Prognostic value of ^{18}F-FDG PET/CT prior to breast cancer treatment. Comparison with magnetic resonance spectroscopy and diffusion weighted imaging

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Abstract

Objective: To investigate the prognostic value of pretreatment fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT), magnetic resonance spectroscopy (MRS), and diffusion weighted imaging (DWI) in breast cancer patients. **Subjects and Methods:** Eighty-three patients who had a tumor larger than 2cm shown by ^{18}F-FDG PET/CT and by 3-Tesla breast MRI, received neoadjuvant chemotherapy (NAC) and subsequent surgical resection. Relationships of PET parameters, including maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG), as well as total choline peak and mean apparent diffusion coefficient (ADCmean) of the primary tumor were evaluated, along with the clinicopathologic factors relapse-free survival (RFS) and overall survival (OS) using log-rank and Cox tests. **Results:** Median overall follow-up was 36.3 months (16.1-76.9 months), during which 11 patients had recurrence and 4 died. Results of receiver operating characteristics curve analysis and log-rank tests showed that high primary tumor SUVmax (≥6.20), MTV (≥5.39), TLG (≥23.23), and total choline peak (≥12.1) values indicated significantly worse RFS as compared to lower values (<6.20, <5.39, <23.23, <12.1, respectively) (P=0.0085, P=0.0029, P=0.013, P=0.016, respectively). The ADC cut-off value (0.833×10^{-3}) was not significant. Furthermore, elevated SUVmax, MTV, TLG, and choline peak levels, progesterone receptor (PR) negative finding, high Ki-67 expression, metastasis to an axillary lymph node, and advanced TNM staging were significantly associated with recurrence, and elevated SUVmax and TLG, PR-negative finding, and axillary node metastases were significantly associated with death. **Conclusion:** Fluorine-18-FDG PET/CT was superior as compared to MRS and DWI for determining recurrence and death prognostic factors, especially primary tumor SUVmax and TLG, in patients with breast cancer.

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Introduction

Breast cancer represents various related diseases with different histological differentiation, as well as clinical course and treatment response. A management plan for an affected patient is typically determined based on tumor-node-metastasis (TNM) stage, histologic tumor grade, and hormone receptor and molecular marker levels in obtained specimens [1]. Factors for immunohistochemical prognosis include hormone receptors, e.g., estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67. On the other hand, for prediction of breast cancer tumor behavior, noninvasive diagnostic tools are becoming increasingly important, with new imaging tools, including magnetic resonance spectroscopy (MRS), diffusion-weighted imaging (DWI) with magnetic resonance imaging (MRI), and fluorine-18-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) [2, 3], reported to provide surrogate imaging biomarkers that correlate with clinicopathological prognostic factors, which can be used for predicting treatment response as well as prognosis, in selected patients.

In MRS findings, choline has a resonance of 3.2ppm and may be an effective imaging biomarker for cell proliferation and also assessment of treatment response, as it has been shown to correlate with histologic prognostic factors related to breast cancer [4-6]. Diffusion-weighted imaging findings reveal the microstructural appearance related to water diffusion in biological tissues. When using DWI, the value for diffusion coefficient (ADC) is primarily affected by cellularity, fluid content, membrane permeability, and tissue blood flow, and it has been reported that the ADC value in primary breast cancer cases is related to clinicopathological prognostic factors [6-8]. On the other hand, ^{18}F-FDG PET/computed

tomography (PET/CT) results show glucose metabolism as well as varied parameters, such as standardized uptake value (SUV), metabolic tumor volume (MTV) and tumor lesion glycolysis (TLG), for characterization of the tumor and have been shown to have correlations with clinicopathological prognostic factors, as well as an ability to predict treatment response and prognosis [5-10].

We have found no previous study that examined surrogate biomarkers related to breast cancer to compare MRS with DWI and ^{18}F-FDG PET/CT findings in regard to prognosis prediction. The capability of DWI as compared to that of ^{18}F-FDG PET/CT for prediction of relapse-free survival (RFS) and overall survival (OS) in patients who received preoperative imaging examinations without neoadjuvant chemotherapy (NAC) has been investigated by two different groups [7, 10]. However, no findings regarding the potential of MRS for prognosis prediction have been presented. In the present study, we examined the utility of MRS, DWI and ^{18}F-FDG PET/CT findings for predicting prognosis (RFS, OS) in breast cancer patients undergoing NAC.

Subjects and Methods

Patients

The requirement for informed consent from the patients was waived and approval for this retrospective study was given by our institutional review board. From January 2012 to June 2016, 113 females with newly diagnosed invasive breast cancer received 3-Tesla breast MRI, including MRS, DWI and whole-body ^{18}F-FDG PET/CT examinations prior to receiving NAC, and then underwent surgical resection. Twenty-four patients with tumors smaller than 2.0cm in diameter and 6 whose follow-up records after surgery were not available were excluded. Finally, 83 patients with indexed breast cancer were included. The enrolled patients' mean age was 56.4±12.8 years (29-86 years), while the interval between MRI and ^{18}F-FDG PET/CT examinations was approximately 2 weeks (13.7±9.8 days).

The patients were treated with either preoperative chemotherapy (n=59) or endocrine therapy (n=24) (Table 1). A regimen containing anthracycline and then taxane, or a regimen based on taxane was administered for NAC. Hormonal therapy was administered for cases that were hormone receptor positive and patients positive for HER2 were given a regimen based on trastuzumab.

After surgery, adjuvant chemotherapy or hormonal therapy was administered, as well as radiotherapy. Mammograph, breast ultrasound, CT, whole-body bone scanning, or ^{18}F-FDG PET/CT examinations were also performed for examining recurrence, metastases and progression. A lesion thought to be cancer was histologically confirmed by fine-needle aspiration cytology or clinical follow-up results, including therapeutic response.

Breast MRI

Magnetic resonance imaging examinations were done with a 3.0-Tesla scanner (Magnetom Verio; Siemens Medical Solutions, Erlangen, Germany) equipped with a bilateral breast phased-array coil. The patient was placed in a prone position and the examination was performed with the following settings: axial and sagittal, fat-suppressed, fast spin-echo T2-weighted imaging sequence (repetition time [TR]/echo time [TE], 5500/79ms; slice thickness, 4mm), axial spin-echo T1-weighted imaging sequence (TR/TE, 620/9.4ms; slice thickness, 4mm), and axial DWI using single-shot echo-planar imaging (b factors 0 and 1000s/mm^2; TR/TE, 6900/74ms; slice thickness, 4mm). A fat-suppressed T1-weighted fast low-angle-shot, three-dimensional, volume-interpolated breath-hold examination sequence [TR/TE, 3.7/1.4ms; flip angle, 15°; matrix, 384×384; field of view (FOV), 330×330 mm; slice thickness, 1mm] was obtained before, and again 1, 2, 3, and 5 minutes after gadolinium injection. Gadopentetate dimeglumine, a gadolinium contrast material (Magnevist, Bayer Healthcare, Berlin, Germany) was infused at 0.2 mL/kg with a power injection at 2.0mL/s and flushed at the same rate with a saline solution (20mL). Raw data were used to produce reformatted sagittal and coronal images. Standard subtraction images were produced by subtracting precontrast images from the early peak post-contrast image (obtained 60 seconds after contrast injection) on a pixel-by-pixel basis. Also, maximum-intensity projection reconstructions were applied to subtraction images.

Table 1. *Patient and tumor characteristics.*

Characteristics	Number	%
Total patients	83	
Age (years)		
Mean (Range)	53.6 (29-77)	
Histology		
IDC (scirrhous/solid tubular/papillary tubular)	77 (49/25/3)	92.8% (59.0%/30.1%/ 3.6%)
Myxoid	6	7.2%
Tumor location		
Right/Left	39/44	47.0%/53.0%
Receptor positivity		
Estrogen receptor	59	71.1%
Progesterone receptor	43	51.8%
HER-2/neu	19	22.9%
Ki-67 index status		
<20% / ≧20%	26/57	31.3%/68.7%

(continued)

Nuclear grade of IDC		
Grade 1/2/3	33/17/27	42.9%/22.1%/ 35.1%
Molecular phenotype		
Luminal A (ER+/HER2-, Ki67<20%)	23	27.7%
Luminal B (ER+/HER2-, Ki67≥20%)	27	32.5%
Luminal-HER2 (ER+/HER2+)	8	9.6%
HER2 positive (nonluminal)	10	12.0%
Triple-negative	15	18.1%
T status		
T2/T3/T4	70//9/4	84.3%/10.8%/4.8%
N status		
N0/N1/N2/N3	42/36/2/3	50.6%/43.4% /2.4%/3.6%
Stage		
Ⅱ/Ⅲ	72//11	86.7%/13.3%
Chemotherapy regimen		
TC	2	2.4%
FEC and Docetaxel	14	16.9%
FEC and Paclitaxel	3	3.6%
Docetaxel, Herceptin, and FEC	8	9.6%
Paclitaxel, Herceptin, and FEC	4	4.8%
FEC, Docetaxel, and Letrozole	6	7.3%
EC	1	1.2%
EC and Docetaxel	2	2.4%
EC, Docetaxel, and Capecitabine	5	6.0%
EC, Paclitaxel, and Herceptin	2	2.4%
Epirubicin and Capecitabine	1	1.2%
Docetaxel and Letrozole	1	1.2%
Docetaxel and Herceptin	5	6.0%
Herceptin and Capecitabine	1	1.2%
Herceptin and Paclitaxel	2	2.4%
Herceptin and FEC	1	1.2%
Paclitaxel	1	1.2%
Herceptin	1	1.2%
Endocrine therapy regimen		
Letrozole	19	22.9%
Tamoxifen	5	6.0%
Type of Surgery		
Breast-conserving surgery	25	30.1%
Modified radical mastectomy	58	69.9%
Diagnostic tool of axillary node		
Aspiration cytology	8	9.6%
Aspiration cytology and SLNB	12	14.5%
Aspiration cytology and ALND	18	21.7%
Aspiration cytology, SLNB and ALND	6	7.2%
SLNB	32	38.6%
ALND	5	6.0%
SLNB and ALND	2	2.4%
Pathological treatment response		
pCR	22	26.5%
non-pCR	61	73.5%

Single-voxel ^{1}H MRS was finally done using a point-resolved spectroscopy sequence (PRESS), with the following parameters; 1500/100, voxel size 15×15×15mm^{3}, 128 acquisitions, spectral width 1400Hz, 1024 data points, and acquisition time of 7 minutes. To place voxels, the scout images were coronal and sagittal contrast-enhanced T1-weighted MR images, with the voxel of interest placed so as to include the lesion. Shimming was performed automatically, then manual shimming was performed of water resonance for homogeneity optimization in each volume of interest. Typically, water-peak line widths of 17-40Hz [full width at half-maximum (FWHM)] were obtained. After shimming, we acquired spectra with water suppression using 3 chemical shift selective excitation pulses. Transverse magnetization was

then selectively dephased before and after the second spin-echo pulse using spectral suppression with dual band-selective inversion and gradient dephasing.

Spectroscopy examination results were evaluated in a semi-quantitative manner to determine total choline peak using calculations of the area under the curve (AUC), by 2 experienced radiologists (each had 6 years of experience with breast MRS), who had no knowledge regarding other imaging results and were not aware of no clinical or histopathologic findings, other than breast cancer presence, with all decisions based on consensus. The AUC was automatically calculated using a software as the area of total choline peak under 3.2 parts per million (ppm) in the spectrum, with that value noted for each of the lesions.

Two experienced radiologists each with 8 years of experience in breast DWI retrospectively reviewed all ADC maps, with decisions based on consensus. Apparent diffusion coefficient values were calculated using the following formula: ADC=[1/(b2 – b1)] ln(S2/S1), where S1 and S2 represent the signal intensity in the region of interest (ROI) obtained by 2 gradient factors, b2 and b1 (b1=0 and b2=1000s/mm^2). Based on previously published methods [6, 8], as many multiple circular 25mm^2 ROI (diameter approximately 5.6mm) as possible were positioned inside the tumor on the ADC map while referring to the enhanced solid portion shown by dynamic contrast enhanced imaging and T2WI. Each ROI was carefully placed inside the tumor in order to avoid the cystic portion or visual artifacts, then mean ADC values were recorded within each ROI. The averages of the mean ADC values were calculated for all ROI within the tumor (ADCmean).

Fluorine-18-FDG PET/CT

A PET/CT scanner (Gemini GXL16 or Gemini TF64; Philips Medical Systems, Eindhoven, The Netherlands) including a gadolinium oxyorthosilicate detector was employed to perform ^{18}F-FDG PET/CT examinations. Patients fasted for 5 hours before the procedure, then blood glucose was measured immediately prior to injection of 4.0MBq/kg body weight of ^{18}F-FDG for the GXL16 or 3.0MBq/kg for the TF64. No patient had a level of blood glucose exceeding 150mg/dL. Approximately 60 minutes after injection, static emission images were obtained. Helical CT scanning from the top of the head to the bottom of the feet was performed for attenuation correction and anatomic localization, with the following parameters used: tube voltage, 120kV; effective tube current auto-mA up to 120mA/second (GXL16) or 100mA/second (TF-64); gantry rotation speed, 0.5 seconds; detector configuration, 16×1.5mm (GXL16) or 64×0.625mm (TF64); slice thickness, 2mm; and transverse FOV, 600mm. Immediately following CT completion, PET imaging from the head to mid-thigh was performed for 90 seconds for each bed position and from the mid-thigh to the toes for 30 seconds for each of the bed positions with a variable sampling method. Next, images were acquired in three-dimensional mode at 12-14 bed positions, each for 90 seconds, and again for 6-7 bed positions, each for 30 seconds, with between 22 and 26 minutes, respectively, of emission scanning required for the patients. Normal breathing was allowed during the PET scanning sessions. A line-of-response row-action maximum likelihood algorithm (subsets n/a, 2 iterations) was sued for the GXL16 and an ordered-subset expectation maximization iterative reconstruction algorithm (33 subsets, 3 iterations) for the TF64, then attenuation-corrected PET images were reconstructed.

Two experienced readers (with oncologic ^{18}F-FDG PET/CT reporting experience of 9 and 4 years, respectively) with no knowledge of other imaging results, or clinical or histopathologic findings, other than the presence of breast cancer, retrospectively reviewed all ^{18}F-FDG PET/CT images, with decisions based on consensus. The commercial software package GI-PET (AZE Co., Ltd., Tokyo, Japan), capable of harmonizing SUV obtained with different PET/CT systems using phantom data [11], was employed. SUVmax, defined as maximum SUV within the target volume, was calculated as follows: concentration of radioactivity in volume of interest (VOI) (MBq/mL)×total body weight (kg)/injected radioactivity (g/MBq). Standardized uptake value mean was determined as the summed SUV in each voxel in the target volume divided by the number of voxels within the target volume. With the margin threshold set at 40% of SUVmax, MTV (milliliters) was automatically measured inside the tumor VOI. We then calculated TLG (grams) as SUVmean×MTV, which took both metabolic activity and tumor burden into consideration.

Histologic analysis

Following immunohistochemical staining, the expression levels of ER, PR, HER2, and Ki67 were examined with paraffin-embedded tissue samples fixed with formalin using previously described techniques for quantitative expression levels of the examined proteins and antibodies [12]. We then determined nuclear staining percentage in cancer cells for ER and PR, with the cutoff value set at 1%, and Ki67, with the cutoff value set at 20%. HER2-positive tumors were defined based on an immunohistochemical score of 3 or in situ hybridization-positive fluorescence using an immunohistochemical score of 2.

Statistical analysis

For comparisons of patients with or without recurrence or death, non-parametric test was used. For this long-term follow-up examination, we evaluated RFS, time elapsed from date of treatment initiation to recurrence, and OS, defined as the time until death. When progression or death did not occur during the follow-up period, the final follow-up date was used. Using the Kaplan-Meier method and log-rank test results, survival curves were estimated.

For evaluations of individual variables in regard to their prognostic value, Cox proportional hazards logistic regression was employed. The risks of recurrence and death for the variables primary T stage, ER status, PR status, HER2 status, Ki-67, nuclear grade, axillary lymph node metastases, TNM stage, histology subtype, pathological complete response (pCR), primary tumor SUVmax, MTV, TLG, ADCmean, and total choline peak were quantified using univariate Cox proportional hazards modeling. Thereafter, except for parameters with insufficient available data, significant or borderline univariate variables ($P<0.1$) were subjected to multiva-

riate analysis. Cox model results are expressed as hazard ratio with 95% confident interval (CI). SAS, version 9.3 (SAS Institute Inc., Cary, NC, USA), was used for statistical analysis, with a value of P<0.05 considered to be significant.

Results

Patient characteristics

Characteristics of the patients and tumors are shown in Table 1. Magnetic resonance imaging and clinical examination results were used to determine T status. The axillary node diagnostic tool was determined based on overall assessment of aspiration cytology, sentinel lymph node biopsy, and axillary lymph node dissection. Core needle biopsy and surgical resection findings were used to decide histopathologic characteristics.

RFS analysis

The median overall follow-up period for all 83 patients was 35.8 months (on page 16: 35.3 months) (6.5-73.1 months), of whom 11 (13.2%) had recurrence. For the 72 with no recurrence, the median overall follow-up was 36.9 months (16.1-73.1 months), while that was 27.6 months (6.559.9 months) for the 11 patients with recurrence. Among those 11, there was 1 with local recurrence, 2 with regional lymph node metastasis, and 8 with distant metastasis (liver 2, bone 2, brain 2, lung 1, skin 1). A representative case is shown in Figure 1.

A higher SUVmax value was seen for patients with as compared to without recurrence (8.89±3.80 vs. 5.11±3.97, P=0.085). Results of receiver operating characteristic (ROC) curve analysis and a log-rank test indicated that patients with an elevated primary tumor SUVmax value (≥6.20) had a significantly lower RFS rate than those with a lower SUVmax value (<6.20, P=0.0085) (Figure 2a). Those with cancer recurrence also had a higher MTV value (20.43±30.56 vs. 12.23±10.28, P=0.12). Also, patients with an elevated MTV value (≥5.39) had a significantly lower RFS rate as compared to patients with a low MTV value (<5.39) (P=0.029) (Figure 2b). Furthermore, a higher TLG value was seen in patients without recurrence (108.54±124.19 vs. 57.74±82.53, P=0.083). Furthermore, findings of ROC curve analysis and log-rank testing indicated that patients with an elevated primary tumor TLG value (≥23.23) had a significantly lower RFS rate than those with a low TLG value (<23.23) (P=0.013) (Figure 2c).

As for ADCmean values, they were lower in patients with cancer recurrence as compared to those with no recurrence ($0.771\pm0.137\times10^{-3}$ vs. $0.863\pm0.215\times10^{-3}$ mm^2/s, P=0.17). Using ROC curve analysis and log-rank test findings, we divided the patients into 2 groups according to a mean cut-off value of 0.833×10^{-3} mm^2/s, but found no significant difference (P=0.13). Patients with recurrent cancer also had a higher total choline peak as compared to those without recurrence (19.67±17.18 vs. 10.27±8.91, P=0.0060), while ROC curve analysis and log-rank test findings indicated that those with an elevated primary tumor total choline peak (≥12.1) had a significantly lower RFS rate as compared to those with a low total choline peak (<12.1, P=0.016) (Figure 2d).

Results of univariate analysis showed that SUVmax (P=0.0085), MTV (P=0.029), TLG (P=0.013), and total choline peak (P=0.016) each had a significant association with recurrence, as did PR-negative (P=0.033), high Ki-67 expression (P=0.014), axillary lymph node metastasis (P=0.010), and advanced TNM stage (P=0.034) findings (Table 2). None of these factors were found to be an independent factor related to recurrence in multivariate analysis (Table 2).

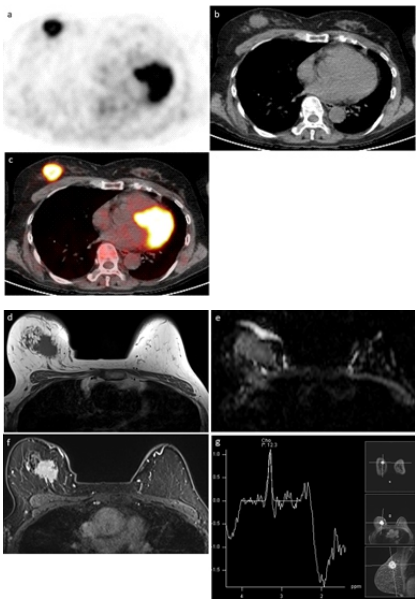

Figure 1. A 63 years old woman with a Luminal B (HER2-negative) type invasive ductal carcinoma (scirrhous cancer, ER 100%, PR 0%, HER2 1+, Ki-67 30%, grade 1, T2N1M0) showed recurrence (liver metastasis) at 19.1 months and died 21.0 months after NAC initiation. Axial (a) ^{18}F-FDG PET, (b) CT, and (c) fused images showed intense uptake, while SUVmax, MTV, and TLG values in the right breast tumor were 7.64, 13.44mL, and 54.52g, respectively. (d) Axial T1WI showing a well-defined, irregular edged, hypo-intense mass measuring 32mm in length. (e) Axial ADC map showing low signal intensity from the tumor (ADCmean 0.828×10^{-3} mm^2/s). (f) Axial fat-suppressed T1-weighted 3-dimensional imaged obtained at 3 minutes after gadolinium injection showing strong enhancement of the mass. (g) The total choline-containing compound peak integral was 12.3 arbitrary units.

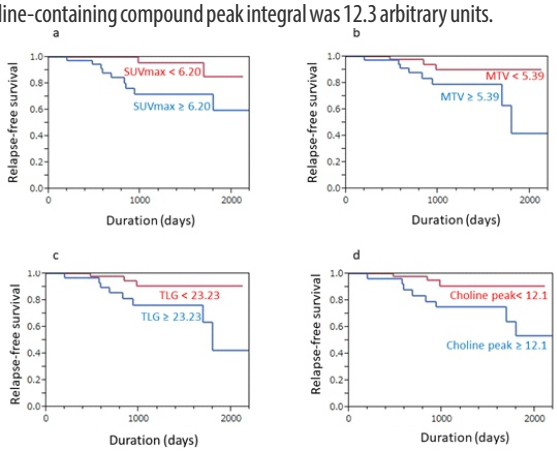

Figure 2. Relapse-free survival (RFS), Kaplan-Meier survival analysis. (a) Patients with a high SUVmax value (≥6.20) had a significantly lower RFS rate than those with a low value (<6.20) (P=0.0085). (b) Patients with a high MTV value (≥5.39) had a significantly lower RFS rate than those with a low value (<5.39) (P=0.029). (c) Patients with a high TLG value (≥23.23) had a significantly lower RFS rate than those with a low value (<23.23) (P=0.013). (d) Patients with a high total choline peak value (≥12.1) had a significantly lower RFS rate than those with a low value (<12.1) (P=0.016).

Table 2. *Factors associated with relapse-free survival (RFS).*

Risk factor for recurrence	Total no. of patients	Patients with recurrence	Univariate analysis		Multivariate analysis	
			P (log-rank)	Hazard ratio (95% CI)	P (log-rank)	Hazard ratio (95% CI)
SUVmax						
<6.20	47	2	0.0085	6.09 (1.57-39.97)	0.094	6.79 (1.01-46.31)
≥6.20	36	9				
MTV (mL)						
<5.39	45	3	0.029	3.39 (1.01-13.05)	0.47	0.47 (0.58-4.42)
≥5.39	38	8				
TLG (g)						
<23.23	52	3	0.013	4.60 (1.18-30.21)	0.35	2.80 (0.28-7.78)
≥23.23	31	8				
ADCmean						
≤0.8325	46	5	0.13	2.65 (0.76-12.12)		
>0.8325	37	6				
Total choline peak						
<12.1	55	3	0.016	4.47 (1.28-20.49)	0.19	2.63 (0.61-14.29)
≥12.1	28	8				
Histology						
mucinous	6	0	0.37	2.02 (0.37-6.56)		
IDC	77	11				
Estrogen receptor statue						
Positive	59	6	0.083	2.76 (0.79-9.20)	0.55	0.62 (0.13-3.29)
Negative	24	5				
Progesterone receptor status						
Positive	43	3	0.033	3.91 (1.11-18.05)	0.27	2.87 (0.43-20.36)
Negative	40	8				
HER2 status						
Negative	64	9	0.32	1.94 (0.34-5.14)		
Positive	19	2				
Ki-67 index status						
<20%	26	0	0.014	5.79 (1.34-34.84)	0.16	3.02 (0.87~25.44)
≥20%	57	11				

(continued)

Nuclear grade						
1,2	50	9	0.58	1.55 (0.39-2.55)		not applicable
3	27	2				
T stage						
T2	70	9	0.44	1.85 (0.27-3.64)		
T3,T4	13	2				
Axillary lymph node metastasis						
Absent	42	2	0.010	6.23 (1.54-42.13)	0.15	3.11 (0.66-22.08)
Present	41	9				
TNM stage						
Ⅱ	72	8	0.034	4.06 (0.85-15.60)	0.29	2.56 (0.42-14.89)
Ⅲ	11	3				
Pathological treatment response						
pCR	22	0	0.12	3.02 (0.82-13.43)		
non-pCR	61	11				

CI; confident interval, SUVmax; maximum standardized uptake value, MTV; metabolic tumor volume, TLG; total lesion glycosis, ADC; apparent diffusion coefficient, IDC; invasive ductal carcinoma, HER2; human epidermal growth factor receptor 2, pCR; pathological complete response. Primary tumor's nuclear grade was analyzed in 77 patients.

Overall survival analysis

For all 83 patients, the median overall follow-up period was 36.3 months, during which 4 (4.8%) died. As for the 79 who remained alive, the median follow-up was 36.5 months (16.1-76.9 months), while that period for those who died was 19.4 months (16.5-44.8 months). A representative case is shown in Figure 1. Patients who died of cancer had a higher SUVmax value as compared to those who remained alive (9.17±4.55 vs. 6.06±3.97; P=0.097). Receiver operating characteristic curve analysis and log-rank test findings indicated that patients who had an elevated primary tumor SUVmax value (≥6.20) demonstrated a significantly lower OS rate as compared to patients showing a low SUVmax value (<6.20; P=0.021) (Figure 3a). Furthermore, those who died from cancer had a higher MTV value as compared to those who did not (21.92 ±37.14 vs. 12.79±17.06, P=0.13), while patients with an elevated MTV value (≥5.65) had a reduced OS rate as compared to patients with a reduced MTV value (<5.65), though the difference was not significant (P=0.088) (Figure 3b).

A higher TLG value was seen in patients who died of cancer as compared to those who remained alive (95.77±112.18 vs. 50.17±79.52, P=0.052). Furthermore, findings obtained with ROC curve analysis and log-rank testing indicated that patients with an elevated TLG value (≥13.23) for the primary tumor had a significantly lower OS rate as compared to patients with a reduced TLG value (<13.23) (P=0.041) (Figure 3c). Also, patients who died of cancer had a lower ADCmean value as compared to those who remained alive (0.819± 0.213×10^{-3} vs. $0.886\pm0.079\times10^{-3}mm^2/s$, P=0.53). Using ROC curve analysis and log-rank test results, we divided the patients into 2 groups according to an ADCmean cut-off value of $0.833\times10^{-3}mm^2/s$, though no significant difference was seen between them (P=0.27). Patients who died from cancer also had a higher total choline peak than those who did not (16.23±8.84 vs. 11.27±10.80, P=0.17), while ROC curve analysis and log-rank test findings indicated that patients with an elevated primary tumor total choline peak (≥12.1) had a lower OS rate as compared to those with a low total choline peak (<12.1), though the difference was not significant (P=0.11) (Figure 3d).

Univariate analysis results showed a significant association with death from cancer for SUVmax (P=0.021) and TLG (P= 0.041) were, as well as PR-negative (P=0.023) and presence of axillary lymph node metastases (P=0.037) (Table 3). In multivariate analysis results, none of these factors were found to be independently related to death (Table 3).

Table 3. *Factors associated with overall survival (OS).*

Risk factor for death	Total no. of patients	Patients with death	Univariate analysis		Multivariate analysis	
			P (log-rank)	Hazard ratio (95% CI)	P (log-rank)	Hazard ratio (95% CI)
SUVmax						
<6.20	47	0	0.021	13.42 (0.32-178.69)	0.12	3.36 (0.41-79.7)
≥6.20	36	4				
MTV (mL)						
<5.65	49	1	0.088	6.02 (0.74-124.79)	0.49	1.35 (0.26-7.56)
≥5.65	34	3				
TLG (g)						
<13.23	40	0	0.041	8.47 (0.32-137.32)	0.17	2.91 (0.38-40.36)
≥13.23	43	4				
ADCmean						
≤0.8325	46	2	0.27	2.88 (0.34-19.09)		
>0.8325	37	2				
Total choline peak						
<12.1	55	1	0.11	5.32 (0.67-108.19)		
≥12.1	28	3				
Histology						
mucinous	6	0	0.63	1.45 (0.32-17.39)		
IDC	77	4				
Estrogen receptor statue						
Positive	59	2	0.24	3.04 (0.36-25.38)		
Negative	24	2				
Progesterone receptor status						
Positive	43	0	0.023	12.34 (0.28-176.72)	0.093	10.79 (0.82-136.28)
Negative	40	4				
HER2 status						
Negative	64	3	0.84	1.27 (0.062-9.95)		
Positive	19	1				
Ki-67 index status						
<20%	26	0	0.16	4.73 (0.59-77.91)		
≥20%	57	4				

(continued)

Nuclear grade						
1,2	50	3	0.68	1.14 (0.23-17.06)		not applicable
3	27	1				
T stage						
T2	70	3	0.39	2.72 (0.13-29.46)		
T3,T4	13	1				
Axillary lymph node metastasis						
Absent	42	0	0.037	8.65 (0.33-139.61)	0.057	14.19 (1.53-297.23)
Present	41	4				
TNM stage						
Ⅱ	72	3	0.34	3.03 (0.14-31.72)		
Ⅲ	11	1				
Pathological treatment response						
pCR	22	0	0.34	2.98 (0.12-27.43)		
non-pCR	61	4				

CI; confident interval, SUVmax; maximum standardized uptake value, MTV; metabolic tumor volume, TLG; total lesion glycosis, ADC; apparent diffusion coefficient, IDC; invasive ductal carcinoma, HER2; human epidermal growth factor receptor 2, pCR; pathological complete response. Primary tumor's nuclear grade was analyzed in 77 patients.

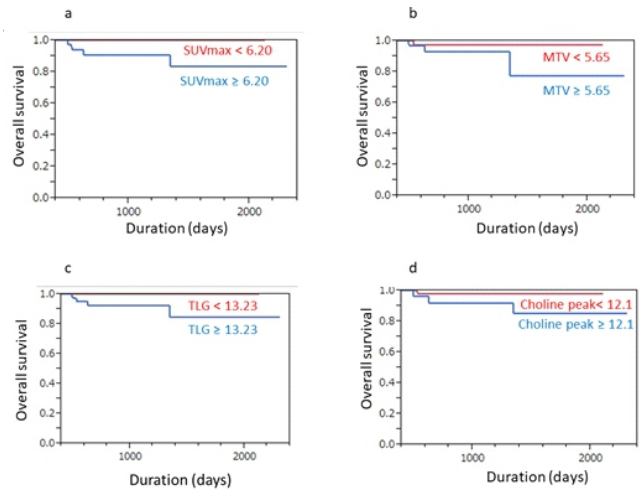

Figure 3. Overall survival (OS), Kaplan-Meier survival analysis. (a) Patients with a high SUVmax value (≥6.20) had a significantly lower OS rate than those with a low value (<6.20) (P=0.021). (b) Patients with a high MTV value (≥5.65) had a lower OS rate than those with a low value (<5.65) without significant difference (P=0.088). (c) Patients with a high TLG value (≥13.23) had a significantly lower OS rate than those with a low value (<13.23) (P=0.041). (d) Patients with a high total choline peak value (≥12.1) had a lower OS rate than those with a low value (<12.1) without significant difference (P=0.11).

Discussion

This is the first known study to examine pretreatment ^{18}F-FDG PET/CT, MRS, and DWI results in patients with breast cancer receiving NAC for prediction of prognosis (RFS, OS). Our findings indicated that ^{18}F-FDG PET/CT was the most useful modality for predicting prognosis regarding both recurrence and death, while MRS results were helpful to predict recurrence but not death, and DWI was not useful for prediction of either. In addition, among the factors tumor SUVmax, MTV, and TLG values, SUVmax and TLG were superior to MTV because they were correlated with both RFS and OS, whereas MTV was only correlated with RFS.

Several groups have reported that ^{18}F-FDG PET results are useful as an indicator of prognosis in cases of breast cancer. In addition, the SUVmax value of the primary tumor has been shown to have a strong correlation with known prognostic pathological parameters [7-10] and also useful for prediction of prognosis, including recurrence or death [7, 9, 10]. As for comparisons of ^{18}F-FDG PET and DWI, it has been demonstrated that SUVmax for primary breast cancer has a stronger relationship with known prognostic pathological parameters as compared to ADC values [7, 8, 10] and may also be more

useful for predicting prognosis [7, 10]. Among those, 2 different studies compared the potentiality of SUVmax and ADC values in patients who had undergone surgery without NAC for predicting prognosis, and found a significant association of SUVmax with both RFS and OS, but not with ADC [7, 10]. The present results were similar, and also the first to evaluate patients who were treated with NAC and subsequently received surgery.

Volume parameters in PET findings can be utilized in clinical situations, as shown in recent reports. In results of evaluations of correlations of primary tumor SUVmax, MTV, and TLG values with clinicopathological parameters in patients without NAC performed in 4 studies, 3 of those found that SUVmax was superior [10, 13, 14], while TLG showed superiority in the other [15]. Additionally, prognosis prediction using primary tumor SUVmax, MTV, and TLG values was examined in one of those studies, with each found useful for predicting prognosis in patients who had undergone surgery without NAC. Similarly, the present results showed that primary tumor SUVmax and TLG values in patients who underwent NAC were quite useful for prognosis prediction. In contrast, a previous report of breast cancer cases with distant metastatic lesions, SUVmax and TLG were not shown to be useful for predicting OS, while whole body MTV was [16].

We found only 2 other studies showing that choline peak in MRS findings is correlated with known prognostic pathological parameters in breast cancer patients, thus indicating the potential for prognosis prediction of MRS [4, 6]. Additionally, the present is the first to evaluate MRS for predicting prognosis in breast cancer patients. Our results clarified that total choline peak is effective to predict RFS. However, additional investigations are needed.

This study has limitations. First, the design was retrospective and relatively few patients from a single institution were enrolled, which may limit generalized conclusions and introduce statistical errors. Furthermore, tumors smaller than 2.0cm in diameter were not included, as those are not considered suitable for optimal VOI positioning and not preferred for spectroscopic evaluations of single voxel 1H-MRS findings [17]. Also, placement of the VOI on a lesion smaller than 2cm can cause incorrect spectral data, since the margin of the lesion is exceeded and it includes the parenchyma surrounding the lesion. Similarly, the small lesion SUV can be underestimated because of effects of partial volume and limited resolution of PET, which has reported to occur not only with spheres of 1cm and smaller but also with larger spheres with a diameter of up to 3-4cm [18]. Another limitation is lack of evaluation of dynamic contrast enhanced (DCE) imaging. Dynamic contrast enhanced MRI with fat suppression provides higher levels of spatial and contrast resolution, allowing detection of very small enhanced lesions, thus our sequences were limited in terms of temporal resolution and a quantitative parametric imaging approach could not be applied with pharmacokinetic models. Compartmental DCE-MRI pharmacokinetic models would enable calculation of a variety of parameters, such as transfer contrast [Ktrans], reverse contrast [kep], and leakage space [Ve]. Several reports have noted that the perfusion metrics of DCE MRI were useful to predict response to NAC [19, 20]. Additionally, gadolinium accumulation in breast cancer can have effects on the choline peak on MRS. Breast cancer MRS at 3.0-T is recommended prior to a contrast-enhanced study, though problems may remain in regard to VOI placement with reference to a noncontrast-enhanced study [17]. Finally, the average follow-up period in the present study was too short. We consider that an investigation with more patients as well as longer follow-up periods is necessary.

In conclusion, we consider that the primary tumor SUVmax and TLG values obtained in the present ^{18}F-FDG PET/CT findings provide useful information in regard to recurrence of breast cancer as well as death in patients who have received NAC and surgery, for more individualized patient care. Furthermore, we found that MRS findings were useful to predict recurrence, but not death, while the contributions of DWI were limited for prognosis prediction in regard to RFS and OS.

The authors declare that they have no conflicts of interest.

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Olympus mountain, the highest in Greece 2.918m seen from the premises of the Hellenic Journal of Nuclear Medicine. Mountain Olympus is shown to be "angry", "calm" or "happy".