Purpose: To use gated (G) 99mTc-Tetrofosmin single photon emission computed tomography (SPECT)-CT combined with coronary calcium (Ca) scores to assess and differentiate patients with left-sided breast cancer, after surgery and doxorubicin (DOX)-based chemotherapy and who had cardiac risk factors and needed to adapt radiotherapy (RT) in order to prevent cumulative cardiac side effects caused by RT.

Methods: Included were 28 female patients (mean age 49±16 years) with asymptomatic left-sided breast cancer, one month after DOX-based chemotherapy (mean 522±36mg) and before RT. A group of 18 patients (study group) with cardiovascular risk factors was included, while a group of 10 patients with no cardiovascular risk factors served as control. 99mTc-Tetrofosmin GSPECT-CT with Ca scores on Symbia T16 (Siemens Medical Solutions Inc, USA), using standard stress protocol was performed. QGS/QPS quantitative analysis of the myocardial perfusion and function was used.

Results: 26 patients had normal perfusion images based on QPS. Hypoperfused defects with mild hypoperfusion and slightly increased Ca scores had 2 (11%) patients from the study group and no patient in the control group: the 2 patients were determined as having coronary atherosclerosis and silent coronary artery disease. Twenty three patients had normal parameters based on QGS. Diastolic and segmental dysfunction had 4 (14%) patients from the study group and one (4%) patient from the controls, determined as caused by chemotherapy-induced cardiotoxicity. Very high hazard for cardiac damage if standard RT was to be performed had 6 (21%) patients in the study group and one (4%) from the controls. These patients received RT, in order to prevent cardiac damage.

Conclusion: 99mTc-Tetrofosmin GSPECT-CT plus Ca scores provide combined cardiac assessment and can serve as a reliable screening method to prevent cardiac damage caused by RT in left-sided breast cancer patients, who have cardiac risk factors and have been administered DOX-based chemotherapy.

Key words: breast cancer, cardiac toxicity, radiotherapy, 99mTc-Tetrofosmin GSPECT-CT

Introduction

In cancer therapy, optimal treatment and quality of life must both be considered when deciding a treatment plan for the individual patient. In two of the major modalities for cancer therapy - radiation therapy and chemotherapy - implementing new techniques and treatment schedules in RT and chemotherapy in order to intensify their antitumor effect with curative intent, may be associated with a higher risk of damaging normal organs and tissues which may not only limit the treatment efficacy but also impact the patient’s quality of life. In the evaluation of normal organ toxicity from cancer therapy, both the early and late effects have to be considered. The first manifestations of injury are predominantly functional, and nuclear medicine techniques are particularly appropriate for monitoring function and enabling damage to be detected at an early stage before
morphological alterations occur [1,2]. Although many acute side effects of cancer therapy have faded as critical issues, cardiotoxicity remains an issue of considerable concern and necessitates careful and continuous clinical attention with high index of suspicion.

Several risk factors that predispose patients to an increased risk of treatment-induced cardiotoxicity have been identified, of which the most important are: combined chemo-RT, age > 65 years, previous cardiac disease (coronary, valvular, or myocardial), hypertension, diabetes mellitus, obesity, hypercholesterolemia and smoking [1,3].

Following RT localized in the thorax, early and late cardiac injuries may be induced. Early manifestation of cardiac damage is pericarditis or myocarditis, while the late injuries affect coronary arteries and myocardial capillaries and lead to ischemic heart disease. Late damages cause loss of capillaries, microvascular ischemia and progressive myocardial fibrosis which clinically manifests as valve dysfunction, coronary artery disease, myocardial infarction and sudden death years after RT. Primary radiation fibrosis results not from the radiation itself but relates to a reparative response of heart tissue to the microvascular injury. Adjutant RT after breast-conserving surgery decreases the risk of local recurrence by two-thirds and results in survival equivalent to that achieved by patients treated with mastectomy [4-6]. RT is also recommended for selected patients after mastectomy to lower the risk of recurrence and possibly improve survival [7-11]. However, 2 population-based studies [12,13] have demonstrated underuse of adjuvant RT; possibly because of concerns about radiation-induced cardiotoxicity [14,15]. In particular, women treated with RT have an increased risk of mortality from ischemic heart disease [6,16,17]. In a meta-analysis of 8 randomized trials that included almost 8,000 women, Cuzick et al. [18] found a 62% increase in cardiac deaths in women who received RT. Similarly, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of approximately 20,000 women who were enrolled in 40 randomized trials of RT found a 30% increase in vascular mortality, although the analysis also documented a statistically significant reduction in breast cancer mortality [6]. One approach to study radiation-associated cardiac mortality is to compare outcomes between patients with left-sided breast cancers with those with right-sided breast cancers. Patients with left-sided breast cancer who are treated with RT have a higher risk of cardiac radiation exposure [16] and higher rates of cardiovascular mortality [14,15,17,19] than patients with right-sided breast cancers. After follow-up times of more than 8 years, women with left-sided breast cancer who received RT had 41-50% higher hazard of death from ischemic heart disease than women with right-sided breast cancer.

The risk for cardiotoxic effects increases when combined chemo- and RT are applied.

Various antineoplastic agents can cause cardiotoxicity. Of them anthracyclines are the best recognized, though other chemotherapeutic and biologic agents are now known to have cardiac side effects [2,20]. The spectrum of cardiotoxicity ranges from myocarditis, pericarditis, myocardial infarction, sudden cardiac death to the most serious side effect-delayed-onset cardiomyopathy (CMP) and congestive heart failure (CHF), which have poor clinical outcomes [21-23]. However, in patients with low-grade myocardial damage and no substantial changes in the ejection fraction at the completion of therapy, it is still possible that CHF with typical features of doxorubicin-induced cardiomyopathy will develop 4-20 years later [24]. Patients with cancer in whom symptoms of cardiomyopathy developed within the first year after doxorubicin therapy may have had an improvement in their condition during the first 4 years, but they subsequently deteriorated and died 6-8 years later.

99 mTc-Tetrofosmin has been used as a popular myocardial perfusion imaging agent in patients with coronary artery disease. In addition, as well as reliable and highly reproducible left ventricular ejection fraction (LVEF), ventricular volume measurement can be obtained by gated 99 mTc-MIBI SPECT, regional wall motion (WM) and wall thickening (WT); these measurements are also reliable and highly reproducible. Since a recent study with echocardiography demonstrated regional dysfunction shortly after DOX therapy, regional dysfunction could also be detected by gated SPECT [25].

Coronary artery calcium scores are calculated as an adjunct to myocardial imaging for cardiac risk stratification. Coronary artery calcium (CAC) plaque documents the presence of coronary artery disease (CAD) in an individual patient as compared with just the presence of risk factors [26].

The purpose of the present study was to use gated 99mTc-Tetrofosmin SPECT/CT combined with coronary calcium scores to assess and differentiate patients with left-sided breast cancer, after surgery and DOX-based chemotherapy and
who had cardiac risk factors including age, obesity, hypertension, diabetes mellitus, and needed adaptation of RT in order to prevent cumulative cardiac side effects caused by RT.

Methods

Patients

Following ethical approval and informed patient consent, 18 female patients with coronary risk factors (study group) and 10 female patients without such factors (control group) mean age 49±16 years (range 29-72), with left-sided breast cancer, were recruited one month after DOX-based chemotherapy (>450 mg cumulative dose) and before RT. All of the patients underwent cardiac evaluation, which included history, physical examination, ECG. All patients from the study group had coronary risk factors: hypertension well controlled with medication, and/or dyslipidemia treated with a statin, and/or obesity and/or well controlled type 2 diabetes mellitus. No patient had a history and manifestation of underlying heart disease such as ischemic heart disease, cardiomyopathy, valvular disease and arrhythmia. All patients had normal ECG. All patients underwent gated 99mTc-Tetrofosmin SPECT-CT combined with coronary calcium scores (Table 1).

Gated 99mTc-Tetrofosmin SPECT-CT

Images were obtained after intravenous injection of 600-740 MBq of 99mTc-Tetrofosmin 45 min after radionuclide administration on Symbia T16 (Siemens Medical Solutions USA, Inc.), using standard stress protocol. Gated images were acquired by using a 64x64 matrix, at 8 frames per R-R interval, using an R-wave window of ± 20% of mean preacquisition heart rate. Heart rate data were recorded automatically in image files. Data were acquired for 30 sec projection, for 45 projections per detector over a total arc of 180°, from the right anterior oblique-45° projection to the left posterior oblique-45° projection, using a dual-headed gamma camera equipped with low-energy, high-resolution, parallel-hole collimators. Immediately after SPECT, CT acquisition was performed for attenuation correction and coronary calcium scores, and prospective ECG triggering was used and set at 42% of the R-R interval. Scans were made without the use of contrast agent, with 150 kV and 40 mA. A single collimation of 3,00 mm and an increment of 3,00 mm was applied. Total radiation exposure was 1 mSv for each patient. The coronary calcium score was obtained using the Agatston method [26].

Reconstruction

Gated 99mTc-Tetrofosmin SPECT was quantitatively analyzed with QGS/QPS software (QGS/QPS; Cedars-Sinai Medical Center, Los Angeles, CA, USA). QGS was used for calculating the end-diastolic volume (EDV), end-systolic volume (ESV), LVEF, functional maps, WT, WM, peak filling rate (PFR), one-third mean filling rate (MFR/3), time to PF (TTPF). Regional WM and WT were evaluated based on 17-segments of a polar map system, and summed function scores SMS, STS were calculated.

Visual analysis and QPS were used for evaluating the relative distribution of the myocardial perfusion. Processing and analysis were done to get the classic short axis, vertical long axis and horizontal long axis slices with application of the segment scoring system for semiquantitative analysis of the defect size to get summed stress score (SSS). The result was interpreted as negative when SSS = 0-3, mild (SSS>3 & <8), moderate (SSS=8 &<12), and severe (>12).

CAC scores were calculated. CAC plaque documents the presence of atherosclerosis in an individual patient and high risk for coronary events. In the literature the Agatston score is used to assess CAC, which measures the amount of calcium in each lesion. Total CAC is the sum of the scores of all the calcified lesions in all the vessels [26].

To avoid misinterpretation, all images were evaluated by 2 independent observers blinded to the patients clinical data.

Statistics

Data were statistically presented as terms of mean ± standard deviation (± SD), frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables was done using the Student’s t-test. SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows was used for all analyses.

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Results

Patient characteristics are displayed in Table 1. Cardiac evaluation indicated no cardiac symptoms and the ECG was normal in all of the investigated patients. There were 11 (39%) patients with arterial hypertension, 2 (7%) with type 2 diabetes mellitus, 9 (32%) with obesity, 7 (25%) smokers and 5 (18%) patients were older than 65 years; 10 (36%) patients from the control group were with no cardiovascular risk factors. All of the patients received DOX-based chemotherapy (mean cumulative dose 522±36 mg).

In the study group (N=18), 16 patients had normal perfusion images based on visual analysis and QPS. Hypoperfused defects with mild to moderate hypoperfusion (52-64% tracer uptake, SSS 7-9) had 2 (7%) patients. The first of them suffered of type 2 diabetes mellitus, hypertension and obesity, and was heavy smoker. The second one had hypertension, obesity and was 71-year-old. Both had increased Ca score (17-499). These 2 patients were determined as having coronary atherosclerosis and silent coronary artery disease. All of the study group patients (N=18) had normal global systolic parameters as determined by QGS.

Figure 1. A patient with left-sided breast cancer and with cardiac risk factors was administered DOX-based chemotherapy. 99mTc-Tetrofosmin GSPECT-CT plus Ca scores indicate normal myocardial perfusion (A) and Ca score 0 (B).

Figure 2. A patient with left-sided breast cancer and with cardiac risk factors was administered DOX-based chemotherapy. 99mTc-Tetrofosmin GSPECT-CT plus Ca scores indicate mild myocardial hypoperfusion (SSS 9), normal systolic and diastolic function (A), and Ca score slightly increased (17) (B).
LVEF mean value was 65±7.05; ESV 32ml±15; EDV 83ml±22; PFR 2.78±0.4; MFR/3 1.39/s±0.34 (range 0.79-1.82); TTPF 167ms±48 (range 93-274). Two (7%) patients had slightly decreased MFR/3, increased TTPF, and regional WT and WM were decreased with STS 2-3 and SMS 5-8, respectively. One patient had decreased MFR/3, increased TTPF and decreased regional WM with SMS 4. One patient had increased TTPF. Diastolic and segmental dysfunction in these 4 (14%) patients was determined as caused by chemotherapy-induced cardiotoxicity. A total of 14 patients had normal parameters, based on QGS.

In the control group (N=10) all of the patients had normal myocardial perfusion, no CAC plaques were found. All of the patients had normal global systolic parameters as determined by QGS with LVEF mean value 74.6%±9.5; ESV 18.4ml±11; EDV 58ml±13; PFR 2.62±0.6; MFR/3 1.5/s±0.4; TTPF 164ms±21. Only one (4%) patient had diastolic dysfunction: MFR/3 0.8/s; TTPF 234 ms; decreased regional WM with SMS 5 (Figure 1 A,B; Figure 2 A,B).

**Discussion**

Our study demonstrated that gated 99mTc-Tetrofosmin SPECT-CT can successfully screen the cardiac functional and perfusion changes in asymptomatic patients with left-sided breast cancer and with high cardiac risk and possible cardiotoxicity after surgery and DOX-based chemotherapy before starting RT.

The role of routine stress test and biomarkers like troponin and B-type natriuretic peptide (BNP) in identifying high risk patients or predicting future cardiovascular events remains to be determined in large studies. New diagnostic methods may provide more simple and effective means of detecting patients at risk at a time before RT when changes in delivering techniques are still possible.

**Conclusion**

Left-sided breast cancer patients, who have cardiac risk factors and have been administered DOX-based chemotherapy, have very high hazard for cardiac damage with standard RT. The prevention consists of previous screening, adapted RT and consistent active follow-up of these patients after treatment. 99mTc-Tetrofosmin GSPECT-CT provides combined cardiac assessment and can serve as a reliable screening method to prevent cardiac damage caused by RT.

**References**

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