99mTc-MIBI myocardial perfusion scintigraphy for assessment of myocardial damage after radiotherapy in patients with breast cancer

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Summary

Purpose: After radiation therapy (RT) to the thorax, cardiac injuries may be induced involving the myocardial capillaries and causing myocardial fibrosis. The aim of this study was to assess the role of 99mTc-MIBI myocardial perfusion scintigraphy (MPS) for mapping the RT-induced cardiac injuries.

Patients and methods: The study involved 56 patients: 46 with left-sided (study group) and 10 with right-sided (control group) breast cancer who, after breast surgery, received postoperative RT. In the cases of the study group, the anterior wall of the myocardium was included in the target field. All of the patients were asymptomatic and without risk factors concerning heart. 99mTc-MIBI MPS was performed using Siemens Diacam gamma camera. 555 MBq of tracer was injected in each occasion. MPS was performed 30-60 min after injection and the images were analyzed using a semi quantitative four-point system.

Results: MPS was normal in all patients of the control group and in 33 (76%) patients of the study group. In 11 (24%) of the patients in the study group MPS indicated moderately reduced perfusion: 7 of the patients had hypoperfusion of the anterior wall segments, 4 had hyperperfused septum and apex. Comparison of the 2 groups showed statistically significant difference (p <0.001).

Conclusion: Cardiac injury after irradiation of the thorax is not rare and its early detection may minimize severe cardiac damage. MPS may be a feasible method to that purpose.

Key words: breast cancer, cardiac damage, 99mTc-MIBI, myocardial scintigraphy, radiotherapy

Introduction

RT plays an important role in the multimodality management of patients with breast cancer. Successful treatment of malignancies has enabled investigators to understand the late effects of anticancer therapies in long-term survivors. The cardiovascular system may be directly or indirectly affected by RT. The direct effects are broad, can affect the pericardium, myo-

cardium, endocardium, valves, coronary arteries and other vessels, and may become clinically significant over time [1]. The rate of hemodynamically significant cardiovascular complications was estimated to be 15 - 30% over 5-10 years of follow-up [2].

Data from animal models suggest that therapeutic irradiation can lead to ischemic heart disease through two pathogenic mechanisms: microvascular damage and macrovascular damage. Microvasculopathy- tree phases of irradiation-induced cardiac injuries were observed. An acute phase, characterized by neutrophilic infiltration involving all layers of the heart, occurred within a few days of RT. A latent phase followed, during which none of the animals manifested any light microscopic signs of cardiac disease. Subsequent to the latent phase, a delayed phase began, manifested by pericardial and myocardial fibrosis. Macrovasculopathy is another line of evidence pointing to the effects of irradiation on the coronary arteries themselves.
RT to the thorax may induce both early and late cardiac adverse effects if portions of the heart are included in the radiation field [3]. The early cardiac damage is predominantly inflammation of pericardium and myocardium, whereas late manifestations affect primarily coronary arteries and small myocardial vessels. Late clinical manifestations, resulting from slowly evolving endothelial cell injury leading to loss of capillaries, ischemia at the microcirculatory level, and progressive fibrosis, include valve dysfunction, conduction defects, coronary artery disease, myocardial infarction, and sudden unexpected death several years after RT [4-8].

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 [9-13]. 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. RT techniques may include large parts of the heart. The target in breast cancer patients includes the chest wall and additional lymph node regions [14]. Generally, nuclear medicine techniques are particularly appropriate for indicating organ damage at an early stage, before clinical symptoms are apparent. The use of scintigraphic myocardial imaging in the context of RT is generally limited to the diagnosis of late cardiotoxicity.

Only few studies have investigated the feasibility of detecting early cardiac damage [15-18]. To understand the pathophysiology of radiation-induced heart disease, several investigators have examined the surrogate endpoints of radiologic changes in myocardial perfusion, wall motion, or ejection fraction (EF) after RT. In 1998, Proznitz and Marks [19] began enrolling patients with left-sided breast cancer onto a prospective study to determine the potential cardiotoxic effects of RT using modern techniques. Patients had modern treatment planning based on computed tomography and pre-RT and serial post-RT single-photon emission computed tomography (GSPECT) - gated cardiac myocardial perfusion scans to assess for changes in heart function. New perfusion defects occurred in 50-63% of women 6-24 months after RT [20, 21]. The incidence of perfusion defects was strongly correlated with the volume of the left ventricle (LV) in the RT field, occurring in 25% of patients with 1-5% of the LV within the tangent fields, and in 55% of patients with more than 5% of the LV within the field. These perfusion defects generally persist at least 3-5 years after RT [22].

Although modern RT techniques have reduced radiation exposure of the heart, they may not have eliminated cardiotoxicity. It appears that contemporary RT methods may still cause cardiovascular disease. Changes in myocardial perfusion, wall motion and EF have been demonstrated in patients undergoing treatment with modern techniques. Whether these radiographic changes will ultimately have clinical significance is unclear [23,24]. The reports by Patt et al. [25] and Giordano et al. [26] provide some reassurance that the magnitude of the problem for the entire population of patients undergoing RT for breast cancer may not be large. However, they do not preclude the possibility that certain subsets of patients may be at high risk of radiation-induced heart disease.

At present, it is necessary that radiation oncologists should use contemporary RT planning and delivery methods that minimize cardiac exposure, such as heart blocks [27] and partially wide tangents [28]. Treatment needs to be delivered accurately, given that small errors in patient setup may increase a patient’s risk of developing a perfusion defect [27]. We and others currently are investigating techniques to further reduce cardiac exposure, such as intensity-modulated RT, respiratory gating, mixed electron/photon beams and tomotherapy [29-35]. With treatment innovation, it is our goal to eliminate incidental irradiation of the heart and to make radiation-induced heart disease a historical footnote.

The purpose of this study was to evaluate the role of 99mTc-MIBI myocardial perfusion scintigraphy for mapping the radiation-induced cardiac damage in patients with breast cancer and postoperative radiotherapy.

Patients and methods

The study involved 56 primary, stage II-III breast cancer patients: 46 patients with left-sided (study group) and 10 patients with right-sided (control group) breast cancer who, after breast surgery, received postoperative RT with total dose 50 Gy, 2 Gy/fraction, in 25 fractions to the chest wall and axilla. In the cases of the study group, the anterior wall of the myocardium was included in the target field. Previous anthracycline-including chemotherapy was not allowed; 23 patients (21 study group, 2 control group) received cyclophosphamide, methotrexate and 5-fluorouracil (CMF) chemotherapy. Exclusion criteria were history of coronary artery disease, hypertension, diabetes mellitus and smoking.

99mTc-MIBI GSPECT myocardial scintigraphy was performed using Siemens Diacam gamma camera, 18 months after RT on average. 555 MBq of tracer was injected in each occasion. GSPECT imaging was per-
formed 30-60 min after injection and the images were analyzed dividing the left ventricle of the heart into 20 segments and each segment was graded according to perfusion using a semi quantitative four-point system. Myocardial function was assessed too (EF, end systolic volume/ESV, end diastolic volume/EDV, wall thickening/WT and segmental motion).

Statistical analysis was performed by SPSS 10 software using paired sample t-test for comparison of the two investigated groups.

Results

All of the patients in both groups had normal kinetics of the LV of the heart: LVEF, ESV, EDV, WT and segmental wall motion were normal.

MPS was normal in all (100%) patients of the control group and in 35/46 (76%) patients of the study group - no hypoperfused defects in the LV myocardium were observed in these patients.

In 11 (19%) of the patients in the study group, MPS showed moderately reduced perfusion - 30-50% tracer uptake in the hypoperfused lesions in comparison to the normally perfused myocardium. The localization of the defects corresponded well with the irradiated volume of the left ventricle. All of the affected segments were in the vascular territory of the left descending coronary artery. Seven of the patients exhibited hypoperfusion of the anterior wall segments (Figure 1). Four patients had hypoperfused septum and apex (Figure 2). Statistical analysis when the two investigated groups were compared showed significant difference (p < 0.001).

Discussion

Cowen et al. found normal ²⁰¹Tl MPS in 17 patients who were treated by RT without adjuvant chemotherapy for left-sided breast cancer, based on planar scintigraphic results [15]. Electrocardiographically gated myocardial SPECT using ⁹⁹mTc-labeled ligands enabled the evaluation of cardiac function and perfusion in an integrated method [36]. Using ⁹⁹mTc-sestamibi gated perfusion SPECT in a preliminary study of cardiac perfusion 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 one patient with known cardiovascular risk factors [17]. On the other hand, new perfusion defects were observed in all 7 patients treated with doxorubicin and RT, if portions of the LV received >50% of the RT dose. Apparently, perfusion 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.

Hojris et al. [37] investigated 17 clinically asymptomatic patients after surgery for left-sided breast cancer treated with or without RT plus systemic hormonal treatment in 6/17 patients (35%) or CMF chemotherapy in 11/17 (65%) patients. The authors showed that perfusion defects on ⁹⁹mTc-sestamibi SPECT were equally distributed between the RT and the no-RT treatment group.

In a prospective study of 17 left-sided breast cancer patients before and after adjuvant RT (and doxorubicin-containing chemotherapy in 3/17 patients)
Gyenes et al. [14] showed 50% new fixed LV perfusion defects using $^{99m}$Tc-sestamibi in 12 patients. The localization of the defects corresponded with the irradiated volume of the LV and neither electrocardiographic changes nor LV segmental wall motion abnormalities could be detected by echocardiography.

In a study by Gustavsson et al. [16], perfusion scintigraphy with $^{99m}$Tc-sestamibi and $^{99m}$Tc-tetrofosmin showed irreversible defects in only 6/90 (7%) patients, all of whom had been treated (with or without adjuvant RT = cyclophosphamide) for either left- or right-sided breast cancer. The observed defects probably related to myocardial fibrosis since, with the exception of one patient, no symptoms of ischemic heart disease were recorded. LV systolic function was normal in all patients, few signs of diastolic and no valve dysfunction of clinical significance were observed by echocardiography. In addition, 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.

Our results are in accordance with the relevant literature. Significant myocardial hypoperfusion (19%) without myocardial functional damage was found in the patients with left-sided carcinoma and RT, indicating radiation-induced myocardial deterioration, probably affecting the microcirculation. There was no damage of LV function at this stage. Long-term follow-up studies are needed to assess whether these findings are a prognostic sign for developing radiation-induced coronary artery disease.

We conclude that cardiac injury after irradiation of the thorax is not rare and its early detection may minimize severe cardiac damage. MPS may be a feasible method to that purpose.

References

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