The Role of Nuclear Medicine in the Prediction and Detection of Radiation-Associated Normal Pulmonary and Cardiac Damage

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Dose–effect calculations used in the planning of modern radiotherapy (RT) involving normal lung or cardiac tissue rely on structural imaging techniques, such as CT, as the basis for measuring and predicting dose–response. However, more accurate methods for predicting dose–response may result if information on the locoregional functional status of the irradiated organ(s) is included in the computational model. For RT cases that involve delivering dose to the lung and heart, this may be achieved by the assessment of tomographic scintographies of lung perfusion (Q) and ventilation (V) and scintigraphic imaging of myocardial perfusion and function, respectively.

Key Words: nuclear medicine; thoracic radiotherapy; adverse effects; prediction; monitoring


In the first part of this review, the focus is on the incremental value of routine and other SPECT techniques to structural imaging for the prediction of radiation pneumonitis and fibrosis and irradiation-induced cardiomyopathy. In the second part, molecular imaging that allows early diagnosis of irradiation-induced pulmonary and cardiac damage is discussed.

LUNG

Acute radiation pneumonitis (RP) occurs in up to 10% of patients after fractionated irradiation. Pathophysiologically, immunologic mechanisms seem to be involved in its onset, in addition to direct injury of the irradiated part of the lung (1). Late radiation toxicity, on the other hand, results in pulmonary fibrosis as a consequence of repair initiated by tissue injury within the radiation portal. Radiation fibrosis may lead not only to decreased lung compliance but also to decreased diffusion capacity resulting in progressive shortness of breath and increased mortality in these patients (2). Although RP mostly precedes fibrosis, both processes may also progress independently of each other (3). The probability and severity of RP depend mainly on the irradiation dose, the fractionation schedule, and the amount of lung volume that is irradiated above a threshold of 20 Gy (4). However, other biologic factors—for example, additional chemotherapy, smoking, and pretreatment pulmonary function—also play a role (5–7).

Although CT-based dose–response has been suggested to predict the development of RP, spatial heterogeneity of local pulmonary function is not considered. Therefore, the issue of whether dose–effect calculations based on a combination of both structural and functional information, as assessed by planar and tomographic lung perfusion (Q) and ventilation (V) scintographies, will enable a more accurate prediction of RP has recently been investigated (5). Also, the predictive value of reduced lung Q and V for the occurrence of radiation fibrosis continues to be studied (5, 10).

Prediction of Radiation-Induced Pulmonary Injury by Planar Scintigraphic Data of Lung Q and V

Quantitative lung Q and V scintographies combined with pulmonary function testing are routinely used in the preoperative assessment of patients with potentially curative resection of lung carcinoma. Several authors showed that quantification of the total radionuclide activity for both lung Q and V within the lung or portions of the lung targeted for resection was predictive of decline of pulmonary function after resection (11, 12). This practice was successfully adapted to the pretreatment evaluation of lung cancer patients scheduled to undergo thoracic radiotherapy (RT). Here, the total lung activity encompassed within the RT field was derived from planar lung scintographies (13). However, further studies applying this method provided disappointing results. In a study by Choi et al., gross over-
estimation of decrease in lung function was documented in 6 patients with resected lung carcinoma treated by postoperative RT (14). Curran et al. evaluated 210 lung cancer patients and noted a lack of agreement between predicted and actual post-RT pulmonary function (15).

Comparison of CT Data with Tomographic Data of Lung Q and V

Lymphoma and Breast Cancer Patients. On the basis of the dose–effect relations for local functional injury, Boersma et al. converted the individual 3-dimensional (3D) dose distribution into 1 overall response parameter to predict overall pulmonary function in lymphoma patients at 3–4 mo after RT (16). The authors demonstrated that the correlation of standard lung function tests—for example, diffusion capacity and forced expiratory volume in 1 s—with the estimated average change of lung tissue density was not as good as the correlation of the estimated average changes of regional lung Q and V and pulmonary function (17,18). The same authors later confirmed a correlation between the estimated average changes of lung Q and V and a decrease of most standard pulmonary function tests in 25 Hodgkin’s disease patients at 3–4 mo up to 18 mo after RT. Furthermore, the estimated average change of local lung Q was related with the incidence of RP at 3–4 mo after RT. However, at 18 mo of follow-up, no significant differences were present in the reduction of lung function parameters between patients with RP and other patients (5). Thus, the presence of RP at 3–4 mo after RT in lymphoma patients may not be indicative of long-term pulmonary function. Theuws et al. investigated dose–effect relations for local pulmonary injury at 3–4 mo after RT in a group of 41 patients with malignant lymphoma and 40 breast cancer patients (19). The authors found that the reduction in pulmonary function test parameters at 3–4 mo after RT, relative to the pre-RT value, was approximately 1% for each increase in mean lung dose of 1 Gy. In a group of 110 lymphoma and breast cancer patients, the same authors studied the late effects of irradiation on local lung Q and V and lung tissue density up to 4 y after RT (10). Partial recovery from early local damage was confirmed up to 18 mo. For V and the air-filled fraction, the latter quantifying changes in CT density, the average recovery between 3 and 18 mo after RT was on average 50% of the value at 3–4 mo and similar for both patient groups. At 48 mo after RT, no further improvement of V and the air-filled fraction was found. In contrast, the average improvement for the Q parameter differed significantly between lymphoma and breast cancer patients, on average 50% and 10% improvement between 3 and 18 mo after RT, respectively, a finding for which no explanation could be provided. At 48 mo after RT, no further improvement was seen in local Q and V. These data may suggest that local function measured at 18 mo probably is a good indicator for long-term functional pulmonary outcome.

Lung Cancer Patients. In a recent study by Levinson et al., changes in CT density as a function of dose were investigated in 13 lung cancer patients, in whom portions of healthy lung were incidentally irradiated (20). The authors showed that changes in CT density as a function of regional dose were only “minimal” in the <20-Gy range, “modest” in the 30- to 60-Gy range, and “dramatic” in the >60-Gy range. Because relative perfusion changes were calculated for the same study volumes as were evaluated for changes in CT density, direct comparison of these 2 indices was possible. In comparison with SPECT lung Q data, a large range of relative Q values over a relatively narrow range of CT density values was found. Therefore, a new kind of characterization of dose–effect is possible with SPECT, and, if couched in the correct model(s), this may ultimately prove to be more predictive of overall response to therapy. Because in lung cancer patients, structural and functional heterogeneities exist within the lung, the use of average values of structural and functional changes over the whole lung to estimate the overall risk of radiation-induced pulmonary injury may not be correct. Seppenwoolde et al. investigated whether local dose–effect relations for non–small cell lung cancer (NSCLC) patients were the same as for lymphoma and breast cancer patients, who were supposed to have healthy lungs before the start of RT treatment (21). Lung cancer patients often suffer from preexistent lung disease—for example, obstructive pulmonary disease—or are heavy smokers. These patient-related factors may influence the dose–effect relation. Additionally, both the presence of a tumor mass as well as shrinkage of the tumor owing to RT can influence the dose–effect relation. The authors documented recovery of perfusion after RT in 18 of 25 NSCLC patients treated with a dose up to 70 Gy. They also showed that, notwithstanding preexistent lung disease, well-irradiated lung regions of NSCLC patients behaved similarly to irradiation as healthy lung tissue of lymphoma and breast cancer patients. Interestingly, regions with reduced perfusion before RT were not accompanied by increased tissue density on CT after RT, again implying that lung density may not be a sensitive marker of irradiation effects in the lung. The most relevant question, however, remains whether changes of structural and functional lung parameters are traceable and result in respiratory symptoms in these patients. Rotstein et al. indicated that there was no correlation between changes in post-RT CT lung density and subjective respiratory symptoms (22). On the other hand, several studies have documented that changes in regional lung Q may be traceable in pulmonary function tests but that measured lung function parameters were usually less reduced than predicted (15,23,24). In these studies, prediction of overall pulmonary function after RT was based on functional irradiated volume determined by planar lung Q images. However, SPECT provides more accurate estimates of pulmonary Q when compared with planar imaging, and these estimates may hypothetically lead to more accurate estimates of changes in overall pulmonary function—either
increases or decreases. On the basis of this hypothesis, the impact of SPECT lung Q scans on the RT treatment planning process in patients with lung cancer has recently been investigated. Cattaneo et al. studied a single patient with SPECT and CT before and after conformal RT treatment for an unresectable lung tumor (25). A comparison was made between irradiation planning techniques with and without SPECT information. The use of SPECT information resulted in sparing of highly functioning lung volume. Marks et al. investigated the location of SPECT lung Q defects in 56 patients with lung cancer and noted reperfusion in areas adjacent to the tumor after RT (26). Analyzing patients with lung cancer and chronic obstructive pulmonary disease, the authors concluded that recognition of areas of decreased perfusion mainly impacted on the treatment planning of lung cancer patients with poor pulmonary function by limiting target volumes (27). The usefulness of quantitative SPECT lung Q scans during CT-based treatment planning for patients with lung cancer was also investigated by Munley et al. (28). The authors reported on the impact of 3D lung Q maps and 18F-FDG PET lung scans on the RT treatment planning process by assessing the frequency and the type of changes of the initial treatment plans. Of 104 SPECT scans performed before RT, 11% were used to modify treatment, primarily by altering beam angles, thus avoiding highly functioning lung tissue. Furthermore, of 35 18F-FDG PET scans performed before RT, providing 3D metabolic images assisting in tumor localization, 34% were used to adjust RT treatment in lung cancer patients, mainly to enlarge portions of beam aperture.

**Role of Functional Tomographic Lung Data in Estimating Dose–Response**

Poor results obtained in previous studies using planar lung Q and V scans to predict pulmonary function after RT may be due to the fact that planar lung Q and V scans do not take into account the spatial inhomogeneity of regional pulmonary function. To obtain better estimations of dose–effect, a 3D method was developed that more reliably predicts reduction of overall pulmonary function after RT (16). Several research reports adopting this methodology in Hodgkin’s disease and breast cancer patients provided evidence that functional pulmonary data and overall pulmonary function were well correlated, whereas CT density and pulmonary function were not. The authors also point out that the information provided by SPECT lung Q scans may be used in the RT treatment planning process to avoid regions of lung tissue with healthy blood flow. Also, lung cancer patients, especially those in whom pulmonary function is compromised, may benefit from implementing functional SPECT information in the RT treatment planning procedure.

**Diagnosis of RP**

Diagnosis of RP depends on high clinical suspicion, because symptoms of dyspnea, cough, and fever are often minimal and nonspecific (29). RP may subside or progress to irreversible pulmonary fibrosis, mainly depending on the delay period of starting corticosteroid therapy (30). Diagnostic procedures used previously for the detection of RP include radiologic and scintigraphic imaging as well as laboratory analyses of bronchoalveolar lavage fluid (1,31–35).

**Radiologic Investigations: Chest Radiography, CT, and MRI.** Both chest radiographs and CT scans lack sensitivity relating to the fact that the diagnosis of RP on chest radiographs and CT scans is strictly based on changes within the radiation fields (36). Several studies, however, have indicated that radiation-induced pulmonary changes also occur in lung regions outside the irradiated areas (37). Also, chest radiographs detect abnormal changes attributed to acute RP significantly later than other imaging modalities (32,36). The specificity of chest radiographs and CT scans also poses a problem in lung cancer patients because interstitial infiltrates of RP may be indistinguishable from infiltrates due to carcinomatous lymphangitis or pulmonary infection. MRI appears to be more sensitive than chest radiographs and CT scans. In fact, alterations in MR signal intensity may be observed much earlier than changes on chest radiographs and CT scans (38).

**67Ga SPECT.** 67Ga scintigraphy has been proposed for the early detection of RP but is primarily limited by its physical properties, resulting in a high total-body radiation burden and a 72-h waiting period between injection of the ligand and image acquisition. Additionally, low photon energy may result in suboptimal image quality, and physiologic uptake in the sternum and the thoracic spine may hamper accurate delineation of lung injury. Nevertheless, in a retrospective study of 103 lung cancer patients that evaluated abnormal 67Ga uptake after RT in sites other than the original or recurrent tumors, increased bilateral lung uptake of 67Ga was demonstrated in all 23 symptomatic patients developing respiratory symptoms after RT (32). This finding suggests a possible role for this technique in the early differential diagnosis of RP.

**SPECT Investigations with Radiolabeled Peptides.** The suggestion that peptide activation in irradiated lung areas may be involved in the pathogenesis of early inflammatory injury has led to exploration of the somatostatin analog 111In-pentetreotide for detecting and monitoring RP (39). Valdés Olmos et al. reported on 11 patients receiving thoracic RT (40). The authors indicated that 111In-pentetreotide was able to detect areas of RP in patients with clinical symptoms. Increased 111In-pentetreotide uptake was associated with decreased V/Q activity in irradiated areas, but abnormal areas were better delineated with 111In-pentetreotide scintigraphy. On the basis of both visual and quantitative rating systems, 9 of 10 symptomatic patients were rated positive, irrespective of whether steroid treatment had been started before the scanning procedure. In 1 symptomatic patient, in whom a final diagnosis of viral pneumonitis was made, 111In-pentetreotide scintigraphy was negative. Also, a single asymptomatic patient in this series had a negative 111In-pentetreotide scan. The authors concluded that imaging of RP with 111In-pentetreotide was feasible and
additionally suggested that $^{111}$In-pentetreotide scintigraphy may have a role in monitoring the response of RP to medical therapy, because a decrease of $^{111}$In-pentetreotide uptake was associated with satisfactory response to steroid treatment in 2 patients. However, Stoffel et al. found abnormal pulmonary uptake of $^{111}$In-pentetreotide in patients free of respiratory symptoms, as long as 10 y after receiving RT to the thorax. This finding indicates that the process of somatostatin receptor–positive inflammatory cell infiltration is still active in patients irradiated in previous years (41).

$^{99m}$Tc-Diethylenetriaminepentaacetic Acid Assessing Vascular Permeability. Other authors have concentrated on increased vascular permeability to visualize early radiation-induced inflammation. Susskind et al. applied $^{99m}$Tc-diethylenetriaminepentaacetic acid ($^{99m}$Tc-DTPA) aerosol for the detection of impaired permeability in radiation-induced lung injury (42). The method is based on deposition of inhaled DTPA particles on the alveolar-capillary membrane surface, followed by diffusion through the alveolar-capillary membrane, solution in capillary blood, and excretion by the kidneys. Irradiation of lung parenchyma causes inflammation, thereby increasing epithelial permeability and resulting in faster DTPA clearance from the blood. In the case of fibrosis, progressive thickening of the alveolar septa and vessel walls with bundles of collagen will lengthen DTPA diffusion and clearance. Changes in DTPA lung clearance from the baseline measurements were observed in 8 patients, as early as after the first irradiation session. The authors decided that uptake of DTPA was a sensitive marker of changes in lung permeability. Unfortunately, others have published conflicting results on the influence of RT on DTPA clearance (43,44).

**Conclusion**

On the basis of the findings mentioned above, it may be concluded that quantitative 3D tomographic pulmonary imaging provides a different type of assessment of therapeutic response than CT and is more precise and accurate than planar pulmonary studies. Thus, if quantitative SPECT data are used to measure pulmonary Q and V, these data could form the basis for more predictive models of dose–response.

Because studies that have addressed early diagnosis and monitoring of RP are few and results are inconsistent, the tracers used either for visualizing increased vascular permeability or for imaging infiltration of inflammatory cells are not yet sufficiently validated for clinical use in symptomatic patients in whom RP is suspected. At the moment, it seems more rational to recommend $^{67}$Ga scintigraphy for this specific indication, irrespective of its relative unfavorable physical features.

**HEART**

RT to the thorax may induce both early and late cardiac adverse effects if portions of the heart are included in the radiation field. The early manifestation of cardiac damage is predominantly inflammation of pericardium and myocardium, whereas late manifestations affect primarily coronary arteries and small myocardial vessels (45–48). A wide range of clinical manifestations has been described. Pericarditis is caused by radiation-induced damage to the mesothelial cells lining the pericardium and epicardium and usually develops within weeks (49). Late clinical manifestations, resulting from slowly evolving endothelial cell injury leading to loss of capillaries, ischemia at the microcirculatory level, and progressive fibrosis, include valvular dysfunction, conduction defects, coronary artery disease, myocardial infarction, and sudden unexpected death several years after RT (47,50–54). The incidence of late radiation-induced cardiac disease depends on the irradiated volume, total irradiation dose, dose per fraction, and the presence or absence of preexisting cardiovascular risk factors (49,55–61). Hodgkin’s disease and breast cancer patients are particularly at risk for developing late myocardial damage, because often a combination of anthracycline-containing chemotherapy and RT is administered to these patients (Tables 1 and 2). RT techniques for both patient groups may include (large) parts of the heart. For Hodgkin’s disease patients, a substantial portion of the heart may be irradiated up to 40 Gy, whereas the target in breast cancer patients includes only the chest wall and additional lymph node regions (62). Generally, nuclear medicine techniques are particularly appropriate for indicating organ damage at an early stage, before clinical symptoms are apparent. Yet, the use of scintigraphic myocardial imaging in the context of RT is generally limited to the diagnosis of late cardiotoxicity (63–68). Only a few studies have investigated the feasibility of detecting early cardiac damage (69,70).

**Hodgkin’s Disease**

Reports in the literature on the incidence of late cardiotoxicity after RT, assessed by planar $^{201}$TI perfusion scintigraphy, in long-term survivors with Hodgkin’s disease, some of whom have also been treated by chemotherapy, are conflicting (Table 1). Several pilot studies, using planar $^{201}$TI myocardial perfusion imaging (MPI), suggested that mediastinal RT for Hodgkin’s disease produced no significant functional sequelae at long-term follow-up. Morgan et al. found normal $^{201}$TI MPI in 25 asymptomatic patients 5–16 y after RT (63). Savage et al. obtained similar results in 12 asymptomatic patients several years after RT (64).

In contrast, Gustavsson et al., using tomographic MPI with $^{201}$TI, found normal results in 9 of 23 patients treated with RT to the mediastinum for Hodgkin’s disease. Also, a disturbed left ventricular function was documented on the basis of echocardiographic findings (71). In a study by Maunoury et al., 31 clinically asymptomatic patients were examined after mantle field RT for Hodgkin’s disease (72). On the basis of both visual and quantitative analysis of $^{201}$TI uptake, 21 of 25 datasets (84%) showed clear abnormalities. Pierga et al. found myocardial Q defects in 22 of 26 asymptomatic patients (85%) after RT for Hodgkin’s disease using $^{201}$TI SPECT (73). In a follow-up study, 41 eligible patients
were investigated and a high rate of myocardial Q defects after RT was confirmed. However, 27 of 41 patients (66%) had received adriamycin-containing chemotherapy before RT (65).

In a study by Glanzmann et al., using tomographic MPI with $^{99m}$Tc-labeled radioligands, 352 Hodgkin’s disease patients after mediastinal RT with ($n = 214$; adriamycin-containing chemotherapy, $n = 94$) or without chemotherapy with partial inclusion of the heart, and applying intermediate total doses between 30–45 Gy, were included (Table 2). In a group of 112 patients, who underwent heart examination including myocardial perfusion scintigraphy with

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<th>Normal MPI results</th>
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<td>Morgan et al.</td>
<td>25/25 (HD)</td>
<td>History and symptoms of cardiac disease not allowed; thyroid and pulmonary function assessed; age &lt; 35 y; Ct in 11/25 patients</td>
<td>5–16</td>
<td>40 Gy, 2.2 Gy/fraction</td>
<td>$^{201}$Tl</td>
<td>Planar</td>
<td>25/25</td>
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<td>Savage et al.</td>
<td>16/12 (HD)</td>
<td>History and symptoms of hypertension and coronary artery disease not allowed; age &lt; 52 y; non–anthracyclin-including Ct in 5/12 patients</td>
<td>2.5–21.5</td>
<td>38.7–45.5 Gy in group 1 ($n = 6$, heart entirely irradiated); 30.6–44.2 Gy in group 2 ($n = 10$, LV partially shielded), 1.5–2 Gy/fraction</td>
<td>$^{201}$Tl</td>
<td>Planar</td>
<td>12/12</td>
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<td>Constine et al.</td>
<td>50/38 (HD)</td>
<td>History and symptoms of hypertension and coronary artery disease not allowed; age &lt; 50 y at RT; Ct in 17/50 patients (in 3/17, adriamycin)</td>
<td>1.1–29.1</td>
<td>18.5–47.5 Gy, 1.5–2 Gy/fraction</td>
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<td>Cowen et al.</td>
<td>17/17 (left-side BC)</td>
<td>History and risk factors of coronary artery disease not allowed; age &lt; 75 y; no previous Ct</td>
<td>4.3–5.4</td>
<td>Breast or chest wall: 46 Gy; internal mammary nodes: 50 Gy, mixed</td>
<td>$^{201}$Tl</td>
<td>Planar</td>
<td>17/17</td>
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<td>Gustavsson et</td>
<td>26/23 (HD)</td>
<td>Age &lt; 45 y; no previous Ct; cardiac complications in 4/26 patients</td>
<td>10–20</td>
<td>35–43 Gy, 1.5 Gy/fraction</td>
<td>$^{201}$Tl</td>
<td>SPECT</td>
<td>9/23</td>
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<td>Maunoury et al.</td>
<td>31/25 (HD)</td>
<td>History of cardiac disease not allowed; age &lt; 45 y; adriamycin-containing Ct in 5 of 16 patients</td>
<td>3–11</td>
<td>39–42.5 Gy, 1.8–2.5 Gy/fraction</td>
<td>$^{201}$Tl</td>
<td>SPECT</td>
<td>4/25</td>
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<tr>
<td>Pierga et al.</td>
<td>32/26 (HD)</td>
<td>Obesity, hypertension, smoking, diabetes, hypercholesterolemia, family history of coronary artery disease, and history and symptoms of coronary artery disease; age &lt; 45 y; adriamycin-containing Ct in 5 of 16 patients</td>
<td>3–13</td>
<td>31–42.5 Gy, 1.8–2.5 Gy/fraction</td>
<td>$^{201}$Tl</td>
<td>SPECT</td>
<td>4/26</td>
</tr>
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<td>Girinsky et al.</td>
<td>42/41 (HD)</td>
<td>History of cardiac disease not allowed; age &lt; 41 y; Ct (MOPP and MOPP/ABVD) in 27/41 patients</td>
<td>2.3–17.3</td>
<td>31–42.5 Gy, 1.8–2.5 Gy/fraction</td>
<td>$^{201}$Tl</td>
<td>SPECT</td>
<td>9/41</td>
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HD = Hodgkin’s disease; LV = left ventricle; BC = breast cancer; MOPP = mechlorethamine, vincristine, procarbazine, and prednisone; ABVD = adriamycin, bleomycin, vinblastine, and dacarbazine.
99mTc-sestamibi, the result was normal in 93 of 100 patients (93%) and definitively abnormal in only 4 of 100 patients (4%). Results were ambiguous—that is, heterogeneous tracer uptake was noted—in 3 of 100 patients (3%) (74).

Savage et al. studied myocardial perfusion by planar 201 Tl scintigraphy and by left ventricular ejection fraction (LVEF) and peak filling rate (PFR) by equilibrium radionuclide angiography using 99mTc-pertechnetate in 12 and 16 irradiated Hodgkin’s disease patients, respectively (64). Myocardial perfusion was normal in all 12 patients. The authors found LVEF and PFR within the normal range, although patients irradiated to large cardiac volumes had

### TABLE 2

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<tbody>
<tr>
<td>Glanzmann et al. (62,74)</td>
<td>112/100 (HD)</td>
<td>Obesity, hypertension, smoking, diabetes, hypercholesterolemia, history of coronary artery disease assessed; previous adriamycin-including Ct allowed; age &lt;65 y at RT</td>
<td>1–31.5 y</td>
<td>30–42 Gy in 93% of cases; 1.3–2.1 Gy/fraction to anterior heart region</td>
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<td>Gyenes et al. (66,75)</td>
<td>17/12 (left-side BC)</td>
<td>Obesity, hypertension, smoking, diabetes, hypercholesterolemia, history of coronary artery disease assessed; age &lt;70 y; adriamycin-including Ct in 3/17 patients</td>
<td>0.7–1.9 y</td>
<td>Breast: 50 Gy ((\gamma)), 25 fractions; chest wall, internal mammary nodes, supraclavicular nodes, axilla: 46 Gy ((\beta) and (\gamma)), 2 Gy/fraction</td>
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<td>Gustavsson et al. (68)</td>
<td>91/90 (left- or right-side BC)</td>
<td>Family history of cardiac disease, smoking, hypertension, diabetes, hypercholesterolemia assessed; age &lt; 65 y; Ct (cyclophosphamide) in 59/90 patients</td>
<td>10–17 y</td>
<td>Supraclavicular/infraclavicular; 45 Gy ((\gamma)); axilla: 48 Gy ((\gamma)); chest wall: 38 Gy (radiography); internal mammary nodes: 48 Gy ((\beta)), 1.9–2.4 Gy/fraction</td>
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<td>Hojris et al. (76)</td>
<td>17/16 (left-side BC)</td>
<td>Obesity, hypertension, diabetes, hypercholesterolemia, smoking, and family history assessed; history of heart disease not allowed; age &lt; 75 y; systemic hormonal therapy in 6/17 patients and non–adriamycin-containing Ct in 11/17 patients</td>
<td>6–12.2 y</td>
<td>Supraclavicular/infraclavicular nodes, axilla, chest wall, internal mammary nodes: median, 50 Gy; 1.9–2.4 Gy/fraction</td>
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<tr>
<td>Hardenbergh et al. (69)</td>
<td>20/20 (left-side BC)</td>
<td>Previous doxorubicin-containing Ct in 10/20 patients</td>
<td>6 mo</td>
<td>Breast, chest wall: 46–50 Gy, tangential beams, upper internal mammary nodes included in tangent fields in 5/20 patients, 2 Gy/fraction</td>
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HD = Hodgkin’s disease; BC = breast cancer.
lower LVEF and PFR compared with patients who had some part of the heart volume shielded. Constine et al. investigated myocardial perfusion and cardiac function in 50 asymptomatic patients treated by mantle RT for Hodgkin’s disease with modern RT techniques, of whom 17 had also received chemotherapy (54). In 2 of 38 patients (5%) who underwent rest and stress scintigraphies using 201TI or 99mTc-sestamibi SPECT, only mild myocardial ischemia was found. The authors also documented normal LVEF and PFR in 48 of 50 patients (96%) and in 42 of 50 patients (84%), respectively, using 99mTc-pertechnetate.

**Breast Cancer**

*Myocardial Perfusion Imaging.* Cowen et al. found normal 201TI MPI in 17 patients who were treated by RT and no adjuvant chemotherapy for left-side breast cancer, based on planar scintigraphic results (67). In a prospective study of 17 left-side breast cancer patients before and after adjuvant RT, Gyenes et al. showed 50% new fixed left ventricular Q defects using tomographic MPI with 99mTc-sestamibi in 12 patients (66). The localization of the defects corresponded with the irradiated volume of the left ventricle. Interestingly, neither electrocardiographic changes nor left ventricular segmental wall motion abnormalities were detected by echocardiography (75). In a study by Gustavsson et al., Q scintigraphy with 99mTc-sestamibi and 99mTc-tetrofosmin showed irreversible defects in only 6 of 90 patients (7%), all of whom had been treated with or without adjuvant RT for either left- or right-side breast cancer (68). It was postulated that the observed defects related to myocardial fibrosis, because no symptoms of ischemic heart disease were recorded in these patients. In addition, left ventricular systolic function was normal in all patients, and few signs of diastolic dysfunction and no valvular dysfunction of clinical significance were observed by echocardiography. Also, no cardiac deaths among a total of 275 patients included in this study were recorded, despite the fact that in some patients older radiation techniques had been applied. Hojris et al. investigated 17 clinically asymptomatic patients after surgery for left-side breast cancer treated with or without RT plus systemic hormonal treatment in 6 of 17 patients (35%) and chemotherapy in 11 of 17 patients (65%) (76). Interestingly, Q defects on 99mTc-sestamibi SPECT were proportionally distributed between the RT and the no-RT treatment group.

*Myocardial Perfusion and Cardiac Function Imaging.* Electrocardiographically gated myocardial SPECT using 99mTc-labeled ligands enables the evaluation of cardiac function and perfusion in an integrated method (77). Using 99mTc-sestamibi gated perfusion SPECT in a preliminary study of cardiac Q changes and LVEF in 10 patients with breast cancer treated with RT and doxorubicin-based chemotherapy, Hardenbergh et al. indicated that cardiac function, as assessed by LVEF, was not altered by the combined treatment of RT and chemotherapy, except in 1 patient with known cardiovascular risk factors (69). On the other hand, new Q defects were observed among 7 of 7 patients treated with doxorubicin and RT, if portions of the LV received >50% of the RT dose. Apparently, Q defects did not seem to correlate with clinical events in this study, but follow-up was short and, thus, clinical relevance is unclear at the moment.

**Other SPECT Tracers for Imaging Cardiac Injury.** SPECT tracers such as 111In-antimyosin and 123I-meta-iodobenzylguanidine (123I-MIBG) have occasionally been explored. Because 111In-antimyosin antibody binds to intracellular myosin only when the sarcolemma is damaged, 111In-antimyosin uptake may correlate with disrupted integrity of myocytes (78). Although radiation-induced cardiac damage is believed to be caused by endothelial cell injury and myocyte integrity is believed to be left intact by RT, Ricart et al. demonstrated increased myocardial uptake of 111In-antimyosin by means of 48-h heart-to-lung ratios in patients who had recently been treated by both low- and high-dose RT (70). Thus, the authors argued that subclinical damage to the heart might occur at doses previously assumed to be without risk of adverse cardiac effects.

123I-MIBG is a guanidine analog that, unlike noradrenaline, is not metabolized by monoamine oxidase or catechol-o-methyl transferase. Initial uptake of the tracer reflects myocardial neuron integrity and adrenergic release function, and 123I-MIBG is well suited for the study of myocardial adrenergic innervation (79). Valdés Olmos et al. demonstrated the feasibility of 123I-MIBG imaging after RT (80). Progressive loss of cardiac function after RT may not be caused exclusively by endothelial cell injury; alterations in sympathetic innervation of the heart may also be involved. During the late phase after RT, cardiac uptake at 4 h after injection and myocardial washout rate of 123I-MIBG were significantly decreased in 18 cancer therapy patients compared with healthy subjects.

**CONCLUSION**

The overall risk of cardiac damage after RT is probably low (49,54,81). The high rate of cardiovascular mortality after RT in pilot studies may be related to outdated treatment regimes, which are no longer in use today (55,59,71). These older RT techniques used higher radiation doses and lacked appropriate cardiac shielding (54). Undoubtedly, these RT treatment features may have influenced the development of cardiac damage, and it is now recommended that ortho-voltage RT and high fraction doses should be avoided to minimize (late) tissue damage to the heart (82). Additionally, the use of tangential fields, which seem to spare the heart from harmful irradiation, is recommended (67). Scintigraphic studies using 201TI indicated that approximately 70% of patients treated with RT with or without chemotherapy had myocardial Q defects (65,71). In contrast, scintigraphic studies with 99mTc-labeled radioligands found an approximately 5% incidence of myocardial Q defects (74). Probably, false-positive defects and temporary reversible abnormalities detected after sustained exercise may have accounted for the high incidence of myocardial Q defects.
visualized with $^{201}$Tl scintigraphy in comparison with $^{99m}$Tc-labeled radioligands. On the other hand, the use of planar scintigraphy, with low sensitivity when compared with tomographic scintigraphic acquisition, may have resulted in false-negative results in $^{201}$Tl studies (63,64,67). Recent SPECT studies with $^{99m}$Tc-labeled radioligands, using strict inclusion criteria, seem to confirm a low rate of late cardiac sequelae after external RT with or without chemotherapy, and an increased risk for ischemic cardiac disease may be observed only in patients with known cardiovascular risk factors (64,68,69,74,76). Yet, every effort must be made to reduce the volume of myocardium irradiated and the dose to the cardiac tissue and the coronary arteries to minimize the risk of radiation-associated adverse events. Assessing cardiac damage by conventional nuclear medicine imaging—that is, myocardial perfusion scintigraphy—may be of complementary use to echocardiographic evaluation for routine follow-up after RT with modern techniques, in a subgroup of patients with known cardiovascular risk factors (62,64,65,71). Further research is needed to establish the clinical value of molecular radioligands, but it may be expected that these nuclear medicine techniques will constitute an essential future step in the evaluation of subclinical cardiac injury afforded by RT with or without chemotherapy.

REFERENCES

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