Am J Nucl Med Mol Imaging 2018;8(5):341-350
www.ajnmmi.us /ISSN:2160-8407/ajnmmi0074064

Original Article

Usefulness of positron emission mammography in the evaluation of response to neoadjuvant chemotherapy in patients with breast cancer

Irma Soldevilla-Gallardo[1], Sevastian S Medina-Ornelas[1], Cynthia Villarreal-Garza[2], Enrique Bargalló-Rocha[4], Claudia HS Caro-Sánchez[3], Rodrigo Hernández-Ramírez[1], Enrique Estrada-Lobato[5]

Departments of [1]Nuclear Medicine, [2]Oncology, [3]Patologhy, [4]Breast Tumors, Instituto Nacional De Cancerología, Mexico, Mexico; [5]Human Health Department International Atomic Energy Agency (IAEA)

Received February 5, 2018; Accepted May 18, 2018; Epub October 20, 2018; Published October 30, 2018

Abstract: Our study examines the association between two Positron Emission Mammography (PEM) semi-quantitative parameters: PUVmax (maximum uptake value) and LTB (lesion to background) baseline and the end of Neoadjuvant chemotherapy (NAC) with pathologic response in each of the following breast cancer subtype: Triple negative breast cancer (TPN), HER2-positive, and ER-positive/HER2-negative cancers. One-hundred and eight patients, 71 with invasive ductal carcinoma and 37 with infiltrating lobular carcinoma were evaluate with ^{18}F-FDG-PEM scans before and after of NAC. We assessed the impact of 2 PEM semi-quantitative parameters for molecular subtype correlated with pathologic response according Miller-Payne grade (MPG). After NAC, an overall reduction of 2 PEM semi-quantitative parameters was found. Neither breast cancer subtypes nor Ki67 modified chemotherapy responses. Compared to PUVmax, an overall increase of LTB was found in baseline condition, independent of the expressed immunophenotype. Post-treatment values of PUVmax revealed a significant reduction compared to baseline values (4.8 ± 0.26 vs. 1.9 ± 0.18; $P < 0.001$) and LTB exhibited a significant decay after the first course of NAC (15.8 ± 1.36 vs. 5.5 ± 0.49; $P < 0.001$). Using the Kruskal-Wallis H test which showed no correlation between the different molecular subtypes and the MPG and PUVmax and LTB ($P = 0.52$). Two PEM semi-quantitative parameters demonstrated a statically significant correlation and equivalence across the different breast cancer subtypes correlated with pathologic response according to MPG. PEM did not allow for prediction of NAC response in terms of breast cancer biomarkers, it is not discarded that this technology might be helpful for individual treatment stratification in breast cancer.

Keywords: Positron emission mammography, breast cancer, neoadjuvant chemotherapy, ^{18}F-FDG-PEM

Introduction

Locally advanced breast cancer is a subset of breast cancer characterized by the most advanced breast tumors in the absence of distant metastasis [1]. According to the American Joint Committee on Cancer, clinical scenarios, including in the locally advanced disease are stages IIB-III, advanced nodal disease and inflammatory carcinomas [1, 2]. Neoadjuvant chemotherapy (NAC) has an important role in patients with locally advanced cancers, treating distant micrometastases, downstaging tumors, improving operability, and sometimes allowing breast-conserving surgery to take place [3, 4].

In response to NAC, tumor cells express metabolic responses. The measurement of glucose metabolic rates after NAC is recognized as an important diagnostic tool due to an early decrease in glucose uptake is related to a better disease-free and overall survival [4, 5]. Positron emission tomography (PET/CT) has shown to be useful in different stages of breast cancer (BC) such as staging, evaluate recurrence, and treatment response assessment, where the sensitivity is poor in lesions less than 10 mm; in these scenario current clinical evidence suggest that ^{18}F-FDG high resolution positron emission mammography (high resolution PEM) has higher sensitivity that PET/CT for very small lesions (< 10 mm) and more accu-

Table 1. Patient characteristics, n = 108

Characteristics	
Age (median, range)	50 (40-77)
Clinical stage (n, %)	
IIB	7 (7%)
IIIA	60 (56%)
IIIB	29 (27%)
IIIC	8 (7%)
Neoadjuvant chemotherapy (n, %)	
Adriamycin and cyclophosphamide	1 (1%)
Adriamycin and cyclophosphamide - paclitaxel	1 (1%)
Doxorubicin and cyclophosphamide	2 (2%)
Paclitaxel y ciplastin-FAC	2 (2%)
Paclitaxel y ciplastin	4 (4%)
Paclitaxel y Herceptin	4 (4%)
Paclitaxel and trastuzumab - FAC and trastuzumab	4 (4%)
Trastuzumab and paclitaxel - fluorouracil, epirubicin and cyclophosphamide	4 (4%)
FAC - Herceptin	4 (4%)
FAC-paclitaxel-Herceptin	9 (8%)
Paclitaxel-FAC	14 (13%)
Paclitaxel - FAC	59 (55%)
Breast cancer subtype	
LUM (n, %)	84, 78%
HER2 (n, %)	13, 12%
TPN (n, %)	11, 10%

Abbreviations: LUM, molecular subtypes of breast cancer including luminal A and luminal B; HER2, human epidermal growth factor receptor 2; TPN, triple negative breast cancer.

rate for detected unsuspected additional lesions [6, 7]. The advantages of such dedicated system include improved geometric sensitivity, higher spatial resolution, shorter imaging time, and reduced attenuation compared with whole-body positron emission tomography systems [8, 9].

To measure glucose metabolism, high resolution PEM use two metabolic parameters: the maximum PEM uptake value or PUVmax and the lesion-to-background ratio or LTB [9, 10]. PUVmax is an uncorrected value that suffers from the effects of the background signal. Meanwhile, the attenuated-corrected ratio (LTB) incorporates the background signal, but the method for measuring the background is unspecified and varies from report to report. Thus, the clinical significance of this improvement has not yet been fully established [9].

On the other hand, it is known that breast carcinomas consist of different subtypes depending on hormone receptors, such as ER+ tumors, HER2 overexpression, and the cell proliferation marker Ki67. All of these biomarkers play a critical role in the glucose metabolism, correlating with the survival outcomes of patients [11-15].

Some histopathological classifications are useful to evaluate tumoral response to NAC. We chose the Miller-Payne grading (MPG) system to assess the pathological response. The MPG system are based on tumor cellularity in the excision/mastectomy specimen compared with the pretreatment core biopsy as follows: grade 1, no reduction in overall cellularity; grade 2, minor (< 30%) loss of cellularity; grade 3, estimated 30%-90% reduction in tumor cells; grade 4, > 90% loss of tumor cells; and grade 5, no invasive carcinoma (IC) [14, 15].

Nevertheless, there is a need to define standardized metabolic criteria of early response to the therapy considering the heterogeneity of subtypes, and to supervise the effectiveness of ^{18}F-FDG-high resolution PEM in monitoring the benefits of chemotherapy.

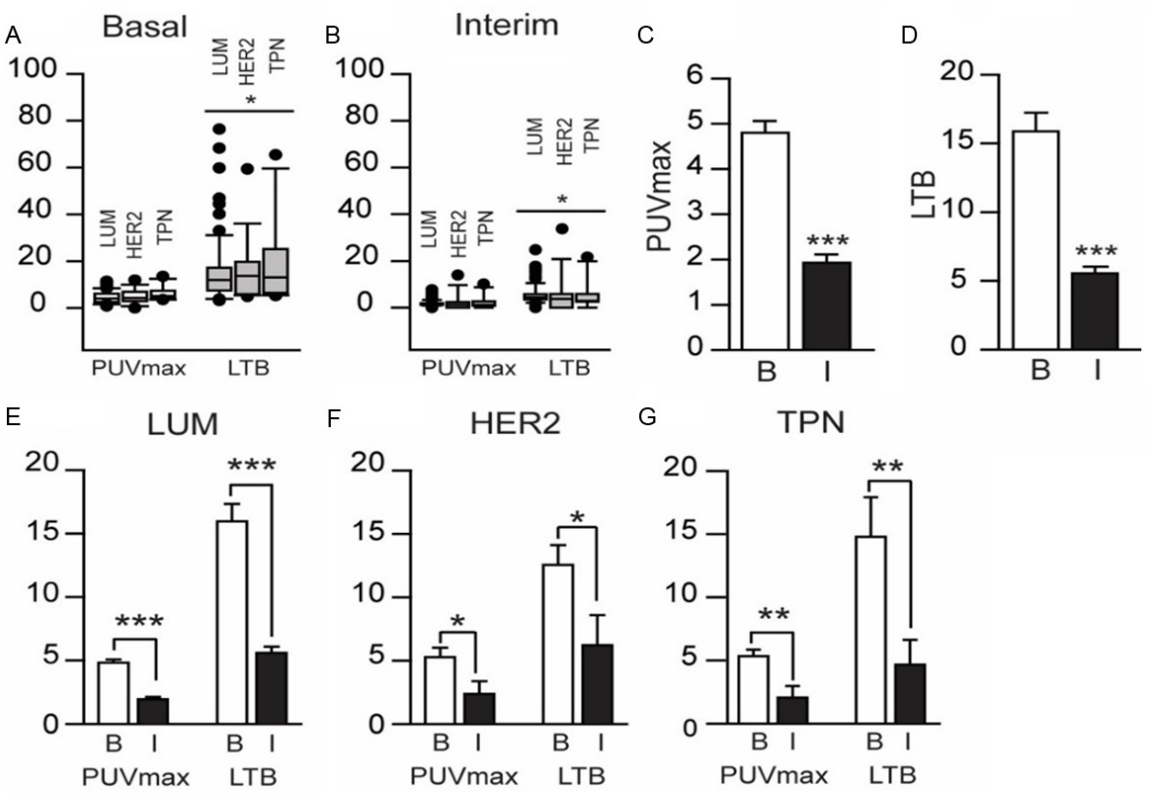

Figure 1. NAC responses according to the breast cancer subtype. ^{18}F-FDG uptake values reflected as PUVmax and LTB *at baseline* (A) and interim (B) *P*EM evaluation for response assessment. Overall, LTB was increased in comparison with PUVmax. Meanwhile, all breast cancer subtypes pooled together exhibited a reduction in both uptake parameters in response to NAC (C and D). Similar responses to NAC were observed in LUM (E), HER2 (F) and TPN tumors (G). Error bars indicate the standard errors of the mean (SEM). *P < 0.05, **P < 0.01 and ***P < 0.01. Abbreviations: NAC: neoadjuvant chemotherapy, LUM: molecular *subtypes* of *breast cancer*, including *luminal* A and *luminal B*, HER2: human epidermal growth factor receptor 2, TPN: triple negative breast cancer.

The main objective of the present study was to examine the association between two PEM examination-parameters: PUVmax (tissue concentration [mCi/g] × weight [g]/injected FDG dose [mCi]); and LTB (lesion to background ratio [the ratio of the lesion's PUVmax to the average background value]) measured at the baseline PEM examination and the end of first course of NAC, and pathologic response in each of the following breast cancer subtype: Triple negative breast cancer (TPN), HER2-positive, and ER-positive/HER2-negative cancers.

Methods and materials

Patients

This is a retrospective study was approved by the institutional review board with waivers of written informed consent. From August 2012 and May 2015, 108 consecutive patients with clinical stage II or III breast cancer underwent two ^{18}F-FDG-high resolution PEM studies, before starting NAC chemotherapy and the end of the first course of NAC. The NAC regimens, the clinical stages and the molecular breast cancer subtypes and the rest of characteristics of study population are summarized in **Table 1**. The exclusion criteria were confirmed distant metastasis and previous NAC or hormone therapy. All patients underwent two PEM studies, before the treatment and the end of the first course of NAC.

High-resolution PEM and quantification of the ^{18}F-FDG uptake

High-resolution PEM imaging was performed in a commercially available high-resolution PEM unit (PEM Flex, Naviscan PET Systems, Inc., Rockville, MD). Technical specifications have

Table 2. Percentage of metabolic response

Treatment response (%)	n	PUVmax (% ± SE)	LTB (% ± SE)	*p*-value
LUM	84	50.6 ± 6.39	48.5 ± 5.50	P < 0.05
HER2	13	65.9 ± 6.50	59.9 ± 7.12	P < 0.05
TPN	11	65.3 ± 7.50	66.8 ± 15.55	P < 0.05
Ki67 < 14%	40	44.5 ± 5.55	37.9 ± 7.37	P < 0.05
Ki67 ≥ 14%	68	47.4 ± 5.50	47.1 ± 5.57	P < 0.05
		P > 0.05	P > 0.05	

Abbreviations: LUM, molecular subtypes of breast cancer including luminal A and luminal B; HER2, human epidermal growth factor receptor 2; TPN, triple negative breast cancer; SE = standard error; PUVmax, maximum uptake value; LTB, lesion to background.

been previously described by Yamamoto et al. [9]. For the quantification of ^{18}F-FDG uptake, a region of interest (ROI) was drawn around the lesion in question, and the maximum absorption was recorded as PUVmax following the formula: tissue concentration (mCi/g) × weight (g)/injected FDG dose (mCi) . The ratio of the lesion's PUVmax to the average background value (LTB), was obtained brief, 2-cm circular ROI was drawn on the slice of nipple, and the ROI was drawn in a homogeneous area of 6 normal breast tissue. The position of this ROI was equal in both studies.

Patients were required to fast for four h before the administration of 185 MBq of ^{18}F-FDG and their serum glucose levels was below 150 mg/dl. The high-resolution PEM scan was performed 45 min after FDG injection. The acquisition time was 5 min, and the view mammograms were cephalocaudal (CC) and mediolateral oblique (MLO). High-resolution PEM produces a 12-slice tomographic image display; the slice thickness is equal to the compressed breast thickness divided by 12. Two nuclear medicine physician independently measured semi-quantitative uptake without clinical data using a workstation (MIM viewer PEM 1.0, MIM Software Inc., Cleveland, OH, USA).

Histopathological classification

Breast cancer immunophenotypes were classified as follows: luminal (ER+), HER2 overexpressing (ER-/PR-/HER2+), and triple negative (ER-/PR-/HER2-). Previous studies have subclassified luminal tumors as luminal A or luminal B; however, because these luminal subtypes are clinically similar and not well distinguished by only ER, PR, and HER2 status, all luminal tumors were pooled for further analysis.

Statistical analysis

Quantitative values were shown as mean ± the standard error of the mean. The Wilcoxon signed-rank test was used to compare each uptake parameter at baseline *vs.* those values obtained in the interim evaluation and the Mann-Whitney test was used for comparisons between PUVmax and LTB. Differences in the proportion of the responses were analyzed by Fisher's exact test. The association between PUVmax and LTB was evaluated with a Pearson correlation test. Additionally, we performed a two-sample equivalence test by using the responses to treatment expressed as percentages that were calculated as follows:

$$\Delta PUVmax\ (\%) = 100 \times (PUVmaxF - PUVmaxI)/(PUVmaxI)$$

$$\Delta LTB\ (\%) = 100 \times (LTBF - LTBI)/(LTBI)$$

Correlations with pathologic response (Wilcoxon rank sum test) pathological response and correlation/equivalence between PUVmax and LTB. We analyzed the MPG and PUVmax and LTB measurements for molecular subtype using the Kruskal-Wallis H test.

All hypothesis testing was performed with $\alpha = 0.05$, and statistically significant differences are designated with an asterisk. SPSS 17.0 (SPSS Inc, Chicago, IL, USA) was used for data analysis.

Results

Median tumor size was 52 mm (22-110). 65% of patients (71 out of 108 patients) had invasive ductal carcinoma, whereas 35% (37 out of 108 patients) had infiltrating lobular carcinoma.

Evaluation of response to NAC, according to the immunophenotype

Two hundred and sixteen ^{18}F-FDG PEM scans were performed in all patients. The first was carried out at the beginning of treatment (baseline); and the other one, was performed after

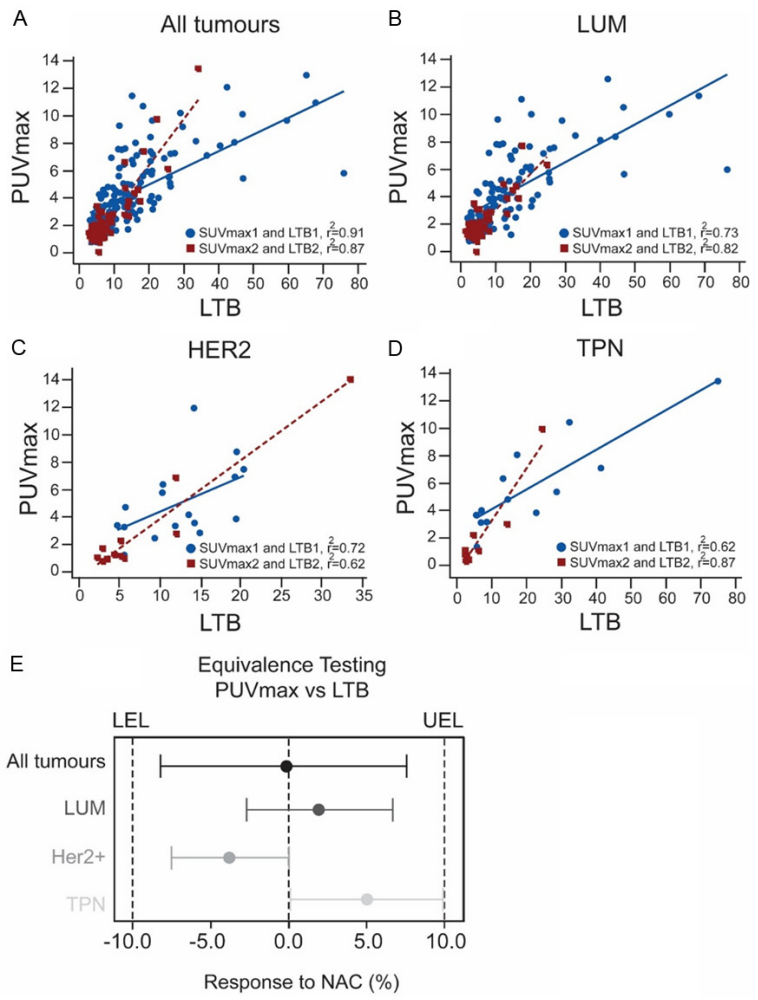

Figure 2. Correlation and equivalence between PUVmax and LTB according to the breast cancer subtype. Scattergrams of PUVmax *vs.* LTB at the baseline (PUVmax 1 and LTB 1) and at the interim evaluation (PUVmax 2 and LTB 2). A significant correlation between both uptake values is followed in all groups (A-D). The equivalence between PUVmax and LTB is exhibited in (E). Equivalence testing was a two-sided test. Thus, the equivalence range was established by the dotted lines and it was confined on both sides. To be considered equivalents, the response rates between PUVmax and LTB should not be differentiated in more than 10%.

the first cycle of NAC (interim) with a median interval of 13 days (range 3-28 d). Compared to PUVmax, an overall increase of LTB was found in baseline condition, independent of the expressed immunophenotype. This phenomenon was also observed after NAC (**Figure 1A** and **1B**).

As the data were pooled together, the post-treatment values of PUVmax revealed a significant reduction compared to baseline values (**Figure 1C**; 4.8 ± 0.26 *vs.* 1.9 ± 0.18; ***P < 0.001). Likewise, LTB exhibited a significant decay after the first course of NAC (**Figure 1D**; 15.8 ± 1.36 *vs.* 5.5 ± 0.49; ***P < 0.001).

Finally, changes in both uptake parameters were analyzed for each immunophenotype, and it was found a reduction in PUVmax and LTB values for LUM (**Figure 1E**; PUVmax: 4.9 ± 0.33 *vs.* 1.9 ± 0.19; LTB: 16.0 ± 1.95 *vs.* 5.8 ± 0.63, P < 0.001), HER2 (**Figure 1F**; PUVmax: 5.2 ± 0.75 *vs.* 2.3 ± 1.0; LTB: 12.5 ± 1.55 *vs.* 6.2 ± 2.37, P < 0.05), and TPN (**Figure 1G**; PUVmax: 5.3 ± 0.51 *vs.* 2.0 ± 0.92; LTB: 14.7 ± 3.14 *vs.* 4.65 ± 1.9; P < 0.01).

Compared to LUM, TPN and HER2-positive patients exhibited a tendency to increase metabolic response based on the change in both semicuantitatives parameters, although the differences were not statically significant (**Table 2**).

Correlation and equivalence between PUVmax and LTB according to the immunophenotype

If a background signal interferes with the PUVmax value, the linear relationship between PUVmax and LTB can exhibit a biased relationship. To discard this possibility, a *Pearson* correlation analysis was used to test the linearity in the relation between both uptake parameters. Additionally, it was applied an equivalence test to determine whether the means for PUVmax and LTB are close enough to be considered equivalent.

The *Pearson* correlation indicates a direct association between both parameters in all of the conditions tested (P < 0.05). This is denoted in **Figure 2A-D**). Moreover, the confidence intervals at the 95% supported the equivalence between PUVmax and LTB (all cases 95% CI = -7.65, 7.38; LUM 95% CI = -2.21, 3.41; HER2 95% CI = -7.65, 0; TPN 95% CI = 0, 10.0; **Figure**

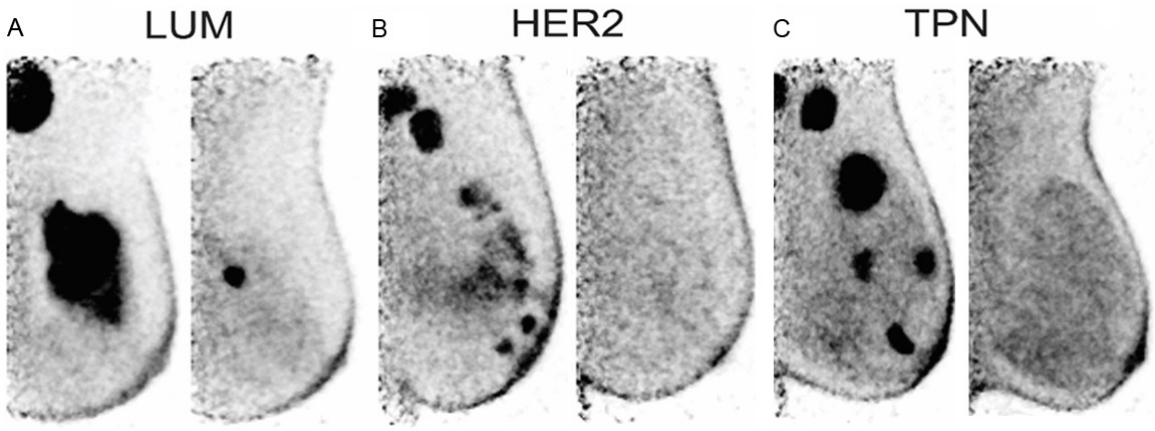

Figure 3. Semiquantification of chemotherapy response of the primary tumors by using both parameters of the ^{18}F FDG-uptake in the high resolution PEM. Images were obtained before and after the first course of NAC. For LUMA (A), PEM revealed 8.46 y 32.99 for PUVmax and LTB, respectively. A significant reduction in both parameters was found after chemtherapy (PUVmax, 2.75; 8.43 LTB). Decreased values in PUVmax and LTB was also observed in HER2 (B), in which baseline and interim values of PUVmax and LTB were: 3.94 for PUVmax and 19.59 for LTB, and 1.11 for PUVmax and 5.28 for LTB. PUVmax and LTB values for TPN (C) were registered as follow: 4.27 for PUVmax and 20.13 for LTB (at the baseline), and 2.85 for PUVmax and 5.61 for LTB (after NAC). The ratio of the lesion's PUVmax to the average background value (LTB), was obtained brief, 2-cm circular ROI was drawn on the slice of around to target lesion, and the second ROI was drawn is a background area of normal breast tissue of the same breast. The position of this ROI was equal in both studies.

2E), suggesting that the results of both parameters were similar or at least not appreciably statistically different.

Evaluation of response to NAC, according to the expression of Ki67, and correlation/equivalence between PUVmax and LTB

In parallel with the immunophenotype recordings, it was assessed the treatment response, according to the expression of Ki67. **Figure 3** shows that PUVmax and LTB at baseline, were significantly higher in patients with Ki67 ≥ 14% than in patients with Ki67 < 14% (PUVmax: 5.9 ± 1.21 *vs.* 3.7 ± 0.45; LTB: 18.0 ± 1.7 *vs.* 12.1 ± 1.7; P < 0.01) (**Figure 4A** and **4B**). Graph results also summarizes the reduction of PUVmax and LTB in both groups (Ki67 < 14% and Ki67 ≥ 14%) after NAC (PUVmax: Ki67 < 14%: 3.7 ± 0.45 *vs.* 1.9 ± 0.5, P < 0.05; Ki67 ≥ 14%: 5.9 ± 1.21 *vs.* 2.0 ± 0.77, P < 0.001; LTB: Ki67 < 14%: 12.1 ± 1.71 *vs.* 4.9 ± 0.5, P < 0.05; Ki67 ≥ 14%: 18.0 ± 1.7 *vs.* 5.3 ± 0.91, P < 0.001).

Compared with patients with Ki67 < 14%, tumors with Ki67 ≥ 14% also show a tendency to exhibit an increased metabolic response (**Table 2**).

Lastly, the measurements of the correlation between PUVmax and LTB revealed that there were significant associations between PUVmax and LTB in patients with high and low expression of Ki67 (**Figure 4C** and **4D**). In agreement with these results, equivalence test shows that metabolic responses were indistinguishable between PUVmax and LTB, corroborating the equivalence among both parameters (**Figure 4E**); Immunohistochemical stains for Ki-67 in patients with high and low expression of Ki67 (**Figure 4F** and **4G**). Using the Kruskal-Wallis H test which showed no correlation between the different molecular subtypes and the MPG and PUVmax and LTB (P = 0.52), but if a correlation was found between the response rate by MPG and both semiquantitative parameters (**Table 3**).

Discussion

Multiple research groups recommend the use of metabolic imaging as a diagnostic and predictive tool, imaging modality of choice is whole body ^{18}F-FDG PET/CT [16, 17]. However, the fundamental limitation of this technique remains its difficulty in accurately characterizing the metabolic activity of lesions smaller than 2.5 cm due to partial volume effects and smoothing. Information obtained from semiquantitative analysis of PEM appears to be beneficial for quantifying the metabolic activity of lesions smaller than those seen with whole

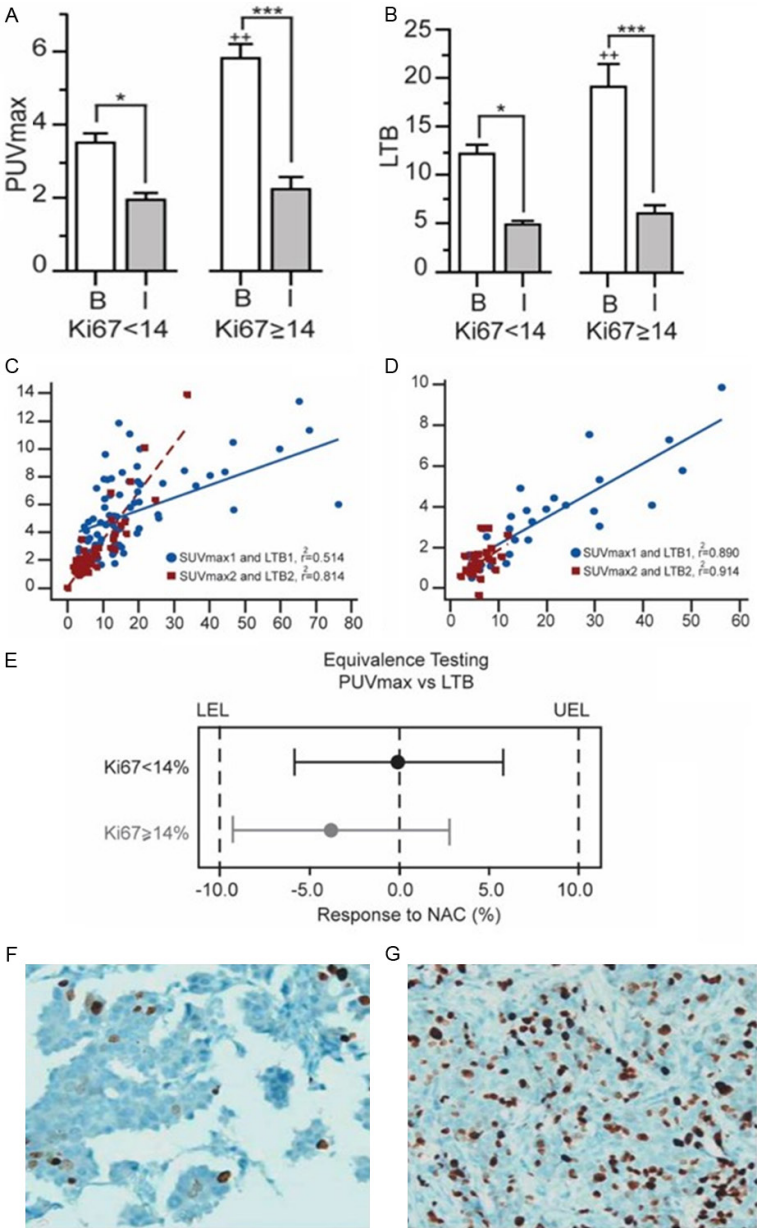

Figure 4. NAC responses according to the expression of Ki67, and correlation and equivalence between PUVmax and LTB. Graph results show increased PUVmax and LTB values at baseline in patients with high expression of Ki67. Meanwhile, a significant reduction of both uptake parameters at the interim was recorded in patients with high and low expression of Ki67 (A and B). Analysis of correlation indicates a strong association between PUVmax and LTB in both groups (C and D), while equivalence between both uptake parameters also was corroborated (E). Immunohistochemical stains for Ki67 in Luminal A (< 14%) (F) and Luminal B (> 14%) (G) based on Eye-10 method (× 100).

body PET/CT [19]. The technological advancement of PEM will allow progress not only in making the diagnosis of the disease at an early stage, but also in determining early tumor responses to treatment, which is now a key component for optimizing therapies [7]. Here, we provide a detailed description of the changes in tumors metabolic responses to NAC by using PEM. In view of the fact that variations in glucose metabolism are related to specific tumor markers we also stratify those metabolic responses according to the subtypes of breast cancer and to the expression of Ki67 [19, 20].

This retrospective study demonstrated that LUM, HER2 and TPN had similar PUVmax and LTB values in baseline PEM scan. Also, a substantial reduction of PUVmax and LTB after NAC occurred in pooled data of all subtypes of breast cancer. Moreover, metabolic responses for each subtype were as considerable as those recorded in the pooled data.

Regarding percentages of chemotherapy responses, we found no substantial changes neither across subtypes nor between PUVmax and LTB. In all cases, response rates to NAC were greater than 40%. Based on previous demonstrations, it is feasible that this percentage may predict a good rate of pathological complete response [21, 22].

On the other hand, correspondences between PUVmax and LTB suggests that background activity does not affect metabolic measurements. In favor of this observation, we also recorded high positive correlations between both uptake parameters. Moreover, the equivalence test indicates that the metabolic responses measured with LTB were within the margin of the PUVmax. Since equivalence implies that PUVmax and LTB are similar enough that there is no practical consequence to assuming that they are equal, this corrobo-

Table 3. Miller-Payne grade with molecular subtypes and correlation with PEM values

MPG	Luminal A		Luminal B		HER2		TPN		x^2	*p*-value
	n	%	n	%	n	%	n	%	2.83	0.52
1	13	37.14	16	32.65	7	54.84	6	54.54		
2	12	34.28	22	44.89	3	23.07	4	36.36		
3	8	22.85	4	8.16	2	15.38	1	9.09		
4	2	5.71	2	4.08	1	7.69	0	0		
5	0	0	0	0	0	0	0	0		
Total	35	100	49	100	13	100	11	100		

Abbreviations: MPG, Miller-Payne grade; HER2, human epidermal growth factor receptor 2; TPN, triple negative breast cancer.

rates that background activity had no effects on the evaluation of metabolic responses [23].

It has been described that failures on the corrections for count rate effects, attenuation, or scattered photons, may not accurately reflect a full quantitative recovery of counts in calculating ^{18}F-FDG uptake [24]. However, in agreement with our results, previous works suggest that PUVmax and LTB are so similar as to be regarded equivalent. For example, Yamamoto and coworkers found substantial overlaps between both PEM uptake parameters among invasive carcinoma, *in situ* ductal carcinoma and benign lesions. Additionally, the accuracy of PUVmax and LTB was comparable in predicting overall survival rates [9].

A explanation that would clarify the low effect of the background signal/noise in measuring tumor glucose metabolism is related to the lesion size and the partial volume effect (PVE) [24]. Pixels on edges of source include both source and background tissues. Thus, part of the signal emanating from source is seen outside actual object and, therefore, is described as spilling out. PVE strongly depends on the size of the tumor. The smaller the tumor, the greater the underestimation of the uptake value. A higher resolution decreases this effect, resolving the affectation of the background signal, such as that occurring in the high resolution PEM [25].

Regarding BC biological characteristics, we did not observe differences in the primary metabolic activity between LUM, HER2 and TPN tumors. This finding is partially in opposition to those of Wang et al., Who described that TPN tumors have significantly higher SUVmax and LTB than those values observed in tumors positive for hormone receptors [26]. Furthermore, differences in the interim treatment responses per-subtype were neither observed, which also disagree with previous results showing that changes in SUVmax after NAC are most adequate for TPN and HER2-positive breast cancers [20, 27].

Many breast cancer subtypes have good chemotherapy response, however, seems to be reflected in the percentage of response that were improved in TPN and HER2-positive related with LUM, although without being statistically significant. We suggest that the lack of significance could be the consequence of a low proportion of HER2 and TPN cases. Therefore, we cannot rule out the possibilities that these may be chance findings or may reflect no changes in the metabolic activity of tumors, requiring a much larger sample size to improve this observation.

However, if correspondences in the interim responses to NAC between subtypes will confirmed; then, our results might be in accordance with the hypothesis that cell killing during chemotherapy follows a first-order kinetic model, where a large absolute change in the number of viable tumor cells must occur early in the course of therapy to achieve a complete or subtotal tumor response. In fact, it is previously described that, even in nonresponding tumors, the number of tumor cells may decrease by up to 90%, resulting in a corresponding decrease of ^{18}F-FDG uptake [28].

Remarkably, patients with high levels of Ki67 showed high pre-treatment values of both metabolic parameters in comparison with patients with low levels of Ki67. This finding confirms that the overexpression of cell proliferation markers induces exacerbated metabolic responses [29, 30]. Nevertheless, posttreatment PUVmax or LTB were similar between patients with low and high levels of Ki67. Also, the response rates were comparable between groups and, once more, differences between PUVmax and LTB were not registered.

Even though our results are not conclusive, we might infer that Ki67 has not a prognostic role

in NAC responses. However, results expressed as percentage newly leads us to observe a tendency for patients with Ki67 ≥ 14%, who eventually had increased responses, supposing a more adept response to chemotherapy in the neoadjuvant setting [31]. Still, with no conclusive data, the main question remains whether Ki-67 provides prognostic information for interim-PEM reporting [32].

Our study has some limitations. First, the number of patients studied was relatively small and, second, the median follow-up duration was quite short. Therefore, the subgroup analysis does not have much power, and the lack of statistical significances should be interpreted with caution. Despite these limitations, our data suggest that PUVmax and LTB have a similar potential to reflect early chemotherapy responses in breast cancer, showing the value of the high resolution efficiency.

Conclusion

LTB demonstrated a statically significant correlation and equivalence with PUVmax across the different breast cancer subtypes correlated with pathologic response according to MPG, suggesting that PUVmax has a low-affectation of the background signal. On the other hand, there is a need for further development of follow-up studies that can accurately distinguish biomarkers influencing breast cancer prognosis between subjects.

Acknowledgements

We thank Nuclear Medicine Department at Instituto Nacional de Cancerologia, México.

Disclosure of conflict of interest

None.

Address correspondence to: Sevastian S Medina-Ornelas, Department of Nuclear Medicine and Molecular Imaging, Instituto Nacional De Cancerología, México. Sevastián S. Medina Ornelas. Av. San Fernando, 22 Col. Sección XVI, Del. Tlalpan, C.P. 14080, Ciudad de México, México. Tel: 0155 47471027 Ext. 10115; E-mail: dr.sevastian@outlook.com

References

[1] Garg PK, Prakash G. Current definition of locally advanced breast cancer. Curr Oncol 2015; 22: e409-10.

[2] Giordano SH. Update on locally advanced breast cancer. Oncologist 2003; 8: 521-30.

[3] Gianni L, Eiermann W, Semiglazov V, Manikhas A, Lluch A, Tjulandin S, Zambetti M, Vazquez F, Byakhow M, Lichinitser M, Climent MA, Ciruelos E, Ojeda B, Mansutti M, Bozhok A, Baronio R, Feyereislova A, Barton C, Valagussa P, Baselga J. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet 2010; 375: 377-84.

[4] Teshome M, Hunt KK. Neoadjuvant therapy in the treatment of breast cancer. Surg Oncol Clin N Am 2014; 23: 505-23.

[5] Weber WA. Assessing tumor response to therapy. J Nucl Med 2009; 1: 1S-10S.

[6] Glass SB, Shah ZA. Clinical utility of positron emission mammography. Proc (Bayl Univ Med Cent) 2013; 26: 314-9.

[7] Vercher-Conejero JL, Pelegrí-Martinez L, Lopez-Aznar D, Cózar-Santiago MP. Positron emission tomography in breast cancer. Diagnostics (Basel) 2015; 5: 61-83.

[8] Rosen EL, Eubank WB, Mankoff DA. FDG PET, PET/CT, and breast cancer imaging. Radiographics 2007; 27: S215-29.

[9] Yamamoto Y, Tasaki Y, Kuwada Y, Ozawa Y, Katayama A, Kanemaki Y, Enokido K, Nakamura S, Kubouchi K, Morita S, Noritake M, Nakajima Y, Inoue T. Positron emission mammography (PEM): reviewing standardized semiquantitative method. Ann Nucl Med 2013; 27: 795-801.

[10] Schilling K, Narayanan D, Kalinyak JE, The J, Velasquez MV, Kahn S, Saady M, Mahal R, Chrystal L. Positron emission mammography in breast cancer presurgical planning: comparisons with magnetic resonance imaging. Eur J Nucl Med Mol Imaging 2011; 38: 23-36.

[11] Weigel MT, Dowsett M. Current and emerging biomarkers in breast cancer: prognosis and prediction. Endocr Relat Cancer 2010; 17: R245-62.

[12] Yersal O, Barutca S. Biological subtypes of breast cancer: prognostic and therapeutic implications. World J Clin Oncol 2014; 5: 412-24.

[13] Dai X, Xiang L, Li T, Bai Z. Cancer hallmarks, biomarkers and breast cancer molecular subtypes. J Cancer 2016; 7: 1281-94.

[14] Ogston KN, Miller ID, Payne S, Hutcheon AW, Sarkar TK, Smith I, Schofield A, Heys SD. A new histological grading system to assess response of breast cancers to primary chemotherapy: prognostic significance and survival. Breast 2003; 12: 320-27.

[15] Phipps AI, Malone KE, Porter PL, Daling JR, Li CI. Body size and risk of luminal, HER2-overex-

pressing, and triple-negative breast cancer in postmenopausal women. Cancer Epidemiol Biomarkers Prev 2008; 17: 2078-86.
[16] Kelloff GJ, Hoffman JM, Johnson B, Scher HI, Siegel BA, Cheng EY, Cheson BD, O'shaughnessy J, Guyton KZ, Mankoff DA, Shankar L, Larson SM, Sigman CC, Schilsky RL, Sullivan DC. Progress and promise of FDG-PET imaging for cancer patient management and oncologic drug development management and oncologic drug development. Clin Cancer Res 2005; 11: 2785-808.
[17] Weissleder R. Molecular imaging in cancer. Science 2006; 312: 1168-71.
[18] Zhu A, Lee D, Shim H. Metabolic positron emission tomography imaging in cancer detection and therapy response. Semin Oncol 2011; 38: 55-69.
[19] Rahim S, Mawlawi O, Fox P, Taylor S, Millican R, Swanston NM, Brown JE, Rohren EM. Correlation of PUV and SUV in the extremities while using PEM as a high-resolution positron emission scanner. Skeletal Radiol 2014; 43: 453-8.
[20] Groheux D, Giacchetti S, Delord M, de Roquancourt A, Merlet P, Hamy AS, Espié M, Hindié E. Prognostic impact of 18F-FDG PET/CT staging and of pathological response to neoadjuvant chemotherapy in triple-negative breast cancer. Eur J Nucl Med Mol Imaging 2014; 42: 377-85.
[21] Esserman LJ, Berry DA, DeMichele A, Carey L, Davis SE, Buxton M, Hudis C, Gray JW, Perou C, Yau C, Livasy C, Krontiras H, Montgomery L, Tripathy D, Lehman C, Liu MC, Olopade OI, Rugo HS, Carpenter JT, Dressler L, Chhieng D, Singh B, Mies C, Rabban J, Chen YY, Giri D, van 't Veer L, Hylton N. Pathologic complete response predicts recurrence-free survival more effectively by cancer subset: results from the I-SPY 1 TRIAL - CALGB 150007/150012, ACRIN 6657. J Clin Oncol 2012; 30: 3242-9.
[22] Fasching PA, Heusinger K, Haeberle L, Niklos M, Hein A, Bayer CM, Rauh C, Schulz-Wendtland R, Bani MR, Schrauder M, Kahmann L, Lux MP, Strehl JD, Hartmann A, Dimmler A, Beckmann MW, Wachter DL. Ki67, chemotherapy response, and prognosis in breast cancer patients receiving neoadjuvant treatment. BMC Cancer 2011; 486: 1471-2407.
[23] Counsell A, Cribbie RA. Equivalence tests for comparing correlation and regression coefficients. Br J Math Stat Psychol 2015; 68: 292-309.
[24] Karakatsanis NA, Fokou E, Tsoumpas C. Dosage optimization in positron emission tomography: state-of-the-art methods and future prospects. Am J Nucl Med Mol Imaging 2015; 5: 527-47.
[25] Soret M, Bacharach SL, Buvat I. Partial-volume effect in PET tumor imaging. J Nucl Med 2007; 48: 932-45.
[26] Wang CL, MacDonald LR, Rogers JV, Aravkin A, Haseley DR, Beatty JD. Positron emission mammography: correlation of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 status and 18F-FDG. AJR Am J Roentgenol 2011; 197: W247-55.
[27] Humbert O, Berriolo-Riedinger A, Riedinger JM, Coudert B, Arnould L, Cochet A, Loustalot C, Fumoleau P, Brunotte F. Changes in 18F-FDG tumor metabolism after a first course of neoadjuvant chemotherapy in breast cancer: influence of tumor subtypes. Ann Oncol 2012; 23: 2572-7.
[28] Wieder HA. Time course of tumor metabolic activity during chemoradiotherapy of esophageal squamous cell carcinoma and response to treatment. J Clin Oncol 2004; 22: 900-8.
[29] de Azambuja E, Cardoso F, de Castro G, Colozza M, Mano MS, Durbecq V, Sotiriou C, Larsimont D, Piccart-Gebhart MJ, Paesmans M. Ki-67 as prognostic marker in early breast cancer: a meta-analysis of published studies involving 12,155 patients. Br J Cancer 2007; 96: 1504-13.
[30] von Minckwitz G, Schmitt WD, Loibl SS, Müller BM, Blohmer JU, Sinn BV, Eidtmann H, Eiermann W, Gerber B, Tesch H, Hilfrich J, Huober J, Fehm T, Barinoff J, Rüdiger T, Erbstoesser E, Fasching PA, Karn T, Müller V, Jackisch C, Denkert C. Ki67 measured after neoadjuvant chemotherapy for primary breast cancer. Clin Cancer Res 2013; 19: 4521-31.
[31] Inwald EC, Klinkhammer-Schalke M, Hofstädter F, Zeman F, Koller M, Gerstenhauer M, Ortmann O. Ki-67 is a prognostic parameter in breast cancer patients: results of a large population-based cohort of a cancer registry. Breast Cancer Res Treat 2013; 139: 539-52.
[32] Ács B, Zámbó V, Vízkeleti L, Szász AM, Madaras L, Szentmártoni G, Tőkés T, Molnár BÁ, Molnár IA, Vári-Kakas S, Kulka J, Tőkés AM. Ki-67 as a controversial predictive and prognostic marker in breast cancer patients treated with neoadjuvant chemotherapy. Diagn Pathol 2017; 12: 1-12.