[18F]-Fluorodeoxyglucose Positron Emission Tomography Can Contribute to Discriminate Patients with Poor Prognosis in Hormone Receptor-Positive Breast Cancer

Sung Gwe Ahn1, Minkyung Lee2, Tae Joo Jeon2, Kyunghwa Han3, Hak Min Lee1, Seung Ah Lee5, Young Hoon Ryu2, Eun Ju Son4, Joon Jeong1*

1 Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, 2 Department of Nuclear Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, 3 Biostatistics collaboration unit, Gangnam Medical Research Center, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, 4 Department of Radiology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, 5 Department of Surgery, Eulji University College of Medicine, Seoul, Republic of Korea

Abstract

Background: Patients with hormone receptor-positive breast cancer typically show favorable survival. However, identifying individuals at high risk of recurrence among these patients is a crucial issue. We tested the hypothesis that [18F]-fluorodeoxyglucose positron emission tomography (FDG-PET) scans can help predict prognosis in patients with hormone receptor-positive breast cancer.

Methods: Between April 2004 and December 2008, 305 patients with hormone receptor-positive breast cancer who underwent FDG-PET were enrolled. Patients with luminal B subtype were identified by positivity for human epidermal growth factor receptor-2 (HER2) or high Ki67 (≥14%) according to criteria recently recommended by the St. Gallen panelists. The cut-off value of SUVmax was defined using the time-dependent receiver operator characteristic curve for recurrence-free survival (RFS).

Results: At a median follow up of 6.23 years, continuous SUVmax was a significant prognostic factor with a hazard ratio (HR) of 1.21 (p = 0.021). The cut-off value of SUVmax was defined as 4. Patients with luminal B subtype (n = 82) or high SUVmax (n = 107) showed a reduced RFS (p = 0.031 and 0.002, respectively). In multivariate analysis for RFS, SUVmax carried independent prognostic significance (p = 0.012) whereas classification with immunohistochemical markers did not (p = 0.274). The Harell c-index was 0.729. High SUVmax was significantly associated with larger tumor size, positive nodes, HER2 positivity, high Ki67 (≥14%), high tumor grade, and luminal B subtype.

Conclusions: Among patients with hormone receptor-positive breast cancer, FDG-PET can help discriminate patients at high risk of tumor relapse.

Citation: Ahn SG, Lee M, Jeon TJ, Han K, Lee HM, et al. (2014) [18F]-Fluorodeoxyglucose Positron Emission Tomography Can Contribute to Discriminate Patients with Poor Prognosis in Hormone Receptor-Positive Breast Cancer. PLoS ONE 9(8): e105905. doi:10.1371/journal.pone.0105905

Editor: Ju-Seog Lee, University of Texas MD Anderson Cancer Center, United States of America

Received April 18, 2014; Accepted July 23, 2014; Published August 28, 2014

Copyright: © 2014 Ahn et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. Relevant data are included within the Supporting Information files.

Funding: This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF), funded by the Ministry of Education, Science and Technology (grant 2013R1A1A2007759). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* Email: gsjjoon@yuhs.ac

Introduction

In patients with hormone receptor (HR)-positive breast cancer, which accounts for approximately 75% of breast cancers [1], endocrine therapies targeting the estrogen receptor (ER) or estrogen synthesis have reduced annual recurrences by 41% and deaths by 34%. Nevertheless, treatment failure still occurs in 30% of patients who are treated with tamoxifen [2], therefore identifying patients with a poor prognosis among those with HR-positive breast cancer has become a critical issue in clinical field. Recent advances in molecular studies based on gene expression profiling have classified subtypes of breast cancer and suggest that HR-positive breast cancer is a clinically and biologically heterogeneous entity [3,4]. These studies identified at least two major groups of HR-positive tumors, known as luminal A and B. Identification of luminal B tumors among HR-positive cancers using immunohistochemical (IHC) markers has become accepted in clinical practice [5,6], however, debate against current classification based on IHC markers still remains.
[18F] fluorodeoxyglucose positron emission tomography (FDG-PET) is a well-established imaging tool for the diagnosis and staging of various malignancies [7]. In addition, the degree of FDG uptake can reflect the biologic characteristics of a tumor and is a validated prognostic factor in various malignancies [8,9]. In breast cancer, it is well known that ER-positive tumors are characterized by rather low FDG uptake. Previous studies suggest that high FDG uptake is correlated with negative estrogen receptor (ER) expression, negative progesterone receptor (PR) expression, positive human epidermal growth factor receptor-2 (HER-2) expression, high histologic grade, and high proliferative marker such as Ki67 [10-12]. Therefore, among ER-positive breast cancer, tumors with increased FDG uptake can be considered to show more aggressive behavior than tumors with decreased uptake. Here, we tested the hypothesis that FDG-PET can help predict prognosis in patients with hormone receptor-positive breast cancer.

Materials and Methods

Patient selection

Between January 2004 and December 2008, 835 consecutive women underwent surgery for breast cancer. Of these 835 patients, 682 had undergone preoperative FDG-PET. Patients were excluded on the basis of the following criteria: known bilateral breast cancer (n = 28); preoperative chemotherapy, because chemotherapy can affect tumor characteristics related with FDG uptake (n = 65); ductal carcinoma in situ (n = 83); and distant metastases at initial assessment (n = 41). Among these patients, 309 women with ER-positive and/or PR-positive tumors were identified. These HR-positive patients were classified as two intrinsic subtypes according to criteria recently recommended by the St. Gallen panelists [5,6]. The Ki67 cut-off value of 14% also adhered to these criteria. Two subtypes were defined as follows: luminal A (ER-positive and/or PR-positive, HER2-negative and Ki-67<14%); or luminal B (ER-positive and/or PR-positive, HER2-negative, and Ki-67≥14%, or ER-positive and/or PR-positive and HER2-positive, irrespective of Ki67 index). Patients missing data for any IHC marker were excluded (n = 2). Patients with an IHC score of 2+ for HER2 but without fluorescence in situ hybridization (FISH) results for HER2 amplification were also excluded (n = 2). Data for the remaining 305 patients were entered into the analysis (Figure S1).

For IHC evaluation of four markers, formalin-fixed paraffin-embedded tissue sections obtained from surgical specimens were stained with appropriate antibodies for ER (Novocastra, Newcastle upon Tyne, UK), PR (Novocastra), HER2 (Ventana Medical Systems, Tucson, AZ, USA), and Ki-67 (MIB-1; Dako, Glostrup, Denmark). ER and PR were determined by nuclear staining, which was graded from 0 to 8 according to the Allred score [13]. The results were categorized as positive when the total score, expressed as the sum of the proportion score and intensity score, was ≥3 or greater. For HER2 evaluation, membranous staining was graded as 0, 1+, 2+, or 3+ [14]. HER2 status was deemed to be positive for a score of 3+ and negative for a score of 0 or 1+. Tumors with a score of 2+ were sent for FISH analysis using the PathVysion HER2 DNA Probe Kit (Abbott-Vysis, Des Plaines, IL, USA).

Staging was performed according to the American Joint Committee on Cancer (AJCC), 7th edition. The modified Scarff-Bloom-Richardson grading system was used for tumor grading. Adjuvant systemic therapy and/or radiotherapy were considered according to the standard guidelines based on patient age, primary tumor characteristics, and axillary lymph node status. Endocrine therapy was delivered to all patients. The institutional review board (IRB) of Gangnam Severance Hospital, Yonsei University, Seoul, Korea, approved the study in accordance with good clinical practice guidelines and the Declaration of Helsinki. The IRB waived the need for written informed consent from the participants because of the retrospective design.

FDG-PET method

Prior to FDG-PET, each patient fasted for a minimum of 8 hours and blood glucose level was controlled to lower than 130 mg/dl. Patients received an intravenous injection of 0.14 mCi MBq 18F-FDG in the arm contralateral to the primary tumor. At 60 min after injection of 18F-FDG, whole-body emission scans were obtained using a Philips Allegro PET camera (Philips Medical Systems, Cleveland, Ohio, USA). All patients were studied in the supine position with their arms raised. Attenuation-corrected transaxial images were reconstructed with an iterative transmission algorithm called a row-action maximum likelihood 3D protocol using a 3D image filter into a 128×128 matrix. For semi-quantitative evaluation, $SUV_{max}$ was calculated by measuring the absorption of 18F-FDG by tumors in the region of interest (ROI) as follows:

$$SUV_{max} = \frac{[\text{maximal radioactivity concentration in ROI (µCi/g)}]}{[\text{injected dose (µCi/patient’s weight (kg))}]}.$$  

Statistical analysis

Age was presented as median value with range and compared by Mann-Whitney U test. Discrete variables were compared by chi-square test. The cut-off point of $SUV_{max}$ was defined using the time-dependent ROC curve for recurrence-free survival (RFS). The primary end-point was RFS. RFS was measured from the date of the first curative surgery to the date of the first loco-regional recurrence or distant metastasis. The Kaplan-Meier method was used to estimate the RFS, and the estimated survival curves were compared using the log-rank test. Significant prognostic factors associated with recurrence-free survival were selected using Harrell c-statistic [15] and a Cox proportional hazard regression model was applied for multivariate survival analysis. Student’s t-tests were conducted to compare $SUV_{max}$ according to subtype or prognostic factors. All analyses were performed using SPSS version 18 (SPSS; Chicago, IL) and R (http://www.r-projet.org). Statistical significance was defined by a P-value<0.05 or a 95% confidence interval (CI) that did not include 1.

Results

Patients’ characteristics

Table 1 shows patient characteristics according to the intrinsic subtypes (luminal A and luminal B). The two groups did not differ significantly in T stage, N stage, and AJCC stage, representing tumor burden, or in ER and PR status. In contrast, median age of the luminal A subgroup was significantly higher than that of the luminal B subgroup whereas histologic grade was significantly higher in luminal B than in luminal A. Furthermore, median $SUV_{max}$ was significantly higher in luminal B than in luminal A (4.7 vs. 2.6, respectively). There were no significant differences in adjuvant treatments except for adjuvant endocrine treatment. The higher rate of tamoxifen use in the luminal B subgroup suggested that more premenopausal women were classified as luminal B and was discordant with the lower median age of patients with the luminal B subtype.
Table 1. Baseline characteristics of patients according to intrinsic subtypes.

| Characteristics                  | All patients (n = 305) | Luminal A (n = 223) | Luminal B (n = 82) | P-value* |
|----------------------------------|------------------------|---------------------|-------------------|----------|
| Age years, median (range)        | 48 (25–80)             | 48 (28–80)          | 45 (25–80)        | 0.019bh  |
| T stage                          |                        |                     |                   | 0.127    |
| T1                               | 174 (57)               | 135 (60)            | 39 (48)           |          |
| T2                               | 128 (41)               | 86 (39)             | 42 (51)           |          |
| T3                               | 3 (2)                  | 2 (1)               | 1 (1)             |          |
| N stage                          |                        |                     |                   | 0.367    |
| N0                               | 201 (66)               | 146 (65)            | 55 (67)           |          |
| N1                               | 81 (27)                | 63 (28)             | 18 (22)           |          |
| N2                               | 17 (5)                 | 11 (5)              | 6 (7)             |          |
| N3                               | 6 (2)                  | 3 (1)               | 3 (4)             |          |
| AJCC stage                       |                        |                     |                   | 0.284    |
| I                                | 126 (41)               | 98 (44)             | 28 (34)           |          |
| II                               | 155 (51)               | 109 (49)            | 46 (56)           |          |
| III                              | 24 (8)                 | 16 (7)              | 8 (10)            |          |
| Histologic gradec                |                        |                     |                   | <0.001   |
| 1                                | 129 (42)               | 112 (50)            | 17 (27)           |          |
| 2                                | 117 (38)               | 83 (37)             | 34 (41)           |          |
| 3                                | 26 (9)                 | 0 (0)               | 26 (32)           |          |
| Estrogen receptor                |                        |                     |                   | 0.507    |
| Positive                         | 277 (91)               | 204 (91)            | 73 (89)           |          |
| Negative                         | 28 (9)                 | 19 (9)              | 9 (11)            |          |
| Progesterone receptor            |                        |                     |                   | 0.331    |
| Positive                         | 266 (87)               | 197 (88)            | 69 (84)           |          |
| Negative                         | 39 (13)                | 26 (12)             | 13 (16)           |          |
| HER2                             |                        |                     |                   | <0.001   |
| Positived                        | 47 (15)                | 0 (0)               | 47 (57)           |          |
| Negative                         | 258 (85)               | 223 (100)           | 35 (43)           |          |
| Ki67                             |                        |                     |                   | <0.001   |
| High                             | 33 (11)                | 0 (0)               | 33 (40)           |          |
| Low                              | 272 (89)               | 223 (100)           | 49 (60)           |          |
| SUVmax                           |                        |                     |                   | <0.001bh |
| Median (range)                   | 3.1 (0.8–12.8)         | 2.6 (0.8–12.8)      | 4.7 (1.0–11.2)    |          |
| Adjuvant endocrine therapy       |                        |                     |                   | 0.030    |
| Tamoxifen                        | 129 (42)               | 85 (38)             | 44 (54)           |          |
| Toremifene                       | 62 (20)                | 44 (20)             | 18 (22)           |          |
| Letrozole                        | 61 (20)                | 49 (22)             | 12 (15)           |          |
| Anastrozole                      | 53 (18)                | 45 (20)             | 8 (9)             |          |
| Adjuvant chemotherapy            |                        |                     |                   | 0.146    |
| Yes                              | 187 (61)               | 131 (59)            | 56 (68)           |          |
| No                               | 118 (39)               | 92 (41)             | 26 (32)           |          |
| Adjuvant radiotherapy            |                        |                     |                   | 0.999    |
| Yes                              | 119 (39)               | 87 (39)             | 32 (39)           |          |
| No                               | 186 (61)               | 136 (61)            | 50 (61)           |          |

AJCC, American Joint Committee on Cancer; SUVmax, maximum standardized uptake value; HER2, human epidermal growth factor receptor-2.

* Chi-square test, except for bh Mann–Whitney U test.

d * Data with missing values.

d HER-2 positivity was defined by 3+ score on immunohistochemistry or amplification on fluorescence in situ hybridization.

doi:10.1371/journal.pone.0105905.t001
Survival analysis with SUV_{\text{max}}

At a median follow up of 6.12 years there were 17 recurrences: 5 loco-regional and 12 distant metastases. First, we performed univariate analysis using continuous SUV_{\text{max}}. This analysis showed that continuous SUV_{\text{max}} was a significant prognostic factor with a hazard ratio (HR) of 1.21 ($P = 0.018$; 95% CI, 1.03–1.42). Next, we determined the cut-off point of SUV_{\text{max}} using the time-dependent ROC curve in relation to RFS, which yielded an area under the curve (AUC) of 0.721 (95% CI, 0.594–0.884; Fig. 1). Youden’s index was highest for SUV_{\text{max}} of 4.1. With consideration of clinical application, we defined the cut-off for SUV_{\text{max}} as 4, which gave an AUC for RFS of 0.731 (95% CI, 0.592–0.902). Subsequently, high and low SUV_{\text{max}} groups were defined by a cut-off value of 4. Based on univariate analysis, the RFS time differed significantly between groups stratified by SUV_{\text{max}} (SUV_{\text{max}} \leq 4 versus >4; $P = 0.002$; Fig. 2A).

In univariate analyses using other characteristics (Table S1), RFS differed significantly between groups stratified by age ($\leq$35 vs. $>$35 years; $P < 0.001$), intrinsic subtype (luminal A vs. luminal B; $P = 0.031$; Fig. 2B), and PR (positive vs. negative; $P = 0.009$).

SUV_{\text{max}} versus intrinsic subtypes

Kaplan-Meier plots comparing groups stratified by SUV_{\text{max}} and intrinsic subtype are presented in Fig. 3. RFS did not differ significantly according to subtype within the group of low SUV_{\text{max}} (group 1 vs. group 2; $P = 0.315$, log-rank test) or the group of high SUV_{\text{max}} (group 3 vs. group 4; $P = 0.060$, log-rank test). In contrast, within the group of luminal B, RFS significantly differed according to SUV_{\text{max}} (group 2 vs. group 4; $P = 0.018$, log-rank test). Within the group of luminal A, RFS did not significantly differ according to SUV_{\text{max}} (group 1 vs. group 3; $P = 0.290$, log-rank test).

Multivariate analysis

Multivariate analysis using a Cox regression hazard model suggested that high SUV_{\text{max}} (adjusted HR 4.09; 95% CI 1.36–12.31) was an independent prognostic factor for RFS, and age less than 35 (adjusted HR 7.09; 95% CI 2.56–19.60) and negative PR status (adjusted HR 4.47; 95% CI 1.61–12.44) were associated with an increased risk of tumor recurrence (Table 2). However, the intrinsic subtype was not a prognostic factor in multivariate analysis ($P = 0.240$). For this model, the Harrell c-index was 0.729.

In addition, among patients who received adjuvant chemotherapy (n = 187), dichotomized SUV_{\text{max}} was repeatedly shown to be an independent prognostic factor for RFS (adjusted HR 5.96; 95% CI 1.49–23.95; Table S2). The Harrell c-index was 0.741 in this model.

SUV_{\text{max}} according to tumor characteristics

The mean SUV_{\text{max}} in the two groups was compared after stratification by tumor characteristics (Table 3). The mean SUV_{\text{max}} was significantly higher for the following prognostic factors: large tumor size ($P < 0.001$), positive lymph node ($P = 0.011$), positive HER2 ($P < 0.001$), high Ki67 ($P = 0.011$), and high histologic grade ($P < 0.001$), all of which are considered risk factors. In addition, the mean SUV_{\text{max}} of the luminal B subtype was significantly higher than that of luminal A.

Discussion

In this genomic era, molecular profiling of breast cancer has enhanced our understanding of the complexity and heterogeneity of breast cancer [4]. To translate this understanding of intrinsic subtypes into clinical practice, IHC expression patterns have been widely investigated as surrogate markers. The experts of the St. Gallen’s panel recommended optimal guidelines for intrinsic subtyping based on IHC markers [5,6]. In our study, we used these criteria to identify the intrinsic subtypes of HR-positive tumors.

In terms of prognostic discrimination of endocrine-responsive breast cancer, our results suggested that SUV_{\text{max}} is superior to classification based on surrogate IHC markers. SUV_{\text{max}} demonstrated independent prognostic significance in multivariate analysis whereas classification with IHC markers did not. Analysis revealed that our model including SUV_{\text{max}} had good predictive value for RFS, with a Harrell c-index of 0.729. These findings suggest a potential role for FDG-PET in better predicting groups with poor and good prognosis among patients with HR-positive breast cancer.

It is known that HR-positive tumors show lower SUV_{\text{max}} than HR-negative tumors [10–12]. Regarding intrinsic subtypes, SUV_{\text{max}} was lowest in the luminal A subtype and higher in HER2 and triple negative subtypes [16,17]. The increased accumulation of FDG observed in the high SUV_{\text{max}} tumors

Figure 1. Time-dependent ROC curve for recurrence-free survival (n = 305).
doi:10.1371/journal.pone.0105905.g001
reflects highly proliferating and poorly differentiated cancer. Therefore, HR-positive tumors with high SUV\textsubscript{max} might have aggressive behavior and show a propensity for high proliferation. Indeed, our findings suggested that SUV\textsubscript{max} is associated with high Ki67, HER2 positivity, and higher histologic grade, even in HR-positive cancer (Table 3).

To evaluate tumor proliferation based on PET scans, PET imaging using 18F-fluorothymidine (FLT) has been investigated in breast cancer [18,19]. FLT-PET is known to be closely associated with Ki67 expression in breast cancer. Although high SUV\textsubscript{max} of FDG-PET correlated with high Ki67 in our study, FLT-PET is recognized as a better tool than FDG-PET in terms of evaluation of tumor proliferation. FLT-PET was not available for our study, but it will be interesting to compare the prognostic significance of FDG-PET with that of FLT-PET in HR-positive tumors.

Interestingly, in the analysis with combined factor using SUV\textsubscript{max} and intrinsic subtypes (Figure 3), we noted that Group 4 had higher proportion of HER2-positive tumors than Group 2 (Figure S2). As suggested in Table 3, SUV\textsubscript{max} was higher in HER2-positive tumor, thus it seems reasonable that luminal B tumors with high SUV\textsubscript{max} (Group 4) had a higher HER2-positive rate than luminal B tumors with low SUV\textsubscript{max} (Group 2). It is concordant with previous studies that most of HER2-positive luminal B had a higher chance of tumor recurrence among hormone receptor-positive tumors [20,21]. In addition, it is noteworthy that there might be tumors with good prognosis even in HER2-positive luminal B tumors and those tumors can be identified by SUV\textsubscript{max}.

Recent studies suggested that PR status should be considered as a critical prognosticator in HR-positive women [22–24]. Prognostic power of PR is also recognized by the panels of St. Gallen in 2013 [5]. Our data confirm the prognostic significance of PR. The reproducibility of previous findings implied that our cohort showed a reliable outcome and the quality of IHC markers was well controlled. Furthermore, our data suggest that SUV\textsubscript{max} remains a good prognostic marker for HR-positive breast cancer independent of PR.

The limitations of our study reflect its retrospective nature and the heterogeneity of the patient population. One important factor is the inability to control for variations in adjuvant treatments that may influence survival outcomes. Therefore, to minimize the confounding effect of adjuvant treatment, we performed the same analyses in patients with adjuvant chemotherapy. These analyses revealed that SUV\textsubscript{max} still carried prognostic significance for RFS in patients receiving both adjuvant chemotherapy and endocrine therapy.

Despite these limitations, our study highlights the prognostic impact of FDG-PET for patients with HR-positive breast cancer. The prognostic implications of SUV\textsubscript{max} observed in our study warrant further investigation in prospective studies.
### Table 2. Multivariate analysis using Cox regression hazard model for recurrence-free survival.

| Characteristics          | P-value | Adjusted HR | 95% confidence interval |
|--------------------------|---------|-------------|-------------------------|
| Age, years               |         |             |                         |
| >35 (n = 27)             | <0.001  | reference   |                         |
| ≤35 (n = 278)            | 7.09    | 2.56–19.60  |                         |
| Progesterone receptor    | 0.004   |             |                         |
| Positive (n = 266)       | reference |           |                         |
| Negative (n = 39)        | 4.47    | 1.61–12.44  |                         |
| Intrinsic subtype        | 0.274   |             |                         |
| Luminal A (n = 223)      | reference |           |                         |
| Luminal B (n = 82)       | 1.77    | 0.64–4.90   |                         |
| SUV<sub>max</sub>        | 0.012   |             |                         |
| 4< (n = 198)             | reference |           |                         |
| ≥4 (n = 107)             | 4.09    | 1.36–12.31  |                         |

HR, hazard ratio; SUV<sub>max</sub>, maximum standardized uptake value.
* Presented variables are selected using Harrell c-statistic. In this analysis, Harrell c-index was 0.729.
doi:10.1371/journal.pone.0105905.t002

### Table 3. Comparisons of SUV<sub>max</sub> according to tumor characteristics.

| Characteristics          | Mean SUV<sub>max</sub> ± SD | P-value* |
|--------------------------|-----------------------------|---------|
| Age, years               |                             |         |
| >35 (n = 27)             | 3.63 ± 2.31                 | 0.224   |
| ≤35 (n = 278)            | 4.43 ± 3.28                 |         |
| Tumor size               |                             | <0.001  |
| ≤2 cm (n = 174)          | 4.72 ± 2.60                 |         |
| >2 cm (n = 131)          | 2.92 ± 1.94                 |         |
| Lymph node status        |                             | 0.011   |
| Negative (n = 201)       | 3.44 ± 2.36                 |         |
| Positive (n = 104)       | 4.18 ± 2.41                 |         |
| Estrogen receptor status |                             | 0.928   |
| Positive (n = 277)       | 3.69 ± 2.43                 |         |
| Negative (n = 28)        | 3.74 ± 2.33                 |         |
| Progesterone receptor status |                         | 0.394   |
| Positive (n = 266)       | 3.74 ± 2.47                 |         |
| Negative (n = 39)        | 3.43 ± 2.00                 |         |
| HER2                     |                             | <0.001  |
| Negative (n = 258)       | 3.44 ± 2.33                 |         |
| Positive (n = 47)        | 5.12 ± 2.40                 |         |
| Ki67                     |                             | 0.011   |
| <14% (n = 272)           | 3.57 ± 2.35                 |         |
| ≥14% (n = 33)            | 4.70 ± 2.76                 |         |
| Histologic grade<sup>b</sup> |                         | <0.001  |
| 1 and 2 (n = 246)        | 5.85 ± 2.84                 |         |
| 3 (n = 26)               | 3.58 ± 2.27                 |         |
| Subtype                  |                             | <0.001  |
| Luminal A (n = 223)      | 3.22 ± 2.15                 |         |
| Luminal B (n = 82)       | 4.98 ± 2.64                 |         |

HER2, human epidermal growth factor receptor-2.
* Student’s t-tests.
<sup>b</sup> Data with missing values.
doi:10.1371/journal.pone.0105905.t003
In conclusion, among patients with hormone receptor-positive breast cancer, FDG-PET can help discriminate patients at high risk of tumor relapse.

Supporting Information

Figure S1  Consort chart showing the patients identified in our study. (TIF)

Figure S2  HER2-positive rates among the groups classified with IHC markers and SUV\text{max}. (TIF)

Table S1  Univariate analyses according to tumor characteristics. (DOCX)

References

1. Millar EK, Graham PH, McNeil CM, Browne L, O’Toole SA, et al. (2011) Prediction of outcome of early ER+ breast cancer is improved using a biomarker panel, which includes Ki-67 and p53. Br J Cancer 105: 272–280.
2. Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) (2005) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 365: 1607–1717.
3. Oh DS, Troester MA, Usary J, Hu Z, He X, et al. (2006) Estrogen-regulated genes predict survival in hormone receptor-positive breast cancers. J Clin Oncol 24: 1656–1664.
4. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, et al. (2000) Molecular portraits of human breast tumours. Nature 406: 747–752.
5. Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, et al. (2013) Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol 24: 2206–2223.
6. Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thurlimann B, et al. (2011) Strategies for subtypes–dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann Oncol 22: 1736–1747.
7. Fletcher JW, Djalilian B, Soares HP, Siegel BA, Lowe VJ, et al. (2008) Recommendations on the use of 18F-FDG PET in oncology. J Nucl Med 49: 490–508.
8. Cerfolio RJ, Bryant AS, Ohja B, Bartolucci AA (2005) The maximum standardized uptake values on positron emission tomography of a non-small cell lung cancer predicts stage, recurrence, and survival. J Thorac Cardiovasc Surg 130: 151–159.
9. Sco S, Hatanaka H, Higashi T, Hara T, Tada M, et al. (2007) Fluorine-18 fluorodeoxyglucose positron emission tomography predicts tumor differentiation, Pglycoprotein expression, and outcome after resection in hepatocellular carcinoma. Clin Cancer Res 13: 427–433.
10. Osborne JR, Port E, Gonen M, Doane A, Yeung H, et al. (2010) 18F-FDG PET in HR-Positive Breast Cancer

Table S2  Multivariate analysis using Cox regression hazard model for recurrence-free survival in patients receiving adjuvant chemotherapy (n = 187). (DOCX)

Data S1  Data used in this study. (XLS)

Acknowledgments

The authors thank Mr. Dong-Su Jang, Research Assistant, Department of Anatomy, Yonsei University College of Medicine, Seoul, Korea, for his help with the figures.

Author Contributions

Conceived and designed the experiments: SGA JJ. Performed the experiments: SGA ML TJH HML SAL YHR EJS JJ. Analyzed the data: SGA ML KH. Contributed reagents/materials/analysis tools: YHR EJS. Contributed to the writing of the manuscript: SGA JJ.