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CLINICAL TRIAL

Prognostic significance of pretreatment ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography in patients with T2N1 hormone receptor-positive, ERBB2-negative breast cancer who underwent adjuvant chemotherapy

Sangwon Han[1] · Sae Byul Lee[2] · Gyungyub Gong[3] · Jungbok Lee[4] · Sun Young Chae[5] · Jungsu S. Oh[1] · Dae Hyuk Moon[1]

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Abstract

Purpose To determine whether tumor uptake of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is associated with invasive disease-free survival (IDFS) in patients with hormone receptor (HR)-positive ERBB2-negative early-stage breast cancer treated with adjuvant chemotherapy.

Methods This is a single-center cohort study of women with breast cancer who underwent surgery between 2008 and 2015 at Asan Medical Center, Seoul, Korea. Patients were enrolled if they were diagnosed with HR-positive ERBB2-negative breast cancer with histology of invasive ductal carcinoma, had an American Joint Committee on Cancer pathologic tumor stage of T2N1 with 1–3 positive axillary nodes, underwent preoperative ^{18}F-FDG positron emission tomography/computed tomography (PET/CT), and underwent breast cancer surgery followed by anthracycline- or taxane-based adjuvant chemotherapy. The primary outcome measure was IDFS. The maximum standardized uptake value (SUVmax) was dichotomized using a predefined cut-off of 4.14.

Results A total of 129 patients were included. The median follow-up period for IDFS in those without recurrence was 82 months (interquartile range, 65–106). Multivariable Cox analysis showed that SUVmax was independently associated with IDFS [adjusted hazard ratio 2.49; 95% confidence interval (CI), 1.06–5.84]. Ten-year IDFS estimates via the Kaplan–Meier method were 0.60 (95% CI, 0.42–0.74) and 0.82 (95% CI, 0.65–0.91) for high and low SUVmax groups, respectively. The overall association between SUVmax and IDFS appeared to be consistent across subgroups divided according to age, progesterone receptor status, histologic grade, or presence of lymphovascular invasion.

Conclusion High SUVmax on preoperative ^{18}F-FDG PET/CT was independently associated with reduced long-term IDFS in T2N1 HR-positive ERBB2-negative breast cancer patients who underwent adjuvant chemotherapy.

Keywords Breast neoplasms · Fluorodeoxyglucose F18 · Positron emission tomography · Prognosis · Adjuvant Chemotherapy

Sangwon Han and Sae Byul Lee authors contributed equally.

✉ Dae Hyuk Moon
dhmoon@amc.seoul.kr

[1] Department of Nuclear Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

[2] Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

[3] Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

[4] Division of Biostatistics, Center for Medical Research and Information, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

[5] Department of Nuclear Medicine, Uijeongbu Eulji Medical Center, Eulji University School of Medicine, Uijeongbu, Republic of Korea

Introduction

Hormone receptor (HR)-positive and ERBB2-negative breast cancer comprises about 70% of breast cancer [1]. Although this hormonal subtype shows a favorable short-term outcome, relapse can occur at any time in the 10–15-year post-operation, with a 15-year mortality rate of over 20% [2]. Adding chemotherapy to adjuvant endocrine therapy is generally associated with a 30% reduction in disease recurrence. However, the absolute benefit from adjuvant chemotherapy depends on the individual risk of recurrence [3]. The decision to use systemic adjuvant therapy requires consideration and balancing of the risk of disease recurrence with local therapy alone, the magnitude of benefit from applying adjuvant therapy, the predicted short- and long-term toxicities of the therapy, general health status, and comorbidities [4, 5].

In cases where the indications for adjuvant chemotherapy are uncertain, multigene assays such as the 21-gene expression assay (Oncotype-Dx), 70-gene signature (MammaPrint), 50-gene assay (Prosigna), 12-gene assay (EndoPredict), and Breast Cancer Index are recommended for assessing the risk of recurrence and appropriateness of systemic adjuvant chemotherapy [4, 5]. These gene assays are mainly based on estrogen receptor (ER)-signaling and proliferation-related pathway gene members [6] and are applicable to prognosis assessment in various therapeutic settings, including the receipt of adjuvant chemotherapy and patients with 1–3 positive lymph nodes [7, 8]. However, intratumoral genomic heterogeneity [9], frequent disagreement between multiple genomic assays [10, 11], and menstrual cycle- and menopause-associated changes in gene expression [12, 13] may potentially limit the clinical significance of prognostic gene assays. In addition, the cost-effectiveness of the 21-gene assay is still under debate [14].

^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is an imaging modality frequently used for the preoperative staging of breast cancer [15]. It visualizes the enhanced glycolytic activity that is a metabolic hallmark of cancer and that provides the energy, molecules for biosynthesis, and reducing power required to maintain rapid proliferation [16]. The maximum standardized uptake value (SUVmax) on ^{18}F-FDG PET/CT shows strong associations with estrogen and progesterone receptor (PR) status, histologic grade, nodal metastasis, and recurrence score on the 21-gene assay for breast cancer [17–19]. Previous prognostic studies of HR-positive primary breast cancer showed that baseline ^{18}F-FDG PET parameters were independently associated with recurrence or event-free survival [20–22]. However, the patient populations studied were heterogeneous and included patients with advanced stage or HER2-positive disease. In addition, optimum cut-off values were determined on the basis of patient outcome data and were not subsequently validated in an independent dataset. Evidence for the long-term prognostic value of SUVmax in early-stage HR-positive ERBB2-negative breast cancer should therefore still be considered to be exploratory.

Our previous research on patients with ER-positive ERBB2-negative breast cancer who underwent neoadjuvant chemotherapy demonstrated that SUVmax is an independent predictor of long-term clinical outcomes in terms of distant metastasis and death [23]. Although ^{18}F-FDG PET/CT was performed in the neoadjuvant setting in this previous study, ^{18}F-FDG metabolism reflected baseline prognostic features. The purpose of this study was to validate the prognostic value of SUVmax using a separate cohort of HR-positive ERBB2-negative patients who were treated with adjuvant chemotherapy. The primary objective of this study was to determine whether tumor SUVmax categorized as high or low according to a cut-off determined in our previous study can contribute independent prognostic information on invasive disease-free survival (IDFS) in patients with breast cancer. The studied population included women diagnosed with early-stage HR-positive ERBB2-negative breast cancer with one to three positive lymph nodes, in whom gene expression assays are usually indicated to assess prognosis [5]. The prespecified hypothesis tested was that high SUVmax levels in the tumor at diagnosis are associated with shorter IDFS. The secondary objective was to examine whether SUVmax is associated with distant relapse-free survival (DRFS) and overall survival (OS).

Methods

Study design, setting, and patients

This is a single-center cohort study of women with breast cancer who underwent surgery between January 2008 and December 2015 at Asan Medical Center, Seoul, Republic of Korea. During this period, ^{18}F-FDG PET/CT was performed preoperatively, in addition to the standard staging studies. Patients were identified from the local database of the Department of Breast Surgery. Electronic medical records and PET/CT images were reviewed by the authors, who have more than 5 years of experience in breast cancer surgery or PET/CT imaging. Risk factors were assessed in relation to outcomes that had already occurred at the start of the study. Follow-up ended on January 13, 2021. Our local institutional review board approved the study protocol and waived the need for informed patient consent (2020-1648). This study was conducted in accordance with the Declaration of Helsinki and our institutional guidelines.

All the female patients of the study cohort were evaluated for study eligibility. Patients were enrolled if they were diagnosed with HR-positive ERBB2-negative breast cancer with invasive ductal carcinoma histology, had an American Joint Committee on Cancer pathologic tumor stage of T2N1 with 1–3 positive axillary nodes, underwent preoperative ^{18}F-FDG PET/CT, and had breast cancer surgery followed by anthracycline- or taxane-based adjuvant chemotherapy. Patients were excluded if they had double primary malignancy or bilateral breast cancer. The number of patients enrolled during the study period determined the sample size of this study.

PET/CT image acquisition and analysis

Patients fasted for at least 6 h before the PET/CT scanning and had a venous blood glucose level of less than 150 mg/dl. PET imaging was performed from the skull base to the mid-thigh at 50–70 min after intravenous injection of 5.2–7.4 MBq/kg of ^{18}F-FDG using one of the following scanners: Discovery STe 8, Discovery 690, Discovery 690 Elite, Discovery 710 (GE Healthcare, Waukesha, WI, USA), Biograph Sensation 16, or Biograph TruePoint 40 (Siemens Healthineers, Erlangen, Germany). PET/CT images were reconstructed using an ordered-subset expectation-maximization algorithm with attenuation correction using CT maps.

A volume of interest was manually drawn on either the primary breast cancer or metastatic lymph nodes to assess the SUVmax of the tumor. This volume of interest was drawn by a board-certified nuclear medicine physician in a blinded manner using our in-house software ANTIQUE (Asan Medical Center Nuclear Medicine Image Quantification Toolkit of Excellence). The SUVmax was harmonized across different PET/CT scanners using a previously described technique [23, 24]. In brief, the recovery coefficient profiles of variable hot cylinders of American College of Radiology-approved PET phantoms (Data Spectrum, Hillsborough, NC, USA) were compared between PET scanners [25, 26]. By resampling and smoothing with Gaussian kernels, PET images from the higher-resolution scanners were matched to those of the lower-resolution scanners. The spatial resolution of the harmonized PET images was approximately 8-mm full-width-half-maximum.

Variables

The primary outcome measure of this study was IDFS [8, 27, 28]. The secondary outcomes included DRFS and OS. All survival measures used in this study adhere to the Standardized Definitions for Efficacy End Points (STEEP) system [29]. IDFS was defined as the interval from the date of surgery to locoregional recurrence, distant metastasis, death from any cause, or secondary primary invasive cancer. DRFS was measured until the date of occurrence of distant metastasis or death from any cause. OS was defined as the time between surgery and death from any cause. Patients without events were censored on the date of the last follow-up.

Potential predictors prespecified in the study protocol included age, histologic grade, ER/PR status, and the presence of lymphovascular invasion [30–33]. The prognostic significance of the type of breast surgery, chemotherapy regimen, and radiation treatment was also explored. SUVmax values were dichotomized using a predefined cut-off value of 4.14 determined in our previous study [23]. Patients were also dichotomized according to age and histologic grade using commonly used cut-off values relevant for prognosis: age of 20–50 vs. > 50 years [4, 30, 31] and histologic grade of 1–2 vs. 3 [34, 35]. According to the National Comprehensive Cancer Network guideline, ER and PR were considered positive if more than or equal to 1% of cancer cells were positive on immunohistochemical HR testing [5]. Among the ER-positive tumors, those with 1–10% positive cells were regarded as ER low positive. ERBB2 was considered negative when a result of 0 or 1+ was obtained on immunohistochemistry or a result of 2+ on immunohistochemistry with negative on subsequent fluorescence or silver-enhanced in situ hybridization testing [36].

Statistical analysis

Continuous variables are described as median and interquartile range (IQR) and categorical variables as number (%). Two-sided *P* values of less than 0.05 were considered statistically significant. The Wilcoxon rank-sum test or Kruskal–Wallis test was used to compare continuous variables across groups. Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test. The Spearman rank correlation test was used to evaluate associations between two variables.

Survival analyses were predetermined for the primary objectives in the study protocol. Survival curves were estimated using the Kaplan–Meier method and were compared using the log-rank test. Univariable and multivariable Cox proportional hazards regression analyses were performed. The multivariable Cox regression analysis used stepwise model selection based on the Akaike information criterion. Crude and adjusted hazard ratios and 95% confidence intervals (CIs) were derived. The proportional hazards assumption was checked using the log-minus-log plot and Schoenfeld's residual test. The possibility for influential observations was examined using deviance residuals and dfbeta values. Post hoc extended Cox proportional hazards analyses were performed to explore whether overall associations appeared consistent across all subgroups according to the aforementioned

potential predictors of survival. Statistical tests were performed using R software (version 4.0.5, R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

Of 524 initially identified patients, 129 who underwent preoperative ^{18}F-FDG PET/CT were included in our analysis (Fig. 1). The patient characteristics are described in Table 1. The demographics of the included patients and those without ^{18}F-FDG PET/CT were comparable (Supplementary table 1). The median age was 47 years (IQR 40–55). The median time between ^{18}F-FDG PET/CT and surgery was 9 days (IQR, 4–18). The 21-gene assay was performed in 17 patients. Patients received anthracycline- and taxane-based ($n = 104$), anthracycline-based ($n = 11$) or taxane-based ($n = 10$) adjuvant chemotherapy, followed by hormonal therapy with selective ER modulator and/or aromatase inhibitor, except for one patient planning for pregnancy. The remaining four patients received chemotherapy with unknown regimens at outside hospitals.

^{18}F-FDG PET/CT and harmonized SUVmax

The median blood glucose level before ^{18}F-FDG injection was 101 mg/dL (IQR, 92–111). The administered dose of ^{18}F-FDG was 363 MBq (IQR, 289–444). PET/CT imaging was performed a median of 59 min (IQR 55–62) after ^{18}F-FDG injection. The SUVmax was measured in primary breast tumors in 118 patients and axillary lymph nodes in 11 patients. There were no clinical and pathologic difference between the two groups (Supplementary table 2). The median harmonized SUVmax was 4.58, with IQR ranging from 3.08 to 6.82. The harmonized SUVmax was significantly higher in tumors with histologic grade 3 than in those with grades 1–2 [median 5.68 (IQR 4.30–7.46) vs. 4.22 (IQR 2.75–6.40), $P = 0.009$], but was not associated with primary tumor size ($rho = 0.09$, $P = 0.311$), number of positive lymph nodes ($P = 0.516$), PR status ($P = 0.991$), or lymphovascular invasion ($P = 0.553$). It was also not associated with recurrence score on the 21-gene assay ($rho = 0.22$, $P = 0.399$).

Survival analysis

The median follow-up periods for patients without relevant events were 82 months (IQR 65–106) for IDFS, 83 months (IQR 65–104) for DRFS, and 95 months (IQR 74–117) for OS. There were a total of 29 events for IDFS, 18 for DRFS, and 11 for OS during the follow-up period.

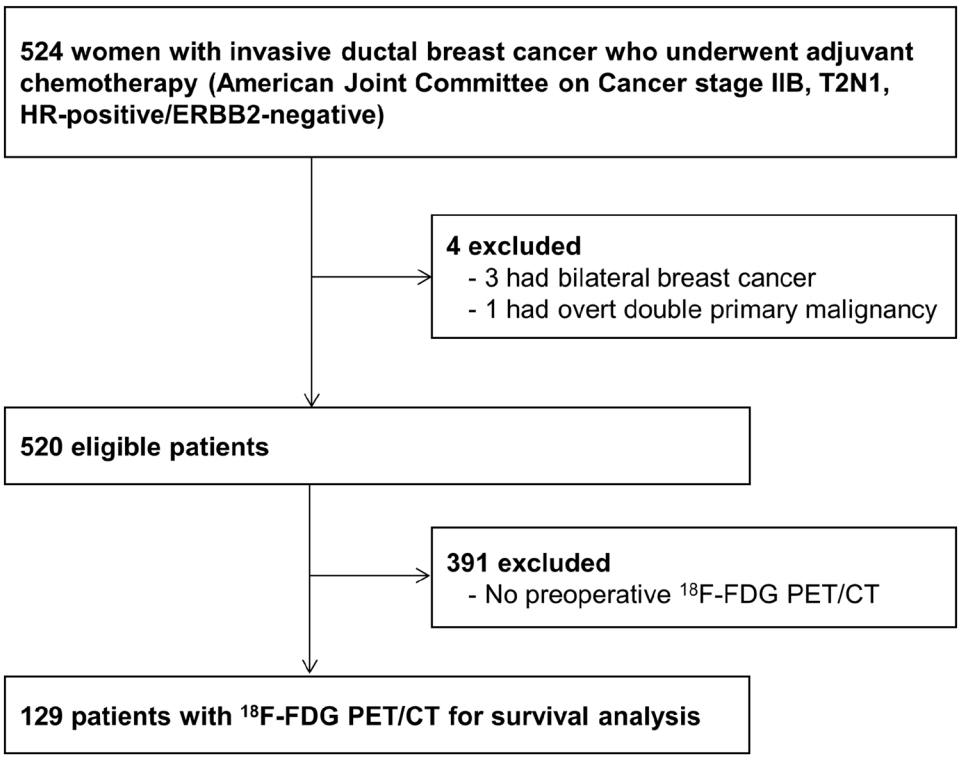

Fig. 1 Flow diagram of the study patients

Table 1 Clinical and pathologic characteristics

Characteristic	Value (interquartile range or %)
Age, years	
20–50	81 (63%)
> 50	48 (37%)
Median tumor size, cm	2.6 (2.4–3.3)
Positive lymph nodes, number	
1	74 (57%)
2	34 (27%)
3	21 (16%)
Histologic grade	
G1–2	100 (78%)
G3	29 (22%)
Estrogen receptor	
Positive	128 (99%)
Low positive	2 (2%)
Negative	1 (1%)
Progesterone receptor	
Positive	113 (88%)
Negative	16 (12%)
Lymphovascular invasion	
Positive	66 (51%)
Negative	63 (49%)
Resection margin	
Positive	4 (3%)
Negative	125 (97%)
Surgery	
Lumpectomy	80 (62%)
Mastectomy	49 (38%)
Radiation therapy	
Done	84 (65%)
Not done	45 (35%)

Univariable Cox proportional hazards regression analyses showed that a high SUVmax above 4.14 was associated with worse IDFS [Table 2, crude hazard ratio 2.51 (95% CI, 1.07–5.87)], whereas the location of SUVmax, age, histologic grade, PR status, lymphovascular invasion, type of breast surgery, chemotherapy regimen and radiation treatment were not. In the stepwise multivariable Cox analysis, SUVmax was independently associated with IDFS [adjusted hazard ratio 2.49 (95% CI, 1.06–5.84)]. Survival curves for IDFS stratified by the SUVmax cut-off of 4.14 are shown in Fig. 2. Ten-year IDFS estimates via the Kaplan–Meier method for high and low SUVmax groups were 0.60 (95% CI, 0.42–0.74) and 0.82 (95% CI, 0.65–0.91), respectively. The overall association between SUVmax and IDFS appeared to be consistent across subgroups divided according to age, PR status, histologic grade, and the presence of lymphovascular invasion (Fig. 3).

Regarding DRFS and OS, patients with low SUVmax tended to have longer DRFS or OS, but the differences were not statistically significant (Supplementary Fig.). The 10-year survival rates of high and low SUVmax groups were 0.73 (95% CI, 0.59–0.90) and 0.88 (95% CI, 0.79–0.99), respectively, for DRFS and 0.87 (95% CI, 0.79–0.97) and 0.94 (95% CI, 0.89–1.00) for OS. In the univariable Cox regression analyses, no other variables were significantly associated with DRFS or OS (Supplementary table 3).

Discussion

The present study evaluated the prognostic value of ^{18}F-FDG PET/CT in patients with early-stage HR-positive ERBB2-negative breast cancer. Considering the spatial resolution of the PET scanners and the prognostic relevance of SUVmax, we studied patients with T2N1 breast cancer. Using a predetermined cut-off value identified in a previous neoadjuvant study, we demonstrated that the SUVmax of ^{18}F-FDG PET/CT was of independent prognostic value in IDFS. To the best of our knowledge, this is the first study to confirm the long-term prognostic value of ^{18}F-FDG PET/CT for early breast cancer of the HR-positive ERBB2-negative subtype. Patients with high-tumor ^{18}F-FDG metabolism should be advised to strictly adhere to their ongoing screening and medication.

Unlike our previous study in a neoadjuvant setting, this study included a cohort of patients who received adjuvant chemotherapy. Although randomized trials demonstrated a similar long-term prognosis when patients were given the same treatment preoperatively compared with postoperatively [5, 37], there were no patients with advanced stages in this study. However, gene expression studies revealed that primary tumor and metastatic node samples from the same patient are usually more similar than those between patients, indicating that the primary tumor's molecular program is retained in advanced tumors [38]. In addition, multigene assays provide the same prognostic information even in patients with lymph node metastasis [39, 40]. Therefore, it is likely that prognostic information provided by ^{18}F-FDG metabolism may be applied regardless of tumor stage. Furthermore, the population enrolled in this study had similar ER and ERBB2 characteristics to the population in our previous neoadjuvant study and the patients were treated in a

Table 2 Cox proportional hazards regression analysis for invasive disease-free survival

Variable	Event/Total	Univariable Hazard ratio (95% CI)	*P*	Multivariable Hazard ratio (95% CI)	*P*
SUVmax					
> 4.14	22/75	2.51 (1.07–5.87)	0.034	2.49 (1.06–5.84)	0.035
≤ 4.14	7/54				
Location of SUVmax					
Primary tumor	25/118	0.65 (0.23–1.87)	0.426	Not included	
Axillary lymph node	4/11				
Age, years					
20–50	19/81	1.00 (0.46–2.17)	0.994	Not included	
> 50	10/48				
Histologic grade					
G3	10/29	2.00 (0.93–4.32)	0.075	Not included	
G1–2	19/100				
Progesterone receptor					
Negative	6/16	2.20 (0.89–5.43)	0.088	2.17 (0.88–5.37)	0.093
Positive	23/113				
Lymphovascular invasion					
Yes	14/66	0.89 (0.43–1.85)	0.764	Not included	
No	15/63				
Surgery					
Lumpectomy	20/80	1.46 (0.66–3.20)	0.349	Not included	
Mastectomy	9/49				
Radiation therapy					
Done	21/84	1.52 (0.67–3.44)	0.312	Not included	
Not done	8/45				
Chemotherapy					
ACT	24/104	0.98 (0.37–2.59)	0.974	Not included	
Other regimens*	5/25				

ACT anthracycline- and taxane-based regimen, *CI* confidence interval

*Anthracycline--, taxane-based, or unknown regimen

similar manner, which indicates that the validation obtained in this study should be legitimate. Therefore, our validation of SUVmax in this separate patient population suggests that ^{18}F-FDG PET/CT is reliable and that SUVmax is likely to be of prognostic value in HR-positive ERBB2-negative patients.

An important question is whether our results on the prognostic value of SUVmax in patients who underwent adjuvant chemotherapy can be applied to those without adjuvant chemotherapy. The prognostic value of SUVmax would be more clinically relevant if it allows determination of those patients who would benefit or not from adjuvant chemotherapy. Previous studies investigating multigene prognostic studies in HR-positive breast cancer after chemotherapy have shown that survival is influenced by baseline biological features and sensitivity to endocrine therapy [41–44]. Sensitivity to chemotherapy does not fully compensate for a poor prognosis and low endocrine sensitivity. Therefore, although ^{18}F-FDG PET/CT was performed in patients who received adjuvant chemotherapy, the ^{18}F-FDG metabolism measured in this study might reflect baseline prognostic features. Our results suggest the complementary use of SUVmax to identify a high-risk population in the adjuvant setting if prognostic gene assays are not available. Prognostication based on SUVmax can be simply performed without additional cost in patients who undergo pretreatment ^{18}F-FDG

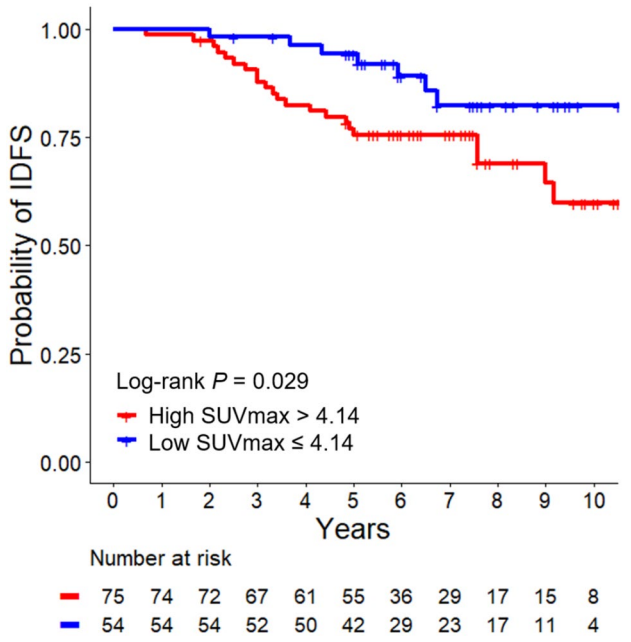

Fig. 2 Kaplan–Meier curves for invasive disease-free survival (IDFS) stratified by SUVmax measured in primary breast cancer or metastatic lymph nodes on ^{18}F-FDG PET/CT

PET/CT for staging purposes, with SUVmax being the most simple and widely used PET parameter in clinical practice. Further studies are warranted to establish the prognostic role of ^{18}F-FDG PET/CT in patients who undergo adjuvant endocrine therapy.

Our study is subjected to several limitations. First, it is retrospective in nature. However, the baseline characteristics of the patients who underwent ^{18}F-FDG PET/CT were not significantly different from those who did not undergo ^{18}F-FDG PET/CT. We enrolled a consecutive series of eligible patients and used predetermined statistical methods for analysis of the primary objectives to minimize possible selection or information bias. Second, we did not show statistical significance in the analysis of DRFS and OS, with there being rather low numbers of events for these secondary endpoints. Third, caution is required when applying our harmonized SUVmax cut-off of 4.14 to other PET centers using different PET scanners. SUVmax is a single-voxel value that shows inter-scanner variability with different resolution, acquisition, and reconstruction parameters [45]. Our harmonization method might be suitable for overcoming the generalizability issue surrounding the use of SUVmax as a prognostic biomarker.

Conclusion

High SUVmax on preoperative ^{18}F-FDG PET/CT was independently associated with reduced long-term IDFS in patients with T2N1 HR-positive ERBB2-negative breast cancer who underwent adjuvant chemotherapy. Therefore, patients with high-tumor ^{18}F-FDG metabolism should be advised to strictly adhere to their ongoing screening and medication.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10549-022-06852-5.

Author contributions Material preparation and data collection were performed by SBL, GG, and SYC. Data analyses were performed by SH, JL, and JSO. Conception and interpretation of data were performed by DHM. The first draft of the manuscript was written by SH, and all

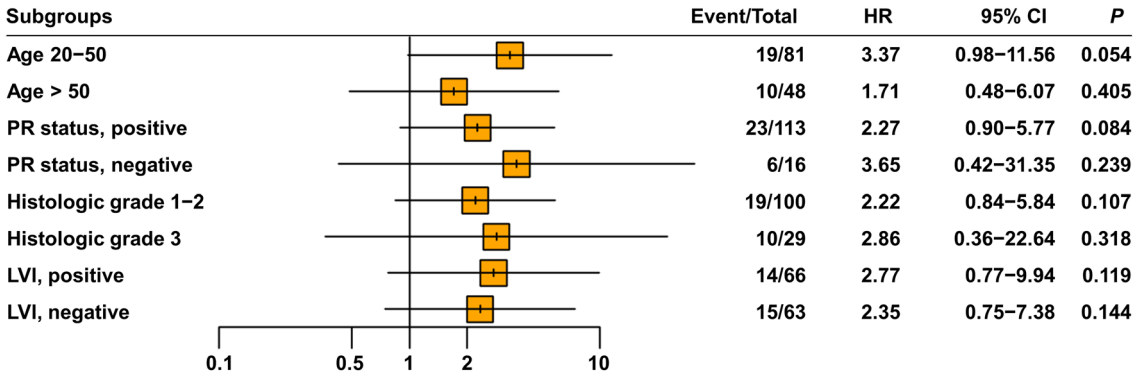

Fig. 3 Extended Cox proportional hazards analyses for invasive disease-free survival according to SUVmax on ^{18}F-FDG PET/CT. CI = confidence interval, HR = hazard ratio, LVI = lymphovascular invasion, PR = progesterone receptor

authors commented on early versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Competing Interests The authors declare no competing interests.

Ethical approval This study was performed in line with the principles of the Declaration of Helsinki and was approved by the institutional review board of Asan Medical Center (2020-1648).

Consent to participate The institutional review board of Asan Medical Center (2020-1648) waived the need for informed consent.

Consent for publication The institutional review board of Asan Medical Center (2020-1648) approved publication of the study results to the research community.

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