Quantitative evaluation of radiation-induced metabolic changes in the ipsilateral breast by FDG-PET/CT

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ABSTRACT

Background and aim: There are no reports of quantitative evaluation of metabolic changes in the mammary gland after radiation therapy. The purpose of this study was to investigate metabolic changes in the ipsilateral mammary gland after radiation therapy and to evaluate the late radiation effects.

Patients and methods: Metabolic changes of the ipsilateral and contralateral mammary glands were retrospectively evaluated by F-18 fluorodeoxyglucose (FDG) PET/CT after whole breast irradiation following lumpectomy in five breast cancer patients. The maximum standardized uptake values (SUVmax) of the ipsilateral mammary gland (S1) and the contralateral mammary gland (S0) were measured. The relative SUVmax (SUVmax/ = S1/S0) was measured immediately before, one year after, three years after, and five years after radiation therapy.

Results: The SUVmax of the ipsilateral mammary gland decreased gradually, but there was no decrease in the SUVmax of the contralateral mammary gland. Relative SUVmax values before, 1, 3, and 5 years after radiation therapy were 1.33 ± 0.20, 1.13 ± 0.35, 0.99 ± 0.26 and 0.62 ± 0.10, respectively. Relative SUVmax value at 5 years was significantly lower than before radiation therapy (P < 0.01).

Conclusions: 18F-FDG PET/CT may be useful in assessing mammary gland function and predict lactation disorders in advance.

KEYWORDS

breastfeeding, metabolism, radiation injury, adverse events, functional imaging

Introduction

Adjuvant whole-breast irradiation (WBI) after lumpectomy has been the standard treatment for most patients with early-stage breast cancer [1]. Severe toxicity after WBI is rare, but moderate late adverse events such as induration, edema, breast atrophy have been reported [2]. Radiation therapy is known to impair lactation by reducing the metabolism and function of the mammary glands [3]. As far as we know, there are no reports of quantitative evaluation of metabolic changes in the mammary gland after radiation therapy. The purpose of this study was to investigate metabolic changes in the ipsilateral mammary gland after radiation therapy and to evaluate the late radiation effects.

Patients and methods

All procedures performed in this study were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki declaration and its later
amendments or comparable ethical standards. Written informed consent was obtained from the patient for use of clinical data in research. Since this is a retrospective observational study, institutional review board approval was waived.

**Patients**

Among 74 breast cancer patients who had undergone underwent F-18 fluorodeoxyglucose (FDG) PET/CT at least twice at our institution, we retrospectively selected 5 patients who underwent FDG-PET/CT before WBI (50 Gy/25 fractions/5 weeks), 1, 3, and 5 years after WBI and had no recurrence for more than 10 years. Patients who received adjuvant therapy other than endocrine therapy were excluded. The median age was 46.0 (Q1/Q3 41.5/48.0) years. Four patients had stage IA and one patient had stage IIA breast cancer (AJCC, 8e). Four patients had invasive ductal carcinoma (IDC) and one patient had IDC with coexisting ductal carcinoma in situ (DCIS). Immunohistochemical subtypes were luminal A in four patients and basal-like in one patient. One patient received neoadjuvant chemotherapy with epirubicin/cyclophosphamide followed by docetaxel. All patients had clear margins after surgical resection, but because of close margins (<2 mm), an electron boost of 10 Gy in 5 fractions was added in two patients. Four patients received 5–10 years of adjuvant endocrine therapy (tamoxifen, anastrozole) and one patient did not receive any adjuvant therapy. At the time of analysis, all patients were followed for more than 10 years with no recurrence. The reason for performing PET/CT was the desire of patients to add PET/CT as part of their regular health checkups. Therefore, no patient underwent PET/CT because of suspected recurrence.

**18F-FDG PET/CT imaging**

185 MBq of 18F-FDG was injected intravenously and the patient was rested for 90 min followed by the PET/CT acquisition on a Biograph 6 PET/CT camera (Siemens, Munich, Germany). Low dose CT was followed by 3D PET emission scan of the whole body for 15 min. Images were reconstructed by VOX-BASE View Fusion software (EJM, Sendai, Japan) and the maximum standardized uptake values (SUVmax) of the ipsilateral mammary gland (S1) that received radiation therapy and the contralateral mammary gland (S0) that did not receive radiation therapy were measured (Fig. 1). The relative SUVmax of the ipsilateral mammary gland (R(x) = S1/S0) was measured immediately before (x = pre), one year after (x = 1-yr), three years after (x = 3-yr), and five years (x = 5-yr) after radiation therapy.

**Statistical analysis**

Data were expressed as mean ± standard deviation (SD). A permutation test was used to compare the values of R(x) between groups. If the p-value is under 0.05, results were considered statistically significant.

**Results**

The SUVmax of the ipsilateral mammary gland decreased gradually, but there was no decrease in the SUVmax of the contralateral mammary gland (Fig. 2). Relative SUVmax values before, 1, 3, and 5 years after radiation therapy were 1.33 ± 0.20, 1.13 ± 0.35, 0.99 ± 0.26 and 0.62 ± 0.10, respectively. The relative SUVmax value at 5 years was significantly lower than that before radiation therapy (R(pre) 1.33 ± 0.20, R(5-yr) 0.62 ± 0.10, P < 0.01). On the other hand, the relative SUVmax values at 1 and 3 years were not significantly different from those before radiation therapy (P = 0.31 at 1 year, P = 0.05 at 3 years) (Fig. 3).

**Discussion**

The results of this study showed that the metabolism of the mammary glands gradually decreased over 5 years after irradiation, and it became significantly lower than that before irradiation. Although there have been reports of breast atrophy and lactation disorders after irradiation [2, 3], this is the first report of quantitative evaluation of metabolic changes in the mammary gland after irradiation. Pathological changes in the mammary gland after irradiation have been reported as epithelial atrophy, fat necrosis, fibrosis of terminal duct lobular unit, and fibroelastic intimal thickening of arteries and veins of various sizes [4–6]. The significant decrease in mammary gland metabolism five years after irradiation is considered to reflect fibrosis and vascular insufficiency [4–6]. 18F-FDG PET/CT may noninvasively monitor metabolic changes in the mammary gland after irradiation without biopsy and predict sequelae.

This study has several strengths. First, metabolic changes after WBI were evaluated noninvasively over time using a quantitative method, 18F-FDG PET/CT. After irradiation, the mammary gland is expected to enlarge temporarily due to inflammation and lymphedema, but after that, the mammary gland will gradually atrophy due to fibrosis and vascular insufficiency, and its metabolism will decrease. Although routine biopsy is not possible due to its invasiveness, 18F-FDG PET/CT may be useful for noninvasive evaluation of pathological and physiological changes in the residual mammary gland. Second, 18F-FDG PET/CT may be able to predict lactation ability before conception. If a woman becomes pregnant after breast-conserving therapy, one of the main concerns is whether the affected mammary glands are capable of lactation. The results of this study suggest that it may be possible to infer mammary gland function from metabolism and predict lactation capacity.

There are several limitations to this study that should be noted, first, this is a small, retrospective observational study of breast cancer patients with different disease states. If we could analyze a larger number of people, we would be able to obtain more detailed research results. The results of this study suggest that mammary gland metabolism does not
decline immediately after radiation therapy, but significantly declines after 5 years, indicating that 18F-FDG PET/CT may become a useful biomarker for mammary gland function. Second, 18F-FDG PET/CT is not recommended for breast cancer patients who have undergone curative treatment without subjective symptoms [1]. This study is a retrospective analysis of 18F-FDG PET/CT performed at the request of patients. It is reported that 50% of patients develop lactation disorders after breast conservation therapy [3]. If 18F-FDG PET/CT can predict lactation disorders in advance, it may reduce the emotional burden on patients during pregnancy and after delivery.

In conclusions, a single retrospective study cannot be generalized without further scientific validation; however, 18F-FDG PET/CT may be useful in assessing mammary gland function and predict lactation disorders in advance.

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Fig. 1. Axial 18F-FDG PET/CT images show that the regions of interest are drawn manually around the ipsilateral and contralateral mammary glands. The maximum standardized uptake values (SUVmax) were measured with commercial software (VOX-BASE View Fusion, EJM, Sendai, Japan)
Fig. 2. Box plots of maximum standardized uptake (SUVmax) of (a) contralateral and (b) ipsilateral mammary glands before, 1 year, 3 years, and 5 years after whole breast irradiation. The SUVmax of the ipsilateral mammary gland decreased gradually, but there was no decrease in the SUVmax of the contralateral mammary gland. X marks correspond to the means. The central horizontal bars are the medians. The lower and upper limits of the box are the first and third quartiles, respectively. Points above or below the whiskers’ upper and lower bounds are outliers.
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REFERENCES


Fig. 3. Mean relative maximum standardized uptake (SUVmax) in the ipsilateral mammary gland decreased gradually and was significantly lower at 5 years after whole breast irradiation than before irradiation.