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Original article

Prognostic significance of preoperative ^{18}F-FDG PET/CT for breast cancer subtypes

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ABSTRACT

Adjuvant treatments for operable breast cancers are determined according to subtypes defined based on estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) status. The ER+/HER2− subtype can be divided into luminal A and luminal B usually by Ki67 expression levels. Although tumor size, lymph node metastasis and tumor grade have been widely accepted in daily clinical practice, the identification of further prognostic indicators especially in the ER+/HER2− subtype is warranted. A total of 387 operated breast cancers for which maximum standardized uptake value (SUVmax) on the ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography (FDG PET/CT) were available at baseline were retrospectively analyzed. The optimal cutoff value of SUVmax for relapse-free survival (RFS) was determined to be 3.585 by means of the receiver operating characteristics curve with an area under the curve of 0.6795 (95% CI: 0.5972 to 0.7618, p = 0.0006, sensitivity: 78.8%, specificity: 57.1%). The RFS of patients with SUVmax-high (n = 178) was significantly (p = 0.0003) worse compared with those with SUVmax-low (n = 209). This significant association was prominently recognized in the ER+/HER2− subtype. By multivariable analysis, SUVmax (hazard ratio: 3.83, 95% confidence interval: 1.28–11.51, p = 0.017), tumor size (4.22, 1.39–12.82, p = 0.011) and lymph node metastasis (4.44, 1.81–10.87, p = 0.0012) were significant and independent prognostic factors for RFS. The ER+/HER2− subtype demonstrated consistently worse RFS in the SUVmax-high patients both in the luminal A (p = 0.037) and luminal B (p = 0.047) subtypes. Combination of Ki67 and SUVmax appears to be useful for selecting patients who have inferior prognosis and need further adjuvant treatment of the ER+/HER2− subtype.

Introduction

It is well established that tumor size and the number of involved lymph nodes are significant prognostic factors for operable breast cancers [1]. However, further understanding of tumor biology revealed that tumor subtypes defined according to estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) status are more precise and useful prognostic indicators than tumor burden [2]. Therefore, adjuvant treatments are currently determined based on these subtypes [3]. Although prediction of patient outcome in each subtype is important for the consideration of adjuvant treatment, prognostic factors of each subtype still remain poorly understood. The ER+/HER2− subtype can be further divided into luminal A and luminal B subtypes by gene expression profiling [4]. These luminal subtypes were therefore defined on the basis of Ki67 expression levels in daily clinical practice and adjuvant treatments were decided by taking into consideration these subtypes as well as prognostic factors including tumor size, lymph node metastasis and tumor grade [3]. However, since additional adjuvant therapy may further reduce recurrence, a more precise predictor of prognosis for each subtype is warranted because patients with poor prognosis represent candidates for such clinical trial.

^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography (FDG PET/CT) is a clinically available imaging tool for the diagnosis of metastases or initial staging of breast cancers [5,6]. In daily clinical practice, ^{18}F-FDG PET imaging is usually performed to detect metastatic sites, and according to

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Cochet et al.'s report, this modality provides additional information for the diagnosis of breast cancer recurrence compared with conventional imaging [7]. In addition to the imaging of tumor location sites in PET, the data of uptake values of ^{18}F-FDG in the tumor are also evaluated as the maximum standardized uptake value (SUVmax). Recently, the prognostic significance of SUVmax determined by ^{18}F-FDG PET has been reported [8–11]. Thus, the value of ^{18}F FDG-PET as a prognostic indicator is known; however, its role in each subtype has not yet been fully disclosed. Because it has been reported that the prognostic significance of SUVmax is independent of tumor size, lymph node metastasis and tumor grade [7,8], the SUVmax is expected to provide further prognostic information in addition to conventional clinical prognostic factors. Interestingly, observations identified in these reports that ^{18}F-FDG uptake is significantly associated with negative expression of ER and positive status of HER2 may indicate a subtype specific role of SUVmax in breast cancers. Although the detail mechanisms of the relationship between FDG uptake and breast cancer subtypes are currently unknown, higher uptake of FDG is significantly associated with proliferative phenotypes of breast cancers including higher mitotic counts and higher expression levels of Ki67 [12]. Because tumor phenotype, especially proliferative activity, appears to be different in each breast cancer subtype, these observations might suggest that SUVmax levels are different depending on subtypes mediated through the aggressiveness of the breast cancers. However, whether or not SUVmax levels correlate with the prognosis of breast cancer patients irrespective of subtypes has yet to be fully disclosed.

The aim of the study presented here is to identify the prognostic significance of ^{18}F FDG-PET examination while taking breast cancer subtypes into consideration and to establish the utility of SUVmax in clinical practice. Furthermore, we examined whether SUVmax provides additional information above that provided by Ki67 for predicting the prognosis of patients in the ER+/HER2− subtype.

Materials and methods

Eligibility of patients

For this retrospective study, 743 consecutive patients with newly diagnosed early breast cancers who underwent operations at the Hyogo College of Medicine between May, 2008 and December, 2014 were recruited. A total of 564 patients with histologically confirmed invasive carcinoma were included, while patients with non-invasive carcinoma (n = 136), concurrent bilateral breast cancers (n = 20) and patients with insufficient clinical data (n = 23) were excluded. Of these 564 patients, 387 with preoperatively obtained data for ^{18}F FDG-PET/CT imaging were enrolled in this study. For patients treated with preoperative chemotherapies (n = 105) and endocrine therapies (n = 19), ^{18}F FDG-PET/CT imaging was performed before beginning treatment.

Adjuvant chemotherapies were administered to 175 patients pre- and/or postoperatively (anthracycline-containing regimens: 21, sequential treatment with anthracycline and taxanes: 90, taxane-based regimens: 53, and others: 11). A total of 290 patients were treated with adjuvant endocrine therapies including luteinizing hormone-releasing hormone (LH-RH) analog alone (n = 1), with tamoxifen (n = 72) or with aromatase inhibitor (n = 1). In addition, tamoxifen (n = 27), aromatase inhibitors (n = 180), tamoxifen followed by aromatase inhibitors (n = 5), LH-RH analog plus tamoxifen followed by aromatase inhibitors (n = 3) and aromatase inhibitors followed by tamoxifen (n = 1) were used. Among the ER+ breast cancers, 11 patients did not receive any endocrine therapy, and the treatment for one patient was unknown. During the median follow-up time of 28.1 months (range: 1–77 months), recurrence occurred in 33 patients (bone: 17, soft tissues: 9, lung: 8, liver: 6, and brain: 5). This study was approved by the Ethics Committee of Hyogo College of Medicine.

Immunohistochemical procedure and subtype classification

ER, progesterone receptor (PgR), HER2 and Ki67 expression levels were examined in formalin-fixed, paraffin-embedded tissue samples. The methods of immunohistochemical staining for quantitative expression levels of these proteins and antibodies used in the test were described previously [13]. The percentages of nuclear staining in cancer cells for ER, PgR and Ki67 were determined, and the cutoff values for ER and PgR were set at 1%. According to Petrelli et al.'s report, we used a cutoff value for Ki67 of 25% [14]. Immunohistochemical score of 3 or fluorescence in situ hybridization-positive with an immunohistochemical score of 2 tumors were defined as HER2− positive. The histological classification and nuclear grade were determined according to the Japanese Breast Cancer Society classification [15]. On the basis of immunohistochemistry, we classified ER+ and HER2− breast cancers into luminal A and luminal B according to Ki67 expression levels (luminal A: Ki67 <25%, luminal B: Ki67 ≥25%).

^{18}F FDG-PET/CT imaging and determination of SUVmax

Whole-body ^{18}F-FDG PET examinations were performed in combination with a CT scanner (Gemini GXL16; Philips Medical Systems, Eindhoven, The Netherlands). The detailed procedures of ^{18}F-FDG PET/CT were described previously [16]. Briefly, 4.0 MBq/kg body weight of ^{18}F-FDG was injected into patients who were fasted for 5 h before scanning, and the scanned imaging was obtained approximately 60 min after the injection. The most intense area of ^{18}F-FDG accumulation in the primary breast cancer was set as a region of interest (ROI), and the SUV was calculated as the regional radioactivity concentration (Bq/mL)/[injected dose (Bq)/patient's weight (g)]. The peak SUV in the pixel with the highest count within the ROI was defined as the SUVmax.

Statistical analysis

Differences of various clinicopathological characteristics between SUVmax-high and -low groups were compared by the Chi square test, Fisher's exact test or Mann–Whitney test as appropriate. SUVmax levels among breast cancer subtypes were calculated by the Mann–Whitney test with Bonferroni correction for multiple comparisons. Relapse-free survival (RFS) in Kaplan–Meier plots for two groups was compared by the log-rank test. Univariable and multivariable analyses of RFS in relation to various characteristics were performed with a Cox proportional-hazards model, which yielded a hazard ratio (HR) and 95% confidence interval (CI) for each variable. Differences were considered statistically significant if they were $p < 0.05$, except for the SUVmax levels among subtypes in which significance was set at $p < 0.0083$. JMP Pro 11 software (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

Results

Determination of the cutoff value of SUVmax and the relationships with clinicopathological characteristics

Clinicopathological characteristics of the 387 patients enrolled and 177 patients excluded because of a lack of PET data were compared as shown in Supplemental Table 1. Significantly higher frequencies of excluded patients were recognized in subsets such as smaller tumor size ($p < 0.0001$), no lymph node metastasis