,* Judith Rian Kroep, MD, PhD,† Petra Dibbets-Schneider,‡
Margriet G.A. Sattler, MD, PhD,§ and Lioe-Fee de Geus-Oei, MD, PhD‡,‖

Breast cancer survival is significantly improved over the past decades due to major improvements in anti-tumor therapies and the implementation of regular screening, which leads to early detection of breast cancer. Therefore, it is of utmost importance to prevent patients from long-term side effects, including radiotherapy-induced cardiotoxicity. Radiotherapy may contribute to damage of myocardial structures on the cellular level, which eventually could result in various types of cardiovascular problems, including coronary artery disease and (non-)ischemic cardiomyopathy, leading to heart failure. These cardiac complications of radiotherapy are preceded by alterations in myocardial perfusion and blood flow. Therefore, early detection of these alterations is important to prevent the progression of these pathophysiological processes. Several radionuclide imaging techniques may contribute to the early detection of these changes. Single-Photon Emission Computed Tomography (SPECT) cameras can be used to create Multigated Acquisition scans in order to assess the left ventricular systolic and diastolic function. Furthermore, SPECT cameras are used for myocardial perfusion imaging with radiopharmaceuticals such as ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin. Accurate quantitative measurement of myocardial blood flow (MBF), can be performed by Positron Emission Tomography (PET), as the uptake of some of the tracers used for PET-based MBF measurement almost creates a linear relationship with MBF, resulting in very accurate blood flow quantification. Furthermore, there are PET and SPECT tracers that can assess inflammation and denervation of the cardiac sympathetic nervous system. Research over the past decades has mainly focused on the long-term development of left ventricular impairment and perfusion defects. Considering laterality of the breast cancer, some early studies have shown that women irradiated for left-sided breast cancer are more prone to cardiotoxic side effects than women irradiated for right-sided breast cancer. The left-sided radiation field in these trials, which predominantly used older radiotherapy techniques without heart-sparing techniques, included a larger volume of the heart and left ventricle, leading to increased unavoidable radiation exposure to the heart due to the close proximity of the radiation treatment volume. Although radiotherapy for breast cancer exposes the heart to incidental radiation, several improvements and technical developments over the last decades resulted in continuous reduction of radiation dose and volume exposure to the heart. In addition, radiotherapy reduces loco-regional tumor recurrences and death from breast cancer and improves survival. Therefore, in the majority of patients, the benefits of radiotherapy outweigh the potential very low risk of cardiovascular adverse events after radiotherapy. This review addresses existing nuclear imaging techniques, which can be used to evaluate (long-term) effects of radiotherapy-induced

*Department of Cardiology, Heart and Lung Centre, Leiden University Medical Center, Leiden, The Netherlands.
†Department of Medical Oncology, Leiden University Medical Center, Leiden, The Netherlands.
‡Department of Radiology, section Nuclear Medicine, Leiden University Medical Center, Leiden, The Netherlands.
§Department of Radiotherapy, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, The Netherlands.
‖Biomedical Photonic Imaging Group, University of Twente, Enschede, The Netherlands.
Address reprint requests to Elissa A.S. Polomski, MD, Department of Cardiology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands. E-mail: e.s.polomski@lumc.nl

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mechanical cardiac dysfunction and discusses the potential use of more novel nuclear imaging techniques, which are promising in the assessment of early signs of cardiac dysfunction in selected irradiated breast cancer patients.

Introduction

Breast cancer is the most common type of cancer in women[1] One of the more serious complications associated with anticancer treatment is cardiotoxicity.[2] Cardiotoxicity has been described for various treatment modalities as systemic therapies (eg, following treatment with anthracyclines) and radiotherapy. Radiotherapy is one of the cornerstones of breast cancer treatment. As this treatment has significantly improved cancer survival and overall survival,[3] the long-term side effects of radiotherapy are becoming more apparent during follow-up of these patients. Radiation-induced heart disease (RIHD) - including pericardial disease, valvular disease, conduction disturbances and coronary artery disease (CAD) - can be a cause of morbidity and mortality after radiotherapy and, due to improved cancer treatment, surpasses cancer-related death after 30 years.[4] Nuclear imaging modalities can measure mechanical heart function, including diastolic dysfunction and the left ventricular ejection fraction (LVEF), which is an important marker of cardiac function and cardiotoxicity before, during and after radiotherapeutic and/or systemic cancer treatment[5-8] and offers opportunities to further investigate future (medicinal) secondary intervention and prevention methods in an early stage. However, alterations in cellular metabolism precede a decline of the left ventricular function. Therefore, several other radionuclide imaging techniques are under investigation and becoming available with the aim to detect and monitor earlier signs of cardiotoxicity, such as inflammation, changes in myocardial perfusion, and denervation of the cardiac sympathetic nervous system.[5,8-13] This review first discusses the pathophysiology of RIHD with an emphasis on risk assessment to select breast cancer patients based on exposed radiation dose to the heart, different radiation techniques and laterality of the breast cancer. Thereafter, radionuclide imaging techniques to detect RIHD will be highlighted.

Pathophysiology

Cardiovascular complications of radiotherapy mostly present after more than 10 years post-irradiation.[14-18] However, recent studies have demonstrated that RIHD can already manifest within 5 years after radiotherapeutic treatment.[19-24] Various older studies performed on patients irradiated 30-40 years ago with long-term follow-up data of breast cancer patients have shown an increased risk of cardiac morbidity and mortality associated with adjuvant radiotherapy.[16,25] A large study by Hooning et al. with 7425 patients treated for early breast cancer between 1970 and 1986 found that patients receiving adjuvant radiotherapy almost had a doubled increased relative risk of cardiac death after 25 years of follow-up in comparison to women who had not received any form of radiotherapy.[17] The patients irradiated after 1979 in this study experience low (postmastectomy radiotherapy) or no (postlumpectomy radiotherapy) excess mortality from cardiovascular disease (CVD). In another study, the same authors showed that radiotherapy, including either the left or right side of the internal mammary nodes (IMN), is associated with an increased risk of cardiovascular disease, primarily due to CAD and heart failure (HF).[18] However, breast irradiation only, was not associated with increased risk of CVD.

The development of RIHD depends on several factors including the radiation technique used, the prescribed treatment dose and target volume, the dose and volume of the heart exposed, time period of radiotherapy, follow-up time, as well as other cardiovascular risk factors, such as smoking, age of the patient and the combination with adjuvant systemic treatment (ie, chemotherapy).[22-24,26] Major risk factors for RIHD (shown in Table 1) are a younger age at exposure, prior radiotherapeutic treatment with doses of >30-35 Gy, larger volumes of the heart and left ventricle (LV) exposed, a longer period of time since radiotherapy, combined treatment with chemotherapy (anthracyclines) and preexisting classical cardiovascular risk factors — hypertension, diabetes mellitus, dyslipidemia, obesity and smoking.[8,9,22,23,26-28] Cellular damage can be induced directly after radiotherapy, but it can take up to 30 years for cardiovascular complications, such as CAD or even sudden cardiac death, to develop.[11,19,21-23,29]

RIHD can develop due to several physiological circumstances that induce (fibrotic) micro- or macrovascular damage.[22,30-33] Whereas radiotherapy is used to induce cell death of malignant cells, damage to healthy surrounding tissue is also observed. Especially endothelial cells are very

Table 1 Major Risk Factors for Radiation-Induced Heart Disease

Younger age at exposure
Prior radiotherapeutic treatment with doses >30-35 Gy
Larger volumes of heart and left ventricle in radiation field
Longer period of time since radiotherapy
Combined treatment with chemotherapy (anthracyclines)
Preexisting cardiovascular risk factors

sensitive to radiation.[22,34,35] Endothelial damage can lead to an inflammatory response and increased oxidative stress, characterized by the release of cytokines, resulting in endothelial dysfunction and cell apoptosis. This process induces the replacement of myocardial tissue by fibrotic tissue, affecting cardiac function.[11,22,34,36-40] Damage on this microvascular level can possibly be the underlying cause of the development of vascular damage, raising the risk of atherosclerotic plaque development due to arterial stiffness that is provoked by radiation.[35,38] Radiation may also lead to myocardial deposition of fibrin and collagen and a pro-thrombotic status, causing narrowing of the vessels and increasing the risk of thrombosis and vessel rupture through fibrous proliferation of the myocardial intima, consisting of foam cells and lipid-containing macrophages. This physiological process can eventually lead to CAD, where focal disease in the left anterior descending artery (LAD) is observed in a minority of the patients treated with radiation for left-sided breast cancer and involvement of the proximal right coronary artery (RCA) is most common after radiation for right-sided breast cancer.[22,37] Figure 1 summarizes the pathophysiological process of RIHD.

Early signs of RIHD are peri- and myocardial inflammation, whereas long-term side effects on macrovascular level include coronary artery damage and injury of the myocardial vessels due to endothelial damage.[41-43] Nuclear imaging techniques that can be used to visualize these pathological processes will be discussed later in this review (see Table 2).

The underlying physiological process of radiation-induced CAD and the classical development of atherosclerotic vascular disease is similar regarding intimal proliferation and the evolution of intimal plaques containing macrophages that can rupture and cause thrombosis.[12,22,37] However, in RIHD, adventitial fibrosis and reduced wall thickness of the media also contribute to the development of atherosclerosis.[24] Moreover, the radiation-induced atherosclerotic plaques tend to consist primarily of soft, elongated and fibrotic tissue, while a minority of lesions contains lipid or calcium deposits in addition to fibrosis.[34] An early manifestation of RIHD used to be pericarditis, which has become very rare over the past decades due to newer radiation techniques with related lower exposed dose and volumes to the heart. Valvular disease can develop after long-term follow-up. Although radiation-induced valve disease is less pronounced in patients with breast cancer in comparison with Hodgkin lymphoma due to minimally exposed dose to the heart valves, patients treated for left-sided breast cancer including the IMN have shown fibrotic aortic valve disease.[18,26,44]

Radiation Doses and Techniques

Radiation tangential beams/fields expose the heart to a certain incidental radiation dose, which can be accurately measured since the last one to two decades on radiation planning computed tomography (CT) scans and is referred to as the mean heart dose (MHD). By measuring the MHD, the volume of the heart receiving a particular dose can be determined.[45] The relative risk of radiation-induced CAD increases linearly with the MHD. Several studies have found that the relative risk of CAD and events increases with 6.4-16.5 per Gy MHD.[19-21,27,29,46] The dose delivered to the heart and coronary arteries varies in the individual patient, but the majority of the left-sided irradiated patients has a MHD of <3 Gy.[47] Patients receiving >20 Gy MHD had a 3.4-fold (95% confidence interval 1.5-7.6) higher myocardial infarction (MI) rate than unirradiated patients, which indicates a dose-effect relation of radiation doses on cardiac outcomes.[31] This is
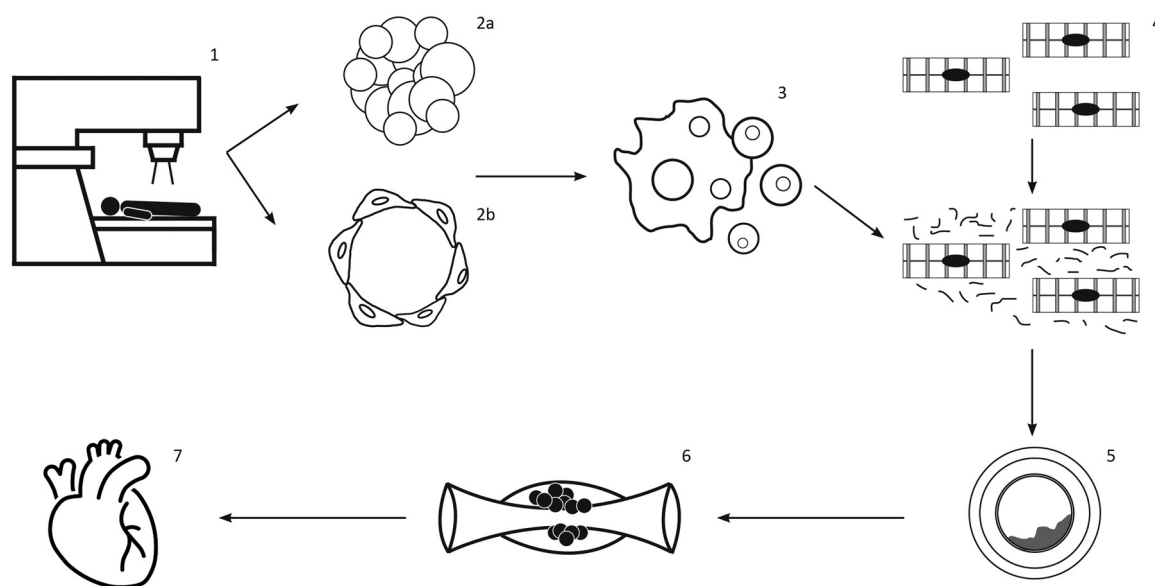

Figure 1 *Overview of the pathophysiology of radiation-induced cardiotoxicity.* Radiotherapy (1) leading to damage of tumor cells (2A), as well as endothelial cells (2B), causing an inflammatory response resulting in cell apoptosis (3). Myocardial tissue is replaced by fibrotic (4) tissue, leading to vascular damage. This process raises the risk of atherosclerotic plaque development, (5) which can lead to vessel narrowing (6) and eventually to coronary artery disease (7).

Table 2 Imaging Radiation-Induced Cardiotoxic Disease

Cardiac Disease	Pathofysiological Process	Imaging Modality	Tracer
CAD	Perfusion defects	MPS SPECT	^{99m}Tc-sestamibi
			^{99m}Tc-tetrofosmin
		MPS PET	[82]Rb
			[15O]H2O
			[13N]NH3
			^{18}F-Flurpiridaz
	Inflammation/Myocardial cell metabolism	PET	^{18}F-FDG
	Fatty acid metabolism	SPECT	^{123}I-BMIPP
HF	Denervation sympathetic nervous system	SPECT	^{123}I-mIBG
		PET	^{11}C-HED
	Decline LVEF	MUGA SPECT	^{99m}Tc-DMP-HSA
			^{99m}Tc-labeled red blood cells
		MPS SPECT	^{99m}Tc-sestamibi
			^{99m}Tc-tetrofosmin
	Diastolic dysfunction	MUGA SPECT	^{99m}Tc-DMP-HSA
			^{99m}Tc-labeled red blood cells
	Myocardial cell injury and necrosis	SPECT	^{111}In-antimyosin
CMP	Denervation sympathetic nervous system	SPECT	^{123}I-mIBG
		PET	^{11}C-HED

CAD, coronary artery disease; HF, heart failure; CMP, cardiomyopathy; MPS, myocardial perfusion scintigraphy; PET, positron emission tomography; SPECT, single-photon emission computed tomography; MUGA, multigated acquisition

associated with the radiation technique used, the treatment time period, the location and extent of the treatment volume, individual anatomy, and radiation of the IMN. Radiotherapy including the IMN increases the MHD in particular for left-sided breast cancer irradiation.[46,48] Nowadays, several modern radiotherapy techniques exist that are used for better heart sparing, such as deep-inspiration breath hold (DIBH), intensity-modulated radiation therapy or volumetric modulated arc therapy, partial breast irradiation, a prone patient treatment position and proton therapy in selected patients. As a result, the MHD for breast cancer irradiation has decreased significantly, further reducing the (minimal) risk of radiation-induced cardiac morbidity and mortality in most breast cancer patients.[27,36,49] The heart is exposed to the least MHD for irradiation of right-sided breast cancer without the IMN, whereas adding radiation of the IMN increases this dose for left-sided breast cancer as well as for right-sided breast cancer.[46,49] A study performed by Boekel and colleagues, showed that anthracycline-based chemotherapy and irradiation using regimens with substantial MHD (9-17 Gy) were associated with increased incidence of several types of CVDs in patients treated during 1970-2009.[26]

However, despite the development of techniques reducing the MHD, cardiac exposure still depends on the extent of the radiation treatment volume. For example, in early-stage breast cancer, only the chest wall/breast is irradiated. A study performed by Taylor et al. on breast cancer patients treated between 1970-2009 showed that, depending on the laterality and extent of the treatment volume, including IMN irradiation can raise the risk of cardiovascular disease for left-sided breast cancer as well as for right-sided breast cancer.[26] The MHD for left-sided breast cancer in studies performed between 1950 and 2013 on breast cancer patients irradiated

(chest wall/breast and/or IMNs, supraclavicular fossa, posterior axilla) varied between 0.9 Gy and 14 Gy.[46,50]

Considering the coronary arteries, the LAD is most exposed to the highest radiation dose, in particularly in the treatment of left-sided breast cancer, as parts of this coronary artery are located closely to the chest wall/breast, which makes this artery, more prone to radiation-induced damage compared to the left circumflex artery (LCX) and RCA (see Fig. 2).[51] The LAD runs close to the left chest wall/breast and can therefore be exposed to high radiation doses of about 35 Gy, which can rise up to doses of 50 Gy, and thereby potentially impacting the MHD.[32,46,52]

Cardiac exposure to radiation is associated with the technique used, whereby the dose increases from 4.7 Gy to 14 Gy in left-sided breast cancer patients using megavoltage vs orthovoltage machines respectively, which were mostly used during the 1970s-1990s for breast cancer irradiation. In studies performed 20-50 years ago, IMN irradiation was more often included in the treatment volume, and larger treatment volumes were used, both resulting in a higher MHD and associated higher cardiac mortality.[53,54]

Nowadays, several improvements in radiation techniques have been introduced over the past decades that make it possible to further lower cardiac radiation exposure, reducing the dose delivered to the heart by 25%-75%.[11,55,56] Improved computerized treatment planning systems are used to increase the distance between the posterior tangential field/dose and the anterior silhouette of the heart. This planning system operates with three-dimensional radiotherapy planning CT scans, making it possible to perform individual patient-specific measurements (see Fig. 3). This results in accurate measurements of the radiation dose in surrounding normal tissues, and treatment dose planning aiming at
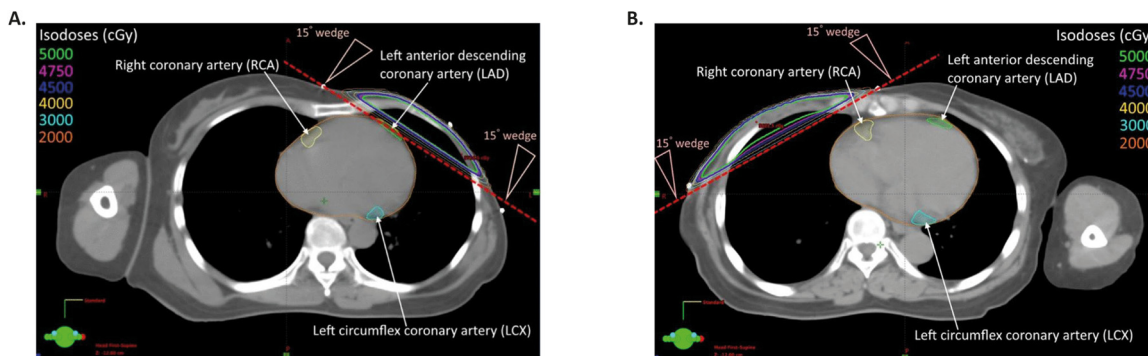
Figure 2 *Dose distribution in left-sided and right-sided breast cancer irradiation.* Treatment planning CT-scans showing the dose distribution from 6MN tangential irradiation in left-sided and right-sided breast cancer after mastectomy. The organs at risk, including the heart, left anterior descending coronary artery, left circumflex artery, and right coronary artery are outlined. (Reprinted with permission from Lai et al.[52])
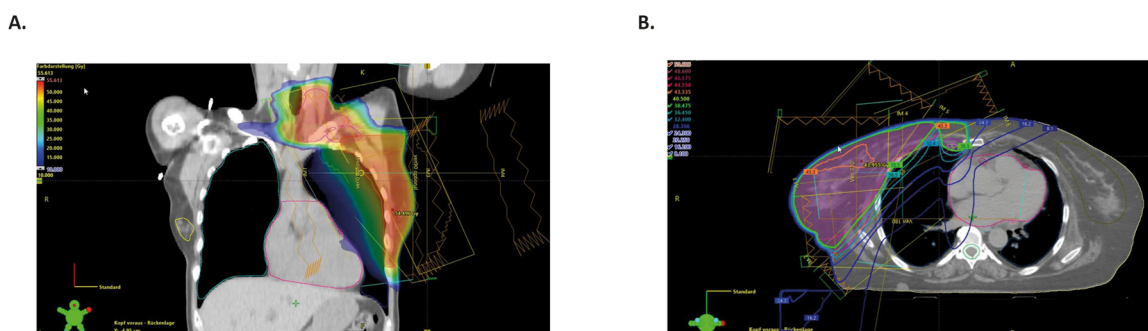

Figure 3 *Treatment planning CT-scans.* Treatment plans for breast cancer irradiation. Figure 3.A shows a modern treatment plan of a female patient undergoing left-sided breast and regional nodal radiotherapy using a 4-field sliding window technique Figure 3.B shows a female patient undergoing right-sided breast and regional nodal radiotherapy including supra-/infraclavicular and internal mammary lymph nodes after breast-conserving surgery using a 5-field sliding window IMRT. (Reprinted with permission from Haussmann et al.[60])

reducing cardiac exposure and therefore minimizing chances of different manifestations of cardiotoxicity.[40,57-59]

In selected patients, a prone position compared to a supine position may further reduce the heart volume exposed in the radiation field by 85%.[40] Applying the DIBH technique — in which the treatment dose is given during deep inspiration breath holding - the heart is moved posteriorly and inferiorly and further outside the tangential fields (Fig. 4). This creates more distance between the heart and the chest wall, lowering the radiation dose to the myocardium and LAD, without affecting the dose delivered to the target treatment volume, which

may reduce the cardiac volume significantly up to 80%, especially when wide tangents are used for treatment.[11,40,55,59-64]

A relatively new technique that can significantly reduce the cardiac radiation dose is proton therapy, by which the MHD can be reduced by 75% in selected patients and, in combination with other techniques, this can even be limited to 0.009 Gy.[65,66] However, it is only useful to apply this technique in patients in whom this reduction will make a clinical relevant difference due to the high costs of proton therapy. In patients without prior chemotherapy or without cardiovascular risk factors, and low MHD (eg, only breast/chest wall irradiation), the risk of
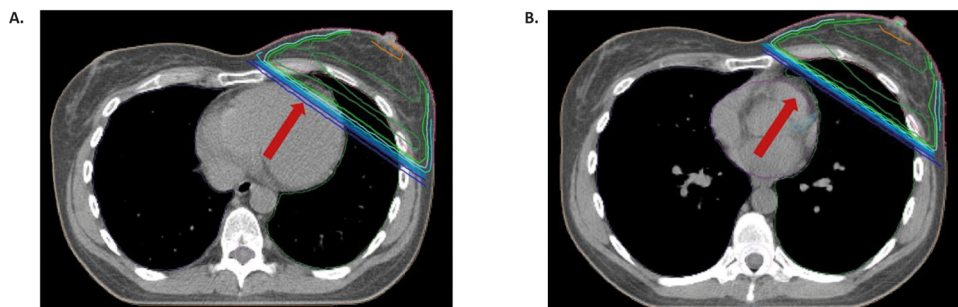

Figure 4 *Deep inspiration breath-hold.* CT-scans showing the anatomic position of the breast target volume in free-breathing (4A) and deep inspiration breath-hold (4B). (Reprinted with permission from Haussmann et al.[60])

RIHD is already low and a therefore a reduction of 75% may not be clinically relevant.[67] To select patients that could benefit from proton therapy, a model-based approach has been implemented, predicting the absolute lifetime risk of acute cardiovascular events <80 years based on the MHD.[68]

Perfusion defects and wall motion abnormalities that have developed after irradiation for breast cancer treatment are usually contributed to older irradiation techniques used decades ago, often combined with or treated previously with chemotherapy. Low cardiac radiation dose exposure usually does not have great clinical impact on the development of CAD.[29,36,49,58,69]

Left-sided Breast Cancer Vs Right-Sided Breast Cancer

Numerous studies over the past 50 years have focused on different cardiac outcomes for women irradiated for left-sided breast cancer vs women irradiated for right-sided breast cancer and their outcomes have shown varying results regarding risks of cardiac morbidity and mortality. Studies on patients irradiated between 1977-2012 concluded that irradiation for left-sided breast cancer compared with irradiation for right-sided breast cancer increased the risk of cardiovascular events and morbidities following radiotherapy, even more than 10-20 years thereafter.[69-73] Data of patients irradiated between 1954-2001 showed an increased risk of cardiac mortality after left-sided breast irradiation,[16,25,36,74,75] with a decreasing trend since the 1980s due to improved irradiation techniques.[76] However, in contrast to the abovementioned, more recent studies show no difference in cardiac mortality after irradiation for left-sided breast cancer compared to right-sided breast cancer.[71,77,78] A study by Nilsson et al. showed that irradiated patients have an increased risk of CAD if irradiated for left-sided or right-sided breast cancer in particular hotspot regions (proximal RCA, mid-LAD and first diagonal branch).[32]

In non-irradiated women, no differences are shown for cardiac morbidity and mortality between left-sided and right-sided breast cancer.[16] When comparing radiotherapeutic treatment to mastectomy for left-sided breast cancer between 1998 and 2005, irradiation (chest wall/breast, IMN supraclavicular), shows an increased risk of cardiovascular events - in particular valvular disease, ischemic heart disease (IHD) and HF.[79] For the incidence of (non-fatal) MI after radiotherapy for breast cancer, no side-related difference has been found.[48,80] The volume of cardiac substructures and the coronary arteries exposed to radiation correlates with the laterality of the breast tumor and the extent of cardiac volume in the radiation field. In right-sided breast cancer irradiation, the RCA may be exposed to radiation, whereas in left-sided breast cancer the LAD and left main artery (LM) may be exposed.[81] However, the exposure of coronary arteries to irradiation also depends on whether only the chest wall/breast is irradiated or if the IMN also is included in the treatment volume. Depending on the laterality, the radiation technique used and exposure of the heart, the anterior parts of the heart, the apex and the LM, LAD and RCA could be included in the radiation field.[83] Therefore, post-radiotherapy, fibrosis is usually more often present in the lateral and anterior wall of the LV as compared to the posterior wall.[11]

Left Ventricular Function

Left Ventricular Ejection Fraction

For accurate follow-up of the LVEF in cancer patients treated with cardiotoxic agents, it is important to obtain a baseline LVEF before the start of treatment.[83] During follow-up, serial measurements of the LVEF are performed to create a risk assessment of cardiotoxicity and to assess cardiac function before, during and after anticancer treatment.[83-85] LVEF can be measured by multigated acquisition (MUGA), quantitative gated blood-pool Single-Photon Emission Computed Tomography (SPECT), two- and three-dimensional echocardiography and cardiovascular magnetic resonance imaging (CMR). MUGA and echocardiography are most widely available, whereas MUGA and cardiac MRI have the greatest reproducibility. In the past, MUGA has been acknowledged as the gold standard for the determination of subclinical LVEF in cancer patients, as it is non-invasive and cost-effective, has good repeatability of LVEF measurements and makes quantification possible (Fig. 5).[5,84,86] MUGA images are created by a gamma (γ) camera using technetium-99m (^{99m}Tc) labelled erythrocytes (in vitro, in vivo or a combined approach) or using technetium-99-m-labeled human serum albumin (^{99m}Tc-HSA) for blood pool imaging.[5,9,84,85,87,88] The γ camera constructs a series of images of the heart projecting each phase of the heart cycle. However, whereas the repeatability of LVEF measurements does not differ, guidelines have introduced echocardiography or CMR for the evaluation of oncologic cardiotoxicity in addition to MUGA, as these modalities do not expose patients to radiation.

The choice of which technique is used for monitoring cardiotoxicity is dependent on the accuracy and suitability for the individual patient. In specific patient groups, some techniques are preferred above others. For example, in pediatric patients, echocardiography is most preferably performed as this technique lacks radiation, whereas acquiring qualitative images in obese patients or patients with specific anatomic thoracic variations is difficult using echocardiography. In addition, which imaging technique is chosen, is also very dependent on the physician's expertise and center's availability.[5]

Monitoring the LVEF with labelled ^{99m}Tc erythrocytes using serial MUGA images contributes to the prevention of HF.[5,87] However, measuring the LVEF can underestimate cardiac damage. In the presence of dysfunctional myocytes, the myocardial compensatory system can generate adequate ventricular output. In this case, an adequate LVEF will not be an accurate measure for the actual cardiotoxicity.[84] Therefore, it has been suggested that these scans can better be performed during exercise than during rest to detect left
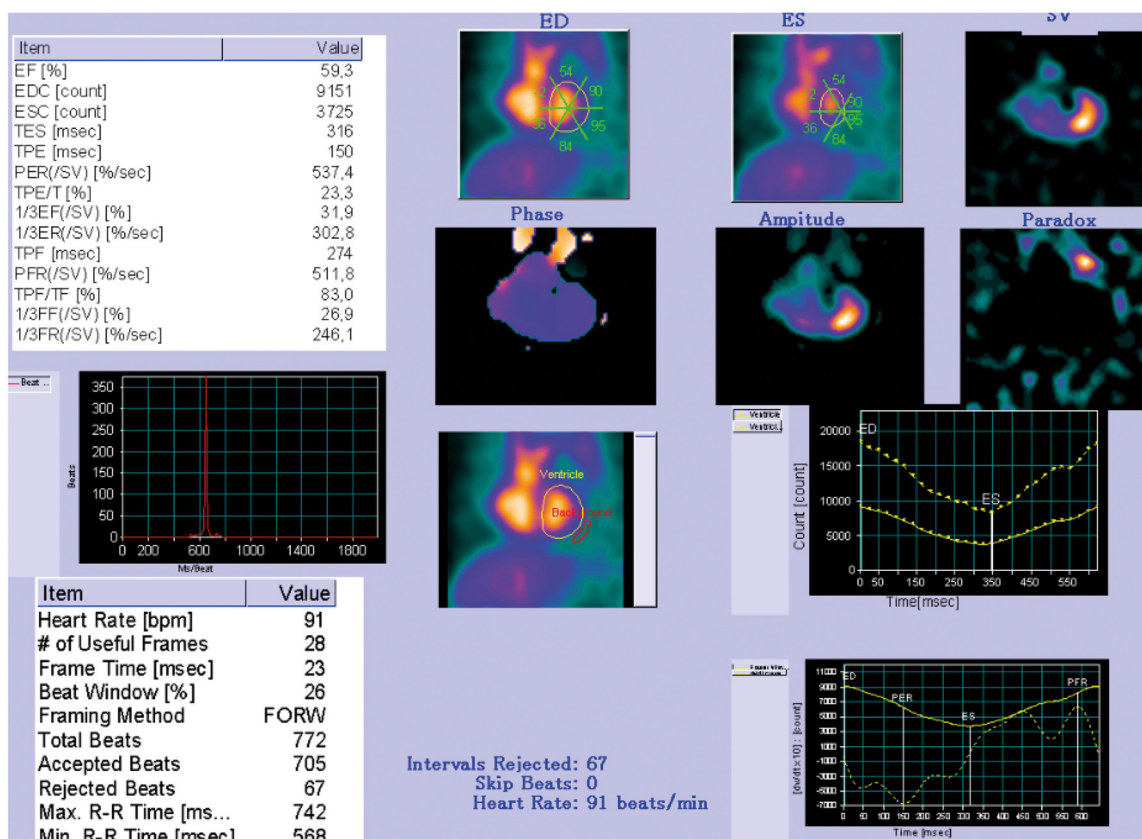
Figure 5 *Multigated acquisition* scan. A multigated acquisition study with regions of interest drawn around the end-diastolic volume (ED) and end-systolic volume (ES) in the left ventricle. The ejection fraction can be calculated by the formula (ED-ES)/ED x 100%. In this patient the calculated ejection fraction is (9151-3725)/9151 × 100% = 59.3%. The phase image with corresponding narrow histogram suggests synchronous contraction of the left ventricular myocardium. The left ventricular time activity curve in this patient is normal. The paradox image does not show any region of the left ventricular myocardium to be in paradox. On the amplitude image maximal count variation is shown in the lateral wall of the left ventricular myocardium.

ventricular dysfunction, because the compensatory mechanism that preserves the end-diastolic volume in HF during rest fails during exercise.

A study by Lapinska et al.[83] showed that 71 patients treated with radiotherapy in addition to chemotherapy (combined treatment with doxorubicin and cyclophosphamide or doxorubicin and paclitaxel/docetaxel) did not show a progressive decrease in LVEF. However, patients irradiated for left-sided breast cancer showed more decline in LVEF compared to patients treated for right-sided breast cancer.

In addition to the above-mentioned scanning technique, SPECT myocardial perfusion scintigraphy (MPS) can also be performed to determine LVEF by using the labelled tracers ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin. In many cancer patients, MPS is performed to assess signs of IHD, as some cancers and CAD share common risk factors, including smoking and age. Although these scans primarily determine myocardial perfusion defects, the LVEF is also obtained as a byproduct. However, LVEF acquired using MPS is not as accurate as LVEF measurements performed with MUGA due to the technical difference that MUGA quantifies the cardiac blood pool and, in MPS, the LVEF is measured by the determination of myocardial contours with higher variability in measurements,[6] since this technique suffers from potential

spillover effects from the myocardium in the left ventricular cavity and will therefore underestimate either end-diastolic or systolic left ventricular volume.

Diastolic Dysfunction

A decrease in LVEF is a relatively late sign of cardiac deterioration. Preceding systolic dysfunction, diastolic dysfunction very likely occurs. Assessment of diastolic function by ^{99m}Tc MUGA scintigraphy is, therefore, an interesting application for early detection of cardiotoxicity. Diastolic dysfunction is characterized by a prolonged isovolumetric relaxation phase, delayed rapid filling and an increased atrial kick. All these parameters can be visualized using the LV time-activity curve, which reflects the radioisotope behavior and is in line with the blood pool behavior at different time points in the cardiac cycle. The peak diastolic filling rate can be calculated by calculating the slope of the LV time-activity curve diastolic phase. The most commonly used cut-off values are a peak filling rate (PFR) ≤ 2.5 end-diastolic volume per second (EDV/s) or a time to peak filling rate (TPFR) ≥ 180 ms.[89] Detection of diastolic dysfunction using ^{99m}Tc MUGA scintigraphy may allow early detection and treatment of preclinical signs of HF.[84,90]

Neuronal Denervation

Preceding a decline in left ventricular function, myocardial cell damage can already be visualized. Myocardial cell injury can be detected by the uptake of [^{123}I]-mIBG on SPECT (Fig. 6) and [^{11}C]hydroxyephedrine ([^{11}C]HED) on Positron Emission Tomography (PET).[91] By performing these scans the myocardial neuronal integrity and functionality of the myocardial adrenergic neurotransmitter system can be visualized. Norepinephrine is a neurotransmitter used by the sympathetic nervous system and interacts with the target tissue via adrenoceptors. MIBG is similar to norepinephrine in terms of release pathway, storage and uptake, but, in comparison to its adrenergic analog, is not metabolized by the same enzymes. Therefore, MIBG remains in the adrenergic receptors for a longer period of time.[5,92] The efferent sympathetic nervous system innervating the cardiac muscle can be visualized by [^{123}I]-mIBG SPECT. In the presence of myocardial cell damage, a compensatory system is activated to increase the heart rate, contractility and conduction of the heart. As in this situation blood flow to essential organs is decreasing, the working of the renin-angiotensin system and sympathetic-adrenergic activity is intensified to ensure perfusion of vital organs. This is accomplished by vasoconstriction of the blood vessels, leading to increased afterload and decreased cardiac output. In patients suffering from HF, elevated plasma levels of renin and norepinephrine can be detected, possibly indicating an impaired left ventricular function.[5] [^{123}I]-mIBG and [^{11}C]HED are able to give information about the severity and prognosis of HF, as uptake of these tracers is significantly lower in patients with HF (Fig. 6).

In comparison to [^{123}I]-mIBG SPECT, imaging the neuronal denervation by [^{11}C]HED gives improved assessment of abnormalities.[91,92] PET surpasses SPECT by the ability to acquire detailed tracer kinetic analysis due to a higher temporal resolution and spatial resolution and PET enables non-invasive quantitative measurement of this neurophysiological process.[5] However, [^{11}C]HED has a short half-life, making wide distribution impossible. Also, for labelling ligands used for PET screening, particular expertise in this field is necessary, which is not available in every center. As visualizing the sympathetic neuronal system can detect mechanisms arising from activated compensatory mechanisms due to myocardial damage, decreased tracer uptake can show abnormal sympathomimetic innervation of the myocardial tissue in an early stage before the LVEF drops.

Myocardial Cell Damage and Necrosis

Performing SPECT using the tracer Indium-111-antimyosin (^{111}In antimyosin) is useful to assess abnormalities that are indicative of clinical HF. [111]In antimyosin is a specific marker for myocardial cell injury and necrosis. Uptake of this tracer gives information about altered integrity of myocytes since this tracer attaches to the intracellular myosin in irreversibly damaged sarcolemma.[41]

Coronary Artery Disease
Perfusion Abnormalities MPS (SPECT)

MPS (SPECT) is a non-invasive modality that is able to assess myocardial perfusion and wall motion accurately and to perform phase analysis.[5,41,93-96] To observe radiation-induced myocardial perfusion abnormalities that may indicate vascular damage or ischemia, MPS (SPECT) can be carried out using the labelled myocardial perfusion tracers ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin, thereby also deriving several other important parameters, including ventricular volumes, LVEF and wall motion abnormalities.[97]

MPS (SPECT) is performed by intravenously injecting a radiotracer of which the uptake corresponds to the myocardial perfusion in that area. MPS can image signals of radiation-induced microvascular damage and CAD and abnormalities in myocardial perfusion are indicated by decreased tracer uptake — for example, in the presence of irreversible (infarction) or reversible (ischemia) perfusion defects.[95,98,99] Perfusion defects on resting MPS are usually attributed to fibrosis and myocardial degeneration, whereas perfusion abnormalities detected on MPS during physical or
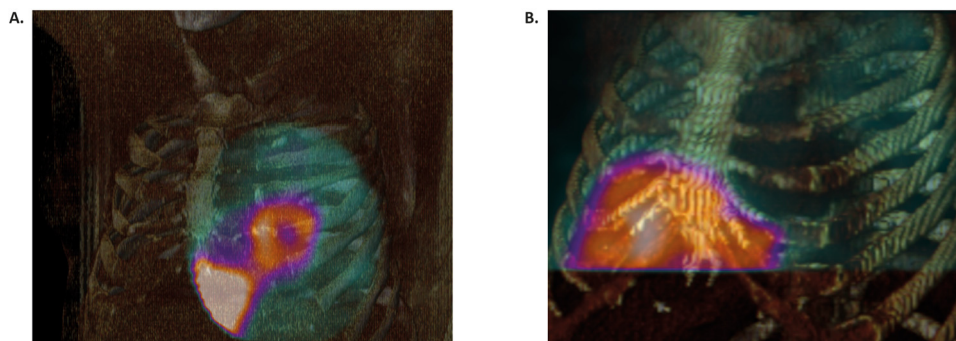

Figure 6 *Uptake of [^{123}I]-mIBG on SPECT.* The uptake of [^{123}I]-mIBG on SPECT in two patients Figure 6.A shows a patient without cardiac denervation. The heart/mediastinum ratio is 2 (normal value: 1.79 +/- 0.22) Figure 6.B shows a patient with cardiac denervation. The heart/mediastinum ratio is 1.08.

pharmacological stress, if not persisting in rest, correlate more strongly with endothelial dysfunction and vasculopathies that can increase the risk of acute coronary syndrome.[100] In the numerous studies over the past decades assessing radiation-induced perfusion abnormalities defined by a decreased uptake of ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin on MPS (SPECT), reversible as well as irreversible defects were seen in 24%-70% of the patients.[93,101-107]

Perfusion defects either detected early or several years after radiotherapy have been described in many studies with a varying follow-up period of six months to ten years, which also included patients who had been treated with chemotherapy prior to radiotherapy.[11,30,101-111] However, in most of these studies, patients were treated before or around the turn of the century, when planning CT-scans were not performed yet and therefore it was more difficult to compare the location of the defects on cardiac imaging to radiotherapy dose and volume effects on the corresponding cardiac area, while nowadays, due to further technological improvements, this association can be better assessed.

MPS (SPECT) can also be used in asymptomatic (left-sided) breast cancer patients with high cardiovascular risk as a screening tool before initiation of radiotherapy.[97]

Multiple studies showed an association between the location of perfusion defects and the irradiated exposed heart area — such as the anterior, anterolateral and apical parts of the LV — and found that perfusion defects are more present in patients of whom larger heart volumes and a larger left ventricular volume are included in the radiation field/exposed to radiation dose, which indicates a dose-dependent relationship for regional perfusion defects.[93-96,102,103,108,109,111-113]

Gyenes et al. found new perfusion defects, assessed with ^{99m}Tc-sestamibi, one year after radiotherapy using partially wide tangents or an IMN field matched to shallow tangents in half of the left-sided breast cancer patients in whom the LV was exposed in the radiation field. However, as this retrospective study only included 17 patients with varying baseline cardiovascular risk factors, systemic therapies and radiotherapeutic treatments, long-term follow-up is necessary to assess the predictive value of this finding for developing radiation-induced CAD.[108] Nevertheless, a study performed by Hojris and colleagues in nine patients with left-sided breast cancer and seven controls more than 8 years after radiotherapy using en face electrons and the same tracer as Gyenes and colleagues, did not show a significant difference in perfusion defects on MPS (SPECT) between irradiated women between 1982 and 1990 and non-irradiated women (40% and 57% respectively).[94] Moreover, the perfusion defects that were seen in the irradiated patient group were not located in the radiation field/exposed heart volume.[94] This difference in the presence of perfusion defects can probably be explained by a different cardiac exposure per patient - resulting in fewer cardiotoxic effects - and the limited number of patients included, but as both studies described a small study population, these discrepancies may also be attributed to variations in baseline cardiovascular risk factors and individual radiotherapeutic dose-volume characteristics.

Radiation-induced perfusion defects imaged by MPS may not always have an immediate clinical impact. A study performed by Seddon et al. on 36 patients found regional wall motion abnormalities in almost one-third of the patients with perfusion defects, in the absence of a LVEF decrease of more than 5%. In this study, left-sided breast cancer patients were only included if the treatment field contained at least 1 cm of the heart.[105] In a study by Yu et al. that included 83 left-sided breast cancer patients treated in the 1990s, abnormalities on MPS could be considered clinically significant, considering that the development of clinical cardiac symptoms was more common in the presence of perfusion abnormalities on MPS (SPECT).[114]

The results following the assessment of myocardial perfusion post-radiotherapy possibly highlight that radiotherapy can accelerate the progress of atherosclerosis, as an atherosclerotic plaque would usually develop over a longer period of time than described in various studies.[99,102,103,114]

Fatty Acids

Fatty acids are highly consumed by the myocardium as a source of energy.[115] Imaging the metabolic status of fatty acids can assess pathological processes of (instable) CAD and MI. SPECT imaging can use [^{123}]I-beta-methyl-p-iodophenylpentadecanoic acid ([^{123}]I-BMIPP) to detect decreased oxidative metabolism of free fatty acids, which is seen in the presence of myocardial ischaemia. The uptake of [^{123}]I-BMIPP correlates with the production of adenosine triphosphate and is lowered in areas with decreased perfusion, as fatty acids cannot be metabolized due to an oxygen deficiency. However, in the acute setting, its uptake can be increased.[116] [^{123}]I-BMIPP is especially used for the evaluation and prognosis of CAD - as it is a reliable marker of myocardial damage -, but SPECT scans using this tracer are also carried out to evaluate CMP and HF.[115]

Perfusion Abnormalities MPS (PET)

Perfusion defects can also be determined by assessing myocardial blood flow (MBF) utilizing tracers of which the uptake is visualized by PET scans. PET scanning for cardiac disease has grown significantly over the past decades. A great advantage of this scanning technique is that it is less time-consuming for patients compared to MPS (SPECT), a.o. due to the shorter half-life of PET isotopes, which allows a shorter interval between rest and stress scans.[117] Another advantage is that shorter half-life also correlates with a reduced radiation exposure. PET scanners, as well as novel tracers, have become more widely available for clinical and research purposes.[118] MPS (PET) scans operating with the tracers Rubidium-82 (^{82}Rb), [^{15}O]H$_2$O, [^{13}N]Ammonia ([^{13}N]NH$_3$) and [^{18}F]Flurpiridaz are particularly useful for monitoring changes in MBF and myocardial flow reserve (MFR). These changes can even be detected on the level of the secondary and tertiary branches of the main coronary arteries.[119,120] Table 3 summarizes the most important PET tracers characteristics for myocardial blood flow quantification. For

Table 3 Myocardial Blood Flow PET Tracers

PET Tracer	[15O] H$_2$O	[18F] Flurpiridaz	[13N] NH3	^{82}Rb
Half-life	123 seconds	2 hours	9.96 minutes	75 seconds
Radiation exposure	0.8 mSv	5.5-6.5 mSv	2 mSv	1.5 mSv
On-site cyclotron	Yes	No, can be produced remotely and transported	Yes	No, produced by a generator
Approved for clinical use?	Yes	No, investigation in phase III trials	Yes	Yes

patients with present or historical cardiotoxic cancer treatments, measuring MBF using the abovementioned PET tracers can be of prognostic value for future cardiac events as this technique is able to detect microvascular coronary disease and myocardial ischaemia, which are early signs of endothelial dysfunction.[121] In comparison to the MPS (SPECT) tracers ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin, the aforementioned PET tracers all show a more linear relationship between tracer uptake and MBF (Fig. 7).[123] In general, the most optimal tracer creates a linear relationship between tracer uptake and MBF, as this tracer characteristic improves the accuracy of detecting ischaemia.[120]

[^{15}O]H$_2$O-PET/CT is the gold standard for the non-invasive measurement of MBF as its uptake is linearly related to the MBF (Fig. 7) and this tracer has the ability to estimate tissue viability by measuring the perfusable tissue fraction (PTF).[118] [^{15}O]H$_2$O diffuses freely along the myocardial cell membrane, which contributes to kinetics that are suitable to perform quantification.[120] [^{15}O]H$_2$O is used for research purposes as well as in clinical practice and has been accepted for detecting CAD.[118,123]

[^{18}F]Flurpiridaz has not yet been accepted for clinical use, but is currently being investigated in phase III clinical trials. It is the most promising tracer for quantifying MBF nowadays by binding to the mitochondrial complex-1.[124] [^{18}F] Flurpiridaz has a short positron range, a very good spatial and contrast resolution and is quickly taken up in the myocardial tissue.[118,120] The relative higher radiation exposure that [^{18}F]Flurpiridaz exposes patients to, is still lower than the 10-16 mSv that MPS (SPECT) examinations using ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin expose patients to.[125] A phase III study performed using [^{18}F]Flurpiridaz-PET/CT investigated its sensitivity for detecting CAD in case of >50% stenosis compared to MPS (SPECT) using ^{99m}Tc-labelled tracers. Results showed that the sensitivity of this PET tracer was significantly higher than the sensitivity of MPS (SPECT) (71.9% vs 53.7%), and this study also concluded that [^{18}F] Flurpiridaz was clinically safe.[125]

[^{13}N]NH$_3$ gives a high image quality due to a short positron range, high spatial resolution and a good contrast resolution.[118,120] It is accepted for use in clinical practice and in for research purposes.[123]

Comparing the abovementioned tracers, ^{82}Rb has the lowest spatial resolution of the MBF PET-tracers due to a long positron range, but still high enough for routine application and higher than the resolution obtained by SPECT-imaging using ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin.[120] Moreover, an important advantage of this isotope is that no on-site cyclotron is needed as it is produced by a generator.[118]

Clinically, PET scanning using MBF tracers is preferably used when diffuse CAD or multivessel disease is suspected, as balanced three-vessel disease can sometimes be missed by MPS (SPECT), but it also has the ability to detect asymptomatic CAD[118]. Moreover, in patients presenting with complaints indicative of myocardial ischaemia, in particular females without significant stenosis on coronary angiography, PET can be performed to detect the presence of microvascular disease.[118,126,127]

Comparing PET to other imaging modalities, the PACIFIC trial and other studies found that the diagnostic accuracy of PET scanning using tracers assessing MBF is exceeding MPS (SPECT) and coronary computed tomography angiography by having an increased sensitivity as well as specificity for significant stenosis.[118,120,128-130] A study by Rasmussen et al. investigating 20 women treated with radiotherapy for breast cancer did not find a difference between the not radiated inferior and radiated anterior myocardial wall with regards to
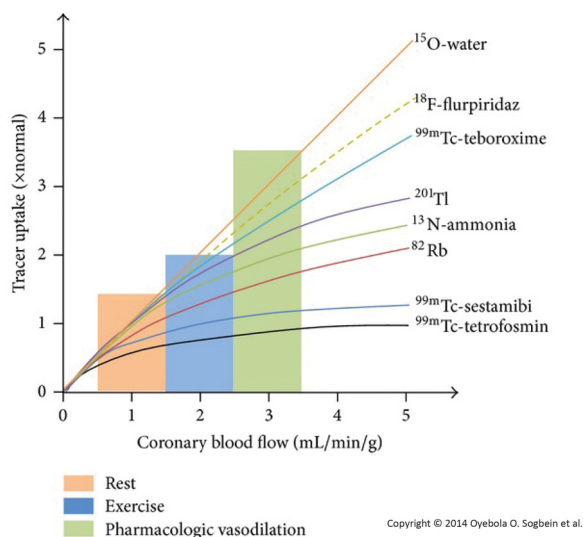

Figure 7 *Correlation between coronary blood flow and tracer uptake*. A schematic representation of cardiac PET and SPECT radiotracers uptake in relation to myocardial perfusion. ^{15}O−H$_2$O demonstrates close to linear uptake whereas the initial linear extraction of technetium-99m labeled compounds plateau at approximately 2 mL/min/g. PET radiotracers ^{13}NH$_3$$^+$ and ^{82}Rb$^+$ fall between ^{201}Tl$^+$ and the ^{99m}Tc-SPECT radiotracers, whereas ^{99m}Tc-teboroxime demonstrates superior extraction at high flow rates. ^{18}F-flurpiridaz rivals ^{15}O−H$_2$O with closer to linear extraction. (Reprinted with permission from Sogbein et al.[122])

MBF and MFR, of which the last-mentioned was overall lower than in the general population.[121] However, this study only had a follow-up period of two years, which is possibly too short to detect myocardial wall abnormalities, and more research on this should be performed including more patients with a longer follow-up period. Zyromska et al. focused on differences in the MBF during stress before and after breast/chest wall irradiation and found increased as well as decreased MBF in both left-sided and right-sided breast cancer patients using [^{15}O]H$_2$O PET examinations.

Summarizing, in comparison to MPS (SPECT), PET has higher sensitivity and specificity to discover obstructive CAD using MBF tracers. Also, these PET tracers make it possible to perform routine-based quantifications of the MBF, which can be of prognostic value for cardiac risk stratification.[120,131,132]

[^{18}F]-FDG PET

Uptake of [^{18}F]-fluorodeoxyglucose ([^{18}F]-FDG) imaged by PET correlates with inflammation in the (coronary) arteries, preceding possible atherosclerotic plaque progression and rupture of macrophages. Uptake of [^{18}F]-FDG can accurately detect changes in the cellular myocardial metabolism, thereby visualizing changes in cardiomyocytes at an early stage, before cardiotoxicity, leading to left ventricular dysfunction, will develop.[38] Patient preparation before performing an [^{18}F]-FDG PET scan for inflammation is carried out to suppress myocardial glucose uptake and to stimulate myocytes to use free fatty acids for their energy consumption, to reduce physiological FDG accumulation in the myocardium, which could interfere with abnormal [^{18}F]-FDG uptake, due to inflammation. Patient preparation, described in various guidelines, includes fasting for 12-18 hours before the scan and a diet rich in fat and low in carbohydrates 12/18-24 hours before the examination. Also, it is recommended to inject unfractionated heparin intravenously prior to the administration of [^{18}F]-FDG.[133] In myocardium exposed to radiation, accumulation of [^{18}F]-FDG takes place and this uptake is increased in hypoperfused regions.[116] As a decrease in LVEF usually is a late manifestation of subclinical myocardial injury, [^{18}F]-FDG PET can be used in research settings where early visualization of radiation-induced inflammation needs to be detected.[5]

Future Perspectives

Cardiovascular imaging is becoming increasingly important in the detection of radiotherapeutic effects that could possibly predict late cardiotoxic effects of therapy. To further investigate the role of radionuclide imaging, larger patient populations and patient-specific data regarding radiotherapeutic heart dose distribution as well as longer follow-up periods are needed to determine the relationship between early detection of cardiac abnormalities and (late) clinical outcomes. As this topic has not been largely investigated yet,

irradiated breast cancer patients nowadays do not undergo routinely cardiac imaging in clinical practice.

Nevertheless, significant improvements have been made in the optimization of nuclear imaging modalities, especially with the introduction of PET tracers measuring the MBF, as well as major technological advances in radiotherapy treatment planning and dose delivery techniques. More research needs to be performed to evaluate the possible contribution of these new imaging techniques to the prevention of RIHD, for example by intervening in an early stage of CAD and initiating prompt treatment before clinical symptoms develop, aiming at preventing cardiac events and mortality.

This review portrays new opportunities in nuclear imaging, moving from the past, where imaging is predominantly used to assess cardiac function and defects years after radiotherapy, to the current situation where these imaging modalities can detect in an early stage the underlying alterations, which may lead to future cardiac impairment. Hereby, nuclear imaging may significantly contribute to early detection and possibly prevention of RIHD.

Conflict of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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