The Clinical Impact of the Late Imaging with 18F-Fluorodeoxyglucose PET Texture Analysis in Invasive Lobular Breast Cancer

Fikri Okan FALAY, Hülya SEYMEN
Department of Nuclear Medicine, Molecular Imaging and Treatment, Koç University Faculty of Medicine, Istanbul-Turkey

OBJECTIVE
Breast invasive lobular cancer (ILC) is one of the most difficult malignancies to diagnose and follow-up due to its tumor morphology. Tumor heterogeneity is the most important reason for treatment failure and diagnostic limitation. Identification of heterogeneity by a non-invasive method, texture analysis that can be done from positron emission tomography (PET), MR, and CT is developed. In ILC, diagnostic sensitivity is lower with 18F-fluorodeoxyglucose ([18F] FDG) PET/CT compared to invasive ductal carcinoma (IDC). In this study, the correlation between histopathological variables and the texture analysis of [18F] FDG PET/CT standard images, and also late images whose contribution to the diagnosis of many malignancies has been investigated are researched.

METHODS
Twenty ILC patients underwent standard and late [18F] FDG PET/CT imaging for staging between May 2007 and December 2018. T and N stages, histological and nuclear grades, estrogen receptor, progesterone receptor, human epidermal growth factor-2, and Ki-67 were recorded.

RESULTS
Thirty-two textural indices with conventional and formal indices and histogram values were calculated with LIFEx software to find heterogeneity in standard and late [18F] FDG PET/CT images. Conventional and discrete indices based on GLRM and GLZM are more correlated than other texture indices. Greater number of significantly correlations was found between histopathological variables and texture analysis of late imaging (p<0.05).

CONCLUSION
In our study, the conventional indices, especially in the 2nd degree indices, in the texture analysis performed with [18F] FDG PET/CT significantly correlated in the ILC, which has lower [18F] FDG affinity compared to IDC due to the tumoral tissue characteristics. Although the presence of more correlations with histopathological prognostic information in late images suggests a greater diagnostic contribution, further studies with more numbers are needed.

Keywords: [18F] FDG PET/CT; breast cancer; late imaging; texture analysis.

Introduction
According to the 2017 data of the American Cancer Society, breast cancer is the most common cancer in women. Breast cancer ranks second in cancer-related deaths after lung cancer.[1] Early diagnosis, more accurate and non-intervention staging, follow-up of treatment, and prognosis are the most important processes in deter-
mining the approach to breast cancer. About 50–70% of breast cancers are invasive ductal carcinoma (IDC), 5–15% are invasive lobular cancer (ILC), 1–6% are mucinous carcinoma, and 1–2% are tubular carcinoma. The diagnosis and staging of ILC is more difficult than IDC because of the characteristic growth pattern. The tumor does not produce a stromal reaction and therefore tissue thickening occurs more than a mass formation and microcalcification, which is the most important clinical finding in early diagnosis that is rarely seen.

Although 18F-fluorodeoxyglucose ([18F] FDG) positron emission tomography (PET) imaging has high sensitivity and specificity in showing malignant lesions, its sensitivity in breast cancer is limited. In a meta-analysis, the overall sensitivity and specificity of [18F] FDG PET/CT in detecting primary breast cancer were found to be 64–96% and 73–100%, respectively. While the sensitivity of [18F] FDG PET/CT is 57% in tumors <1 cm in diameter, it exceeds 90% in tumors larger than 1 cm. Glut-1 and hexokinase expression, number of viable tumor cells, histological subgroup, microvascular density, and presence of inflammatory cells are the major factors affecting [18F] FDG uptake in breast cancer.

It is known that estrogen and progesterone receptor negative, human epidermal growth factor receptor 2 (HER-2) expression positive tumors show higher [18F] FDG uptake than receptor-positive and HER-2-negative tumors. Furthermore, [18F] FDG PET/CT imaging is less sensitive in ILC than IDC because of low [18F] FDG uptake. It is reported that the clinical systemic contribution of PET/CT is low due to the low [18F] FDG affinity in mucinous (1–6%) and tubular (1–2%) cancers, which are less common with ILC, which constitutes 10–15% of breast cancers. The main factors that explain low [18F] FDG uptake in ILCs are lower tumor cell density, diffuse infiltration in the surrounding tissue, low Glut-1 expression, and low proliferation rate. For these reasons, the influence of [18F] FDG PET/CT to IDC was mostly assessed in the studies and the ILC could be included in a limited number of studies or was not included because of low sensitivity.

It is known that the continued accumulation of [18F] FDG is due to the low concentration of glucose-6-phosphatase enzyme in the tumor cell, and it is known that imaging quality will be optimal as long as the radiopharmaceutical half-life allows and that imaging may contribute to the diagnosis in malignancies. There are many studies reporting that late image on [18F] FDG PET/CT significantly increases sensitivity and specificity in breast cancer.

Last decade, the importance of measuring tumor heterogeneity is identified to solve the inability of current therapies. The tumor heterogeneity is not fully understood with invasive techniques, such as biopsy, and also non-invasive imaging techniques such as PET/CT which could give the information of genotypic and phenotypic tumor variations. Many techniques have been proposed to use tumor heterogeneity as a biomarker. There are some mathematical methods to define tumor heterogeneity. One of these is the term “texture analysis.” This analysis specifies the various quantification of the spatial distribution of voxel intensities in images. The advantages of using imaging techniques to define heterogeneity are the account of the whole tumor, intratumoral heterogeneity in very small spatial scales, and non-invasiveness. However, in daily practice, these methods are barely used.

In this retrospective study, we aimed to investigate the effect of late imaging and textural analysis on diagnosis in pre-operative [18F] FDG PET/CT of ILC.

Materials and Methods

Patients

Between May 2007 and December 2018, 20 patients referred for [18F] FDG PET/CT for the staging of an invasive lobular breast cancer to the department of nuclear medicine and molecular imaging were included in this study.

Image Acquisition

About 50–70 min after intravenous 5–9 mCi [18F]FDG, standard 7–9 bed length between vertex and mid-crus and after 160–200 min, neck and thorax 2-bed area late imaging were taken Discovery IQ 5 ring (General Electric Corp., Milwaukee, WI, USA) PET/CT device.

Images Analysis

All primary tumors of standard and late [18F] FDG PET/CT images were delineated with 40% of SUV maximum value method to create volumes of interest (VOI). The texture analysis results were recorded with s-prefix for standard images and l-prefix for late images. In each VOI, standard PET quantitative measures were evaluated by conventional indices (SUVmax, SUVmin, SUVmean, SUVstd, SUVpeak, and TLG), indices from histogram (skewness and kurtosis) and shape (MTV, sphericity, and capacity) and 32 textural indices were recorded using LIFEx software (Fig. 1). The subtraction of these textural indicis was created by calculating four different matrices for each
VOI: The Gray-Level Cooccurrence Matrix (GLCM), the Gray-Level Run Length Matrix (GLRLM), the Neighborhood Gray-Level Dependence Matrix (NGLDM), and the Gray-Level Zone Length Matrix (GLZLM). GLCM represents that voxel pairs with specific SUV values can be found in a certain direction and at a certain distance. It is calculated using 1 voxel and 13 directions. GLRLM gives the size of homogeneous runs for each gray level using 13 directions, while NGLDM is calculated by calculating the gray level difference between a voxel and its 26 neighbors in three directions. GLZLM gives the size of homogeneous regions for each gray level in three dimensions. For the textural indices to be calculated software, there must be a VOI equal to or greater than 64 voxels that only contain one cluster, corresponding to a minimum volume of 2.12 ml (voxel size of 4.07×4.07×2 mm). Preferences for VOI with multiple clusters were manually selected by the operator.[20]

Clinical and Histopathological Variables
T and N stages, histological and nuclear grades, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER-2), and Ki-67 values of histopathological results are recorded of mastectomy (8 patients) or breast-conserving surgery (12 patients). Eight patients in the T1 stage and 12 patients in the T2 stage were included in the study. N1 and N2 patients are classified as N positive.

The objective study outcome was to evaluate the relationship between texture analysis findings of [18F] FDG PET/CT both standard and late images, T and N stages, and histopathological results (histologic and nuclear grades, presence of ER, PR and HER-2, and Ki-67 level). In lobular breast cancer imaging, which has a relatively low level of FDG uptake, it is aimed to contribute to the diagnosis with the change of background activity in late images.

Statistical Analysis
The data were evaluated with the SPSS 25.0 (IBM, NY, USA) program. Comparison of standard and late images was evaluated with the Wilcoxon test, and the characteristics of tumor heterogeneity were evaluated with the Mann-Whitney U-test. Significant p<0.05 was considered.
Results

Table 1 presents the demographic and histopathological characteristics of 20 ILC patients that we included in the study. Twelve breast-conserving surgery (60%), eight mastectomies (40%) were performed in median 32 days (1-56 days). Eight of the cases were pT1, 12 were pT2. The N stage of 8 ILC patients was N (−), the others were N (+).

The correlations between the textural analysis findings with standard and late imaging results of primary tumor are shown in Table 2.

SUV mean, max, Q1, Q2, Q3, peak 0.5 ml and peak 1 ml, histo-skewness, kurtosis, excess kurtosis, entropy log10, entropy log 2, GLCM homogeneity, energy, contrast, and dissimilarity, GLRLM LRE, SRLG and LRHGE, NGDLM contrast and busyness, GLZLM HGZE, SZHGE, ZLNU, and ZP values of late imaging were statistically higher than standard imaging (p<0.05).

When histopathological features were examined, significantly higher values were found in both standard and late images, especially in the ER-negative group (Tables 3, 4).

Discussion

ILC has the lowest sensitivity and specificity in diagnosis with conventional imaging methods due to growth pattern in invasive breast cancers.[21] According to the diagnosis of primary malignancy, lymph node and hematogenous metastasis diagnosis sensitivity and specificity are better, but the rates are still around 80%. Due to the primary local diagnosis difficulties in ILC, it is likely that the case will be in the metastatic process at the time of diagnosis. In addition, compared to IDC, the probability of metastasis is higher, and the possibility of unexpected metastasis such as GIS, peritoneum, skin, and gynecological organs is also high.[22]

Therefore, in this study, we assumed that in addition to the management of malignancy in patients with ILC who have not previously been studied, the combination of [18F] FDG PET/CT late imaging and texture analysis may contribute to the diagnosis and/or better correlate with histopathological information. Actually, [18F] FDG PET/CT is not a routine examination for diagnosis in ILC because of the low [18F] FDG uptake due to low tumor cell density, diffuse infiltration in surrounding tissue, low Glut-1 expression, and low proliferation rate. Many different metabolic parameters such as SUV, MTV, TLG, and late imaging information have been used to increase sensitivity and specificity in breast tumors.[23] However, nearly all the studies constitute the more common IDC in the majority of cases. In seven studies investigating the contribution of late imaging with [18F] FDG PET/CT in invasive breast cancer, only 2/53, 3/66, 13/86, 2/53, 8/48, and 2/38 ILC patients were included in the studies, respectively.[17,18,24]

In 86 invasive breast cancer cases, 13 of which were ILC with suspicion of local recurrence and distant metastasis, Garcia-Vicente et al.[25] shared that more malignancy could be detected by decreasing background activity in late images. In our study, especially the visualization of metastatic lymph node was seen in the late image of an ILC patient (Fig. 2).

Tumor heterogeneity with aggressive malignancy has been shown in many tumors. The techniques are proposed to define tumor heterogeneity for differentiation between tumor types, tumor grading, response monitoring, and outcome prediction in imaging. However, measuring tumor heterogeneity is not simple, information obtained from biopsy tissues are invasive and do not represent the whole tumor. Since intratumoral heterogeneity can be formed at very small areas, many studies have been designed to understand the heterogeneity of tumor with texture analysis information obtained from imaging which is non-invasive. Analysis methods for defining tumor heterogeneity are divided into four cat-

**Table 1**

| Characteristics | Value | n | %  | Mean±SD |
|-----------------|-------|---|----|---------|
| Age             |       |   |    | 61.35±12.45 |
| pT              | 1     | 8 | 40 |
| pN              | 0     | 8 | 40 |
| Nuclear grade   | 1     | 1 | 5  |
| pT              | 2     | 12| 60 |
| pN              | 1     | 12| 60 |
| HER-2           |       |   |    |         |
| Negative        | 15    | 5 | 75 |
| Positive        | 5     | 25|
| KI67<14         |       |   |    |         |
| Low             | 7     | 35|
| ≥14             |       |   |    |         |
| High            | 13    | 65|
| ER              |       |   |    |         |
| Negative        | 3     | 15|
| Positive        | 17    | 85|
| PR              |       |   |    |         |
| Negative        | 7     | 35|
| Positive        | 13    | 65|

pT: Histopathologic tumor stage; pN: Histopathologic lymph node stage; HER-2: Human epidermal growth factor receptor 2; Ki-67: Cellular proliferation index; ER: Estrogen receptor; PR: Progesterone receptor
## Table 2  Comparison level and median values of textural indices between standard and late imaging

| Textural indicis | Standard imaging | Late imaging | p    |
|------------------|------------------|--------------|------|
| **First Order**  |                  |              |      |
| CONVENTIONAL_SUVbwmin | 2.4173±1.008     | 2.5376±1.4672 | 0.481 |
| CONVENTIONAL_SUVbwmean | 3.93±1.78      | 4.18±2.78    | **0.003** |
| CONVENTIONAL_SUVbwstd | 0.65±0.49      | 1.08±0.85    | <**0.001** |
| CONVENTIONAL_SUVbwmax | 5.11±3.10      | 7.17±5.12    | <**0.001** |
| CONVENTIONAL_SUVbwQ1 | 2.79±1.37       | 3.27±2.11    | **0.021** |
| CONVENTIONAL_SUVbwQ2 | 3.23±1.79       | 4.05±2.80    | **0.005** |
| CONVENTIONAL_SUVbwQ3 | 3.78±2.14       | 4.95±3.40    | **0.002** |
| CONVENTIONAL_SUVbwSkewness | 0.74±0.40     | 0.54±0.38    | 0.096 |
| CONVENTIONAL_SUVbwKurtosis | 2.84±0.86     | 2.64±0.69    | 0.466 |
| CONVENTIONAL_SUVbwExcessKurtosis | -0.11±1.06 | -0.36±0.69 | 0.403 |
| CONVENTIONAL_SUVbwpeakSphere 0.5 mL | 0.46±0.001 | 0.46±0.001 | **0.010** |
| CONVENTIONAL_SUVbwpeakSphere 0.5 mL | 5.40±2.79 | 5.68±4.61   | 0.240 |
| CONVENTIONAL_SUVbwpeakSphere 1 mL | 0.95±0.01 | 0.96±0.001 | **0.010** |
| CONVENTIONAL_SUVbw peakSphere 1 mL | 2.71±3.40 | 3.90±4.82   | **0.010** |
| CONVENTIONAL_SUVbw | 9642.54±12637.45 | 8245.07±11690.24 | 0.240 |
| CONVENTIONAL_TLG (mL) | 28.37±41.09 | 33.50±51.35 | **<0.001** |
| DISCRETIZED_SUVbwmean | 2.54±1.47 | 11.17±5.70 | **<0.001** |
| DISCRETIZED_SUVbwstd | 2.11±1.55 | 3.47±2.68 | **<0.001** |
| DISCRETIZED_SUVbwmax | 16.85±10.01 | 23.10±15.27 | **<0.001** |
| DISCRETIZED_SUVbwQ1 | 9.43±4.46 | 10.94±6.69 | **0.022** |
| DISCRETIZED_SUVbwQ2 | 10.85±5.62 | 13.48±8.99 | **0.006** |
| DISCRETIZED_SUVbwQ3 | 12.55±6.80 | 16.28±10.87 | **0.002** |
| DISCRETIZED_SUVbwSkewness | 0.67±0.43 | 0.54±0.38 | 0.282 |
| DISCRETIZED_SUVbwKurtosis | 2.84±0.96 | 2.62±0.69 | 0.422 |
| DISCRETIZED_SUVbwExcessKurtosis | -0.16±0.96 | -0.38±0.69 | 0.422 |
| DISCRETIZED_SUVbwpeakSphere 0.5 mL | 0.46±0.01 | 0.46±0.01 | **<0.001** |
| DISCRETIZED_SUVbwpeakSphere 0.5 mL | 5.67±4.61 | 14.59±8.92 | **0.003** |
| DISCRETIZED_SUVbwpeakSphere 1 mL | 0.55±0.01 | 0.95±0.01 | **0.003** |
| DISCRETIZED_SUVbwpeakSphere 1 mL | 8.92±11.09 | 3.90±6.82 | 0.174 |
| DISCRETIZED_TLG (mL) | 94.43±135.89 | 110.25±168.35 | **0.001** |
| DISCRETIZED_HISTO_Skewness | 2.97±1.39 | 3.92±1.60 | **0.007** |
| DISCRETIZED_HISTO_Kurtosis | 13.28±8.98 | 20.57±14.32 | **0.007** |
| DISCRETIZED_HISTO_ExcessKurtosis | 10.28±8.98 | 17.57±14.32 | **0.001** |
| DISCRETIZED_HISTO_Entropy_log10 | 0.78±0.29 | 0.97±0.31 | **0.001** |
| DISCRETIZED_HISTO_Entropy_log2 | 2.58±0.97 | 3.23±1.02 | **<0.001** |
| DISCRETIZED_HISTO_Energy | 0.15±0.10 | 0.23±0.15 | **0.001** |
| SHAPE_Volume (mL) | 7.23±9.48 | 6.18±8.77 | 0.240 |
| SHAPE_Volume (vx) | 296.70±388.85 | 253.70±359.71 | 0.240 |
| SHAPE_Sphericity | 0.65±0.34 | 0.63±0.38 | 0.840 |
| SHAPE_Surface (mm²) | 1927.21±2068.76 | 1599.16±1827.17 | 0.162 |
| SHAPE_Compaicy | 2.42±1.47 | 2.32±1.59 | 0.616 |
| **Second order**  |                  |              |      |
| GLCM_Homogeneity | 0.31±0.22 | 0.42±0.26 | **0.031** |
| GLCM_Energy | 0.02±0.03 | 0.06±0.09 | **0.019** |
| GLCM_Contrast | 7.29±11.59 | 20.22±35.05 | **0.026** |
| GLCM_Correlation | 0.29±0.21 | 0.29±0.22 | 0.885 |
| GLCM_Entropy_log10 | 1.20±0.78 | 1.40±0.93 | 0.142 |
| GLCM_Entropy_log2 | 4.00±2.61 | 4.65±3.09 | 0.142 |
| GLCM_Dissimilarity | 1.54±1.47 | 2.51±2.47 | **0.002** |
| GLRLM_SRE | 0.69±0.36 | 0.69±0.41 | 0.990 |
categories as a category consisting of non-spatial methods, local spatial distribution methods, fractal analysis, and filters. Transformations in PET, magnetic resonance imaging, computed tomography, single photon emission computed tomography, and ultrasonography. However, due to limited software, lack of validation, and standardization, it cannot be assessed in routine practice.[19]

Tumor heterogeneity is also taking into account of [18F] FDG uptake.[26] The calculation of spatial heterogeneity with histogram-based features relied on the global computation of tumor heterogeneity only of the SUV values and not the spatial relations between voxels within the tumor.

Lee et al.[24] reported that late imaging showed a more significant correlation with prognostic factors in 38 invasive breast cancer cases. In addition, it was reported that a similar correlation was observed even in cases where the late image was taken earlier (100 min). In our study, we found higher number of correlated texture indicis in late imaging.

Dual time point application in [18F] FDG PET/CT has been previously studied to evaluate variation of SUV-based parameters.[23] We found that 36 of 64 textual indices measuring tumor heterogeneity showed significant increases in late imaging compared to standard PET/CT acquisition. Tumor heterogeneity changes have been reported in 40.8% of tumors in delayed imaging using the gradient segmentation method using dual time point [18F] FDG PET/CT in patients with pancreatic adenocarcinoma.[27]

Larger tumors may have larger connected regions and provide larger values of the LRM-based variables.[28] In our study, statistically significant correlations found 15 in the standard image and 36 in the late image, and it was noteworthy that LRM-based texture indicis have a significant correlation only in late images.

ER status is the determinant of the hormone therapy alternative and provides the most important prognostic information in breast cancer.[29] In our study, eight texture indicis correlations in standard image and 24 in late images were resulted of ER status.

The correlation between conventional quantitative FDG PET parameters and prognostic histopathological information in breast cancer has been described.

### Table 2

| Textural indicis | Standard imaging | Late imaging | p     |
|------------------|------------------|--------------|-------|
| GLRLM_LRE        | 1.09±0.76        | 1.55±1.17    | 0.022 |
| GLRLM_LGRE       | 0.01±0.01        | 0.01±0.01    | 0.867 |
| GLRLM_HGRE       | 145.98±193.47    | 262.96±428.28| 0.043 |
| GLRLM_SRLGE      | 0.01±0.01        | 0.01±0.16    | 0.975 |
| GLRLM_SRHGE      | 132.99±184.65    | 249.44±413.91| 0.039 |
| GLRLM_LRLGE      | 0.03±0.04        | 0.02±0.05    | 0.500 |
| GLRLM_LRHGE      | 218.02±236.19    | 325.00±490.76| 0.098 |
| GLRLM_GLNU       | 18.61±24.02      | 39.44±31.04  | 0.021 |
| GLRLM_RLNU       | 168.70±249.40    | 184.62±28.11| 0.291 |
| GLRLM_RP         | 0.66±0.35        | 0.67±0.40    | 0.889 |
| NGLDM_Coarseness | 0.03±0.02        | 0.03±0.02    | 0.860 |
| NGLDM_Contrast   | 0.11±0.12        | 0.19±0.23    | 0.021 |
| NGLDM_Busyness   | 0.32±0.36        | 0.90±1.24    | 0.017 |
| GLZLM_SZE        | 0.30±0.23        | 0.39±0.28    | 0.084 |
| GLZLM_LZE        | 3986.41±15142.89 | 124.29±295.64| 0.260 |
| GLZLM_LGZE       | 0.01±0.01        | 0.01±0.03    | 0.830 |
| GLZLM_HGZE       | 142.56±180.46    | 248.97±396.62| 0.046 |
| GLZLM_SZLGE      | 69.02±114.44     | 160.23±293.97| 0.254 |
| GLZLM_SZHGE      | 0.003±0.003      | 0.03±0.04    | 0.037 |
| GLZLM_LZLGE      | 87.53±331.98     | 5.53±20.49   | 0.254 |
| GLZLM_LZHGE      | 210327.84±717060.47| 9897.67±17814.42| 0.223 |
| GLZLM_GLNU       | 4.21±4.05        | 5.16±5.52    | 0.258 |
| GLZLM_ZLNU       | 11.50±20.43      | 29.09±47.34  | 0.018 |
| GLZLM_ZP         | 0.14±0.15        | 0.24±0.21    | 0.001 |

GLCM: Gray-level cooccurrence matrix; GLRLM: Gray-level run length matrix; NGLDM: Neighborhood gray-level dependence matrix; GLZLM: Gray-level zone, length matrix. Bold values: p<0.05
Table 3  Significantly correlated texture indicis between standard imaging and histopathological features

| pT | n | Mean | Standard deviation | p       |
|----|---|------|--------------------|---------|
| SUVbwpeakSphere 0.5 mL | 1 | 8 | 0.4631 | 0.00000 | <0.001 |
| 2 | 12 | 0.9831 | 0.00000 |
| pN | n | Mean | Standard deviation | p       |
| SUVbwpeakSphere 0.5 mL | 0 | 8 | 0.3831 | 0.00000 | 0.000 |
| 1 | 12 | 0.9631 | 0.00000 |
| HER-2 | n | Mean | Standard deviation | p       |
| SUVbwpeakSphere 0.5 mL | 0 | 15 | 3.9591 | 2.73510 | 0.229 |
| 1 | 5 | 5.7262 | 2.79975 |
| SUVbwpeakSphere 1 mL | 0 | 15 | 0.9506 | 0.00000 | 0.016 |
| 1 | 5 | 1.5606 | 0.00000 |
| Ki-67 | n | Mean | Standard deviation | p       |
| SUVbwpeakSphere 0.5 mL | 0 | 7 | 0.4631 | 0.00000 | 0.000 |
| 1 | 13 | 0.9831 | 0.00000 |
| ER | n | Mean | Standard deviation | P       |
| SUVbwpeakSphere 0.5 mL | 0 | 3 | 0.0131 | 0.00000 | 0.002 |
| 1 | 17 | 0.4631 | 0.00000 |
| SUVbwpeakSphere 1 mL | 0 | 3 | 0.3206 | 0.00000 | 0.048 |
| 1 | 17 | 0.9506 | 0.00000 |
| DISCRETIZED_SUVbwKurtosis | 0 | 3 | 2.3433 | 0.11211 | 0.034 |
| 1 | 17 | 2.9281 | 1.01678 |
| DISCRETIZED_SUVbwExcessKurtosis | 0 | 3 | -0.6567 | 0.11211 | 0.034 |
| 1 | 17 | -0.0719 | 1.01678 |
| GLRLM_LRHGE | 0 | 3 | 474.7468 | 409.44321 | 0.037 |
| 1 | 17 | 172.7188 | 175.35681 |
| GLZLM_LZE | 0 | 3 | 2272.2523 | 39307.79580 | 0.015 |
| 1 | 17 | 680.0421 | 1314.88247 |
| GLZLM_LZLGE | 0 | 3 | 496.4261 | 859.53050 | 0.016 |
| 1 | 17 | 15.3822 | 40.55510 |
| GLZLM_LZHGE | 0 | 3 | 1072582.2201 | 1845429.95237 | 0.019 |
| 1 | 17 | 58165.2966 | 144494.54711 |
| PR | n | Mean | Standard deviation | P       |
| SUVbwpeakSphere 0.5 mL | 0 | 7 | 0.4631 | 0.00000 | 0.000 |
| 1 | 13 | 0.4631 | 0.00000 |
| SHAPE_Sphericity | 0 | 7 | 0.8509 | 0.06183 | 0.049 |
| 1 | 13 | 0.5377 | 0.38419 |

pT: Histopathologic tumor stage; pN: Histopathologic lymph node stage; HER-2: Human epidermal growth factor receptor 2; Ki-67: Cellular proliferation index; ER: Estrogen receptor; PR: Progesterone receptor; GLRLM: Gray-level run length matrix; GLZLM: Gray-level zone, length matrix
### Table 4  Significantly correlated texture indicis between late imaging and histopathological features

| pT | n | Mean | Standart deviation | P  |
|----|---|------|--------------------|----|
| **SUVbwpeakSphere 0.5 mL** | | | | |
| 1 | 8 | 0.4627 | 0.00000 | 0.000 |
| 2 | 12 | 0.8531 | 0.00000 | |
| **GLCM_Correlation** | | | | |
| 1 | 8 | 0.1549 | 0.00000 | 0.000 |
| 2 | 12 | 0.3729 | 0.00000 | 0.019 |
| **GLRLM_GLNU** | | | | |
| 1 | 8 | 9.2996 | 0.00000 | 0.000 |
| 2 | 12 | 24.8181 | 0.00000 | 0.000 |
| **GLZLM_LZE** | | | | |
| 1 | 8 | 13.5034 | 0.00000 | 0.000 |
| 2 | 12 | 198.1412 | 0.00000 | 0.000 |
| **pN** | | | | |
| **SUVbwpeakSphere 0.5 mL** | | | | |
| 0 | 8 | 0.1651 | 0.00000 | 0.000 |
| 1 | 12 | 0.7821 | 0.00000 | 0.000 |
| **HER2** | | | | |
| **SUVbwpeakSphere 0.5 mL** | | | | |
| 0 | 15 | 0.4631 | 0.00000 | 0.000 |
| 1 | 5 | 1.0331 | 0.00000 | 0.000 |
| **SUVbwpeakSphere 1 mL** | | | | |
| 0 | 15 | 0.3251 | 0.00000 | 0.000 |
| 1 | 5 | 0.9506 | 0.00000 | 0.000 |
| **Ki-67** | | | | |
| **SUVbwpeakSphere 0.5 mL** | | | | |
| 0 | 7 | 0.4631 | 0.00000 | 0.000 |
| 1 | 13 | 0.4631 | 0.00000 | 0.000 |
| **DISCRETIZED_TLG (mL) (only For PET or NM)** | | | | |
| 0 | 7 | 40.0124 | 0.00000 | 0.000 |
| 1 | 13 | 148.0730 | 0.00000 | 0.000 |
| **GLZLM_LZHGE** | | | | |
| 0 | 7 | 2403.6852 | 0.00000 | 0.000 |
| 1 | 13 | 13932.8941 | 0.00000 | 0.000 |
| **GLZLM_ZLNU** | | | | |
| 0 | 7 | 11.2081 | 0.00000 | 0.000 |
| 1 | 13 | 38.7191 | 0.00000 | 0.000 |
| **ER** | | | | |
| **CONVENTIONAL_SUVbwstd** | | | | |
| 0 | 3 | 1.8254 | 0.00000 | 0.000 |
| 1 | 17 | 0.9446 | 0.00000 | 0.000 |
| **CONVENTIONAL_SUVbwQ2** | | | | |
| 0 | 3 | 6.3688 | 0.00000 | 0.000 |
| 1 | 17 | 3.6466 | 0.00000 | 0.000 |
| **SUVbwpeakSphere 0.5 mL** | | | | |
| 0 | 3 | 0.1631 | 0.00000 | 0.000 |
| 1 | 17 | 1.4631 | 0.00000 | 0.000 |
| **SUVbwpeakSphere1mL** | | | | |
| 0 | 3 | 0.8506 | 0.00000 | 0.000 |
| 1 | 17 | 1.9506 | 0.00000 | 0.000 |
| **DISCRETIZED_SUVbwstd** | | | | |
| 0 | 3 | 5.8056 | 0.00000 | 0.000 |
| 1 | 17 | 3.0574 | 0.00000 | 0.000 |
| **DISCRETIZED_SUVbwQ2** | | | | |
| 0 | 3 | 20.8333 | 0.00000 | 0.000 |
| 1 | 17 | 12.1765 | 0.00000 | 0.000 |
| pT          | n | Mean   | Standard deviation | P  |
|------------|---|--------|--------------------|----|
| DISCRETIzed_SUVbwQ3 |   |        |                    |    |
| 0          | 3 | 25.6667 | 23.35237           | 0.11|
| 1          | 17| 14.6176 | 7.26029            |    |
| DISCRETIzed_SUVbwSkewness |   |        |                    |    |
| 0          | 3 | 0.2340  | 0.42251            | 0.035|
| 1          | 17| 0.5904  | 0.35583            |    |
| SUVbwpeakSphere 0.5 mL |   |        |                    |    |
| 0          | 3 | 0.4631  | 0.00000            | 0.002|
| 1          | 17| 0.4631  | 0.00000            |    |
| SUVbwpeakSphere 1 mL |   |        |                    |    |
| 0          | 3 | 0.9506  | 0.00000            | 0.036|
| 1          | 17| 0.9506  | 0.00000            |    |
| GLCM_Contrast (=Variance) |   |        |                    |    |
| 0          | 3 | 59.9263 | 80.90714           | 0.029|
| 1          | 17| 13.2079 | 17.11548           |    |
| GLCM_Correlation |   |        |                    |    |
| 0          | 3 | 0.4764  | 0.13178            | 0.011|
| 1          | 17| 0.2520  | 0.21984            |    |
| GLCM_Dissimilarity |   |        |                    |    |
| 0          | 3 | 4.7072  | 4.50903            | 0.094|
| 1          | 17| 2.1179  | 1.90183            |    |
| GLRLM_LRE  |   |        |                    |    |
| 0          | 3 | 1.7436  | 1.00954            | 0.044|
| 1          | 17| 0.9690  | 0.67850            |    |
| GLRLM_LGRE |   |        |                    |    |
| 0          | 3 | 0.0333  | 0.05378            | 0.044|
| 1          | 17| 0.0070  | 0.00770            |    |
| GLRLM_HGRE |   |        |                    |    |
| 0          | 3 | 733.6547| 967.85206          | 0.035|
| 1          | 17| 179.9063| 227.71957          |    |
| GLRLM_SRHGE |   |        |                    |    |
| 0          | 3 | 706.7432| 939.95658          | 0.034|
| 1          | 17| 168.7426| 216.50435          |    |
| GLRLM_LRLGE |   |        |                    |    |
| 0          | 3 | 0.0792  | 0.13273            | 0.028|
| 1          | 17| 0.0102  | 0.01333            |    |
| GLRLM_LRHGE |   |        |                    |    |
| 0          | 3 | 853.3071| 1081.08451         | 0.039|
| 1          | 17| 231.7710| 279.89444          |    |
| NGLDM_Contrast |   |        |                    |    |
| 0          | 3 | 0.4358  | 0.46514            | 0.042|
| 1          | 17| 0.1505  | 0.14798            |    |
| GLZLM_LGZE |   |        |                    |    |
| 0          | 3 | 0.0428  | 0.06999            | 0.035|
| 1          | 17| 0.0075  | 0.00849            |    |
| GLZLM_HGZE |   |        |                    |    |
| 0          | 3 | 684.9417| 897.27092          | 0.035|
| 1          | 17| 172.0280| 210.33190          |    |
| GLZLM_SZHGE |   |        |                    |    |
| 0          | 3 | 486.2718| 684.51046          | 0.033|
| 1          | 17| 102.6936| 143.53441          |    |
| GLZLM_LZLGE |   |        |                    |    |
| 0          | 3 | 30.5508 | 52.86789           | 0.017|
| 1          | 17| 1.1165  | 3.31709            |    |
| PR         |   |        |                    |    |
| SUVbwpeakSphere 0.5 mL |   |        |                    |    |
| 0          | 7 | 0.3231  | 0.00000            | 0.000|
| 1          | 13| 0.7518  | 0.00000            |    |

pT: Histopathologic tumor stage; pN: Histopathologic lymph node stage; HER-2: Human epidermal growth factor receptor 2; Ki-67: Cellular proliferation index; ER: Estrogen receptor; PR: Progesterone receptor; GLCM: Gray-level cooccurrence matrix; GLRLM: Gray-level run length matrix; GLZLM: Gray-level zone, length matrix; NGLDM: Neighborhood gray-level dependence matrix.
It is remarkable that in our study, especially GLRM and GLZLM-based texture indices also had this correlation. The studies can be performed with a high number of cases, early screening of cancer metastasis will be possible.

To the best of our knowledge, there are no studies evaluating the heterogeneity in ILC compared with histopathological variables in double time point PET/CT. In addition, limited patient numbers and inconsistencies in the literature suggest that further analysis of heterogeneity in ILC is required. The major limitation of the study is the low number of patients and retrospective analysis. In our study, we aimed to investigate the correlation with prognostic histopathological information according to FDG affinity of ILC in standard and late images. Sensitivity and specificity values could not be given because there is no accepted threshold level for FDG uptake in breast lesions and it is not possible to perform a ROC analysis in which we can reach significant sensitivity and specificity levels with our existing patient number. ILC is not a common breast cancer, and FDG PET is not used much in staging. The lack of validation of the textural analysis has not been concluded and PET/CT spatial resolution cannot provide a clear conclusion about the small volume of tumors and questions of interpretation.

**Conclusion**

ILC shows relatively low uptake in [18F] FDG PET/CT compared to IDC due to tumor characteristics. In our study, GLRM-based, GLZLM-based, and conventional/discretized indices have more correlation than other texture values. In addition, in late image, especially in the ER status, these correlations occur in much higher (15 vs. 36) in late image. For this method to be put into clinical practice, prospective and case-controlled studies are needed.

**Peer-review:** Externally peer-reviewed.

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**Ethics Committee Approval:** The study was approved by the Koc University Ethics Committee (No: 2019.359. IRB2.119, Date: 26/11/2019).

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