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Can Radiomics Analyses in ^{18}F-FDG PET/CT Images of Primary Breast Carcinoma Predict Hormone Receptor Status?

Meme Kanserinde Primer Tümöre Ait ^{18}F-FDG PET/BT Radiomics Parametreleri Hormon Reseptörleri Durumunu Öngörebilir mi?

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Abstract

Objectives: This study aimed to investigate the role of preoperative ^{18}fluorine-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) radiomics features and metabolic parameters of primary breast tumors in predicting hormone receptor (HR) positivity.

Methods: A total of 153 patients with breast carcinoma who underwent preoperative ^{18}F-FDG PET/CT were included. All PET/CT images were retrospectively reevaluated. Radiomics features of primary breast lesions reflecting tumor heterogeneity as well as standardized uptake value (SUV) metrics (SUV_{min}, SUV_{mean}, SUV_{max}, and SUV_{peak}) and volumetric parameters such as metabolic tumor volume and total lesion glycolysis (TLG) were extracted by commercial texture analysis software package (LIFEx; https://www.lifexsoft.org/ index.php). WEKA and SPSS were used for statistical analysis. Binary logistic regression analysis was used to determine texture features predicting HR positivity. Accuracy, F-measure, precision, recall, and precision-recall curve area were used as data-mining performance criteria of texture features to predict HR positivity.

Results: None of the radiomics parameters were significant in predicting HR status. Only SUV metrics and TLG were statistically important. Mean ± standard deviations for SUV_{mean}, SUV_{max}, and SUV_{peak} for the HR-negative group were significantly higher than those in the HR-positive group (6.73±4.36 vs. 5.20±3.32, p=0.027; 11.55±7.42 vs. 8.63±5.23, p=0.006; and 8.37±6.81 vs. 5.72±4.86; p=0.012). Cut-off values of SUV_{mean}, SUV_{max}, and SUV_{peak} for the prediction of HR positivity were 4.93, 8.35, and 6.02, respectively. Among data-mining methods, logistic regression showed the best performance with accuracy of 0.762.

Conclusion: In addition to the relatively limited number of patients in this study, radiomics parameters cannot predict the HR status of primary breast cancer. SUV levels of the HR-negative group were significantly higher than those of the HR-positive group. To clarify the role of metabolic and radiomics parameters in predicting HR status in breast cancer, further studies involving a larger study population are needed.

Keywords: Breast cancer, PET/CT, fluorodeoxyglucose, hormone receptor

Öz

Amaç: Bu çalışmanın amacı preoperative ^{18}flor-florodeoksiglukoz (^{18}F-FDG) pozitron emisyon tomografisi/bilgisayarlı tomografi (PET/BT) radiomics ve metabolik parametrelerinin primer meme tümörünün hormon reseptör (HR) pozitifliğini öngörmedeki rolünün araştırılmasıdır.

Yöntem: Preoperatif ^{18}F-FDG PET/BT yapılan 153 meme kanseri hastası dahil edildi. Tüm PET/BT görüntüleri retrospektif olarak yeniden değerlendirildi. Primer meme tümörünün tümör heterojenitesini yansıtan radiomics parametrelerinin yanında standardize alım değeri (SUV) ölçümleri (SUV_{min}, $SUV_{ortalama}$, SUV_{maks}, SUV_{peak}) ve volümetrik parametreler [metabolik tümör hacmi ve toplam lezyon glikoliz (TLG)] doku analizi yazılım programı (LIFEx) (https://www.lifexsoft.org/ index.php) ile çıkarıldı. İstatistiksel analiz için WEKA ve SPSS kullanıldı. HR pozitifliğini

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öngörülmesi için Binary lojistik regresyon analizi kullanıldı. Doğruluk, F-measure, kesinlik, recall ve precision-recall curve HR pozitifliğini öngörmede doku parametrelerinin veri madenciliği performans kriterleri olarak kullanıldı.

Bulgular: HR durumunun öngörülmesinde hiçbir radiomics parametresi anlamlı bulunmadı. Sadece SUV ölçümleri ve TLG anlamlı bulundu. HR negatif grupta pozitif gruba göre ortalama $SUV_{ortalama}$, SUV_{maks} and SUV_{peak} değerleri istatistiksel olarak yüksek bulundu (6,73±4,36'ya karşı 5,20±3,32 p=0,027, 11,55±7,42'ye karşı 8,63±5,23 p=0,006 ve 8,37±6,81'e karşı 5,72±4,86 p=0,012). $SUV_{ortalama}$, SUV_{maks} and SUV_{peak} için HR pozitifliğini öngörmede eşik değerler sırasıyla 4,93, 8,35 ve 6,02'ydi. Veri madenciliği yöntemleri içinde lojistik regresyon 0,762 doğruluk ile en iyi performansı gösterdi.

Sonuç: Bu çalışmada kısıtlı hasta sayısı olmakla birlikte, radiomics parametreleri primer meme kanserinde HR durumunu öngöremedi. HR negatif grupta, pozitif gruba göre SUV değerleri anlamlı olarak daha yüksekti. Metabolik parametrelerin ve radiomics parametrelerinin meme kanserinde HR durumunu öngörmedeki yerinin netleşebilmesi için daha fazla sayıda hasta içeren ileri çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Meme kanseri, PET/BT, fluorodeoksiglukoz, hormon reseptörü

Introduction

Breast cancer is the most common cause of cancer-related deaths in women worldwide. Clinical outcome is closely related to the disease stage at diagnosis. Early diagnosis and appropriate therapy help achieve favorable outcome. However, breast cancer is a heterogeneous type of tumor with expression of several different receptors and many defined gene mutations. These characteristics at the subcellular micro level have been well investigated as molecular targets of various therapeutic approaches. Estrogen and progesterone receptor positivity is the most important prognostic factor in breast cancer. The existence and loss of hormone receptor (HR) expression have been investigated in the estimation of prognosis (1).

^{18}Fluorine-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT), the most frequently used nuclear oncology method, is also recommended for staging locally advanced breast cancer, where the incidence of distant metastasis or the necessity for neoadjuvant chemotherapy is high. The use of PET radiomics in oncology has recently emerged as a new era of clinical investigation. High levels of maximum standardized uptake value (SUV_{max}) of the primary breast tumor have been associated with high grade and poor prognosis in breast carcinoma (2). Moreover, beyond SUV_{max}, certain features of intratumoral distribution, and volumetrics of ^{18}F-FDG, the most common tracer reflecting metabolic activity of the tumor has also been defined. Some of these features have been associated with the receptor status of breast cancer (3,4,5,6,7). However, these PET features do not reflect spatial intratumoral heterogeneity. Tumor heterogeneity is closely related with proliferation rate and necrosis (8). The era of artificial intelligence in medical imaging and determination of therapy according to individual automated risk classification systems and adopted algorithms has led to further trials in metabolic imaging.

Radiomics is a method of extracting several features from medical images. It uses data reconstruction algorithms to obtain parameters that cannot be recognized by raw data. First-order features refer to histogram analysis based on intensity. Second-order features consider relationships between gray level values within the volume of interest (VOI) and reflect intralesion heterogeneity like gray level co-occurrence matrix and gray level run-length matrix (GLRLM). Higher-order features are obtained statistically from filtered or mathematically transformed medical images. This helps noise suppression, highlighting repetitive patterns or reveal important details (9).

These parameters have been shown to be related with some clinical or histopathological characteristics of disease, in our case, breast cancer. Further processing of these data has also provided information about the prognosis and possible beneficial therapy options (10).

This study aimed to analyze metabolic and radiomics features of primary breast tumors of patients who underwent preoperative ^{18}F-FDG PET/CT and their correlation with histopathological HR status.

Material and Methods

Patients

Ankara University Human Research Ethics Committee approval was obtained (ethical approval no: I1-43-21).

After excluding 32 patients who received neoadjuvant chemotherapy before primary tumor excision, 153 consecutive patients who underwent preoperative ^{18}F-FDG PET/CT with biopsy-proven breast carcinoma in our department between July 2014 and March 2020 were included in the study. All patients underwent surgical excision of the primary tumor after ^{18}F-FDG PET/CT. Histopathological characteristics of the excised tumor were noted including the size, Ki-67 index, estrogen receptor (ER), and progesterone receptor (PR) status of the tumor.

The exclusion criteria were as follows: i) No significant solid lesion on CT (n=1), ii) existence of non-^{18}F-FDG-avid tumors (n=5), iii) uncontrolled diabetes with blood glucose level >150 mg/dL (n=3), iv) multiple primary cancer (n=2), v) unavailability of details of histopathological examination data (n=10), vi) total excision of the primary tumor before ^{18}F-FDG PET/CT (n=9), and vii) existence of primary tumor smaller than 64 voxels (n=12).

Histopathological Analysis

All cases were analyzed for ER and PR status and Ki-67 proliferation rate with immunohistochemical analysis. Immunohistochemical studies were performed with external and internal positive controls; the scattered nuclear positivity of ER and PR in normal breast ducts and acini around the tumor were used as internal positive controls. The percentage of the nuclear ER- and PR-positive invasive tumor cells was recorded. The percentage of at least 1% of the tumor cells reported as positive was recommended (11). The Ki-67 proliferation rate was counted in hotspot areas, where at least 100 tumor cells were counted, and the percentage of the nuclear Ki-67 positive tumor cells were reported (12).

^{18}F-FDG PET/CT Protocol

After 6 h of fasting, approximately 370 MBq ^{18}F-FDG was injected intravenously provided that the blood glucose level was <150 mg/dL. Whole-body PET/CT images were obtained by hybrid PET/CT scanner (Discovery ST or Discovery 710, GE Medical Systems, Milwaukee, USA) from the vertex to the upper thigh 60 min after radiopharmaceutical injection. PET scan was performed 3 min/bed position. Attenuation correction was performed by low-dose CT (140 kV, 70 mA, 0.5 s/tube rotation, and slice thickness of 5 mm). Patients were allowed to breathe normally. The maximum intensity projection and attenuation-corrected PET/CT fusion images were evaluated in three planes (transaxial, coronal, and sagittal) (Advance Workstation Volumeshare 5 GE Medical Systems).

Texture and Volumetric Analysis

Whole-body PET/CT images were retrospectively reevaluated by an experienced nuclear medicine specialist (with >10 years of experience on oncological PET/CT) blinded to all histopathological and clinical data of the case. PET parameters of primary breast lesions were measured. A threshold of 40% of the SUV_{max} used to define the contours of semi-automated VOIs drawn around the primary tumor. Forty-two radiomics features reflecting tumor heterogeneity (first-, second-, and higher-order texture parameters) as well as SUV metrics (SUV_{min}, SUV_{mean}, SUV_{max}, and SUV_{peak}) and metabolic volumetric parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were extracted from the PET/CT images imported in DICOM format by the commercial texture analysis software package (LIFEx; https://www.lifexsoft.org/ index.php).

VOIs on PET and CT images were identical. The resampling setup details for LIFEx were as follows: Intensity discretization with gray levels of 64 bins and intensity rescaling bound 0-20 for PET images and between -1000 and 3000 HU of gray levels of 400 bins and absolute scale bounds for CT images. The analyzed metabolic and radiomics parameters are listed in Table 1.

Statistical Analysis

WEKA 3.7 and SPSS 11.5 programs were used to evaluate the collected data. As descriptive statistics, the mean ± standard deviation and median (minimum-maximum) for quantitative variables and number of patients (percent) for qualitative variables were used. In terms of quantitative variable, a significant difference was found between the categories of the qualitative variables of HR-positive and HR-negative groups, and Mann-Whitney U test was used because the normal distribution assumptions were not met. Binary logistic regression analysis was used to determine the texture features affecting HR positivity. Receiver operating characteristic analysis was performed to determine the cut-off values for different texture features. The significance level was set as 0.05. Classification methods of support vector machine, Hoeffding tree, J48, and multilayer perceptron were used in the WEKA program. The data set was evaluated using the 10-fold cross-validation test option. Accuracy, F-measure, precision, recall, and precision-recall curve area were used as data-mining performance criteria of texture features to predict HR positivity.

Results

A total of 153 patients with locally advanced (stage IIA-III) breast cancer (150 female, 3 male, mean age 55.83±13.37 years) were enrolled. The mean tumor size was 39.92±22.83 (7-140) mm. No patients had T4 tumor (stage IIIB). The demographic characteristics of the patients are given in Table 2. In the final histopathological examination, tumors of 37 patients were negative for HRs.

The CorrelationAttributeEval method in WEKA and binary logistic regression analysis in SPSS were used because the data set contained numerous radiomics features. By using these methods, the importance of the features and their contributions to the data set were examined. The features that were determined to be insignificant by the two methods and considered not important as clinical

information were excluded from the data set. A total of seven features remained as a result. These features were SUV_{mean}, SUV_{max}, SUV_{peak}, gray level zone length matrix long-zone emphasis (GLZLM LZE), TLG, MTV, and GLRLM gray level non-uniformity (GLNU). Descriptions for these features for HR-positive and HR-negative groups are shown in Table 3. The mean ± standard deviations for the SUV_{mean}, SUV_{max}, and SUV_{peak} for the HR-negative group were significantly higher than that in the HR-positive group (6.73±4.36 vs. 5.20±3.32, p=0.027; 11.55±7.42 vs. 8.63±5.23, p=0.006; and 8.37±6.81 vs. 5.72±4.86, p=0.012). Cut-off values for the prediction of HR status for SUV_{mean}, SUV_{max}, and SUV_{peak} were calculated as 4.93, 8.35, and 6.02, respectively (Table 4). Percentages of feature importance according to the HR status were given in Figure 1. When we looked at the binary logistic regression analysis results to determine the risk factors affecting HR status in addition to SUVs, TLG demonstrated significant importance (Table 5). None of the radiomics parameters were found as significant factors to predict HR status. When comparing the data- mining performance results for different methods in Table 6, logistic regression gave the best accuracy with 0.762.

Table 1. List of the studied metabolic and radiomics parameters

Metabolic parameters	Higher-order parameters
SUV_{max}	GLRLM SRE
SUV_{mean}	GLRLM LRE
SUV_{peak}	GLRLM LGRE
MTV	GLRLM HGRE
TLG	GLRLM SRLGE
First-order parameters	GLRLM SRHGE
Skewness	GLRLM LRLGE
Kurtosis	GLRLM LRHGE
$Entropy_{histo}$	GLRLM GLNU
Energy	GLRLM RLNU
SHAPE sphericity	GLRLM RP
SHAPE compacity	GLZLM SZE
Second-order parameters	GLZLM LZE
$Homogenity_{GLCM}$	GLZLM LGZE
$Energy_{GLCM}$	GLZLM HGZE
$Contrast_{GLCM}$	GLZLM SZLGE
$Correlation_{GLCM}$	GLZLM SZHGE
$Entropy_{GLCM}$	GLZLM LZLGE
$Dissimilarity_{GLCM}$	GLZLM LZHGE
	GLZLM GLNU
	GLZLM ZLNU
	GLZLM ZP
	$Coarseness_{NGLDM}$
	$Contrast_{NGLDM}$
	$Busyness_{NGLDM}$

SUV: Standardized uptake value, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, GLCM: Gray level co-occurrence matrix, GLRLM: Gray level run-length matrix, SRE: Short-run emphasis, LRE: Long-run emphasis, LGRE: Low gray level run emphasis, HGRE: High gray level run emphasis, SRLGE: Short-run low gray level emphasis, SRHGE: Short-run high gray level emphasis, LRLGE: Long-run low gray level emphasis, LRHGE: Long-run high gray level emphasis, GLNU: Gray level non-uniformity, RP: Run percentage, GLZLM: Gray level zone length matrix, SZE: Short-zone emphasis, LZE: Level zone emphasis, LGZE: Low gray level zone emphasis, HGZE: High gray level zone emphasis, SZLGE: Short-zone low gray level emphasis, SZHGE: Short-zone high gray level emphasis, LZLGE: Long-zone low gray level emphasis, LZHGE: Long-zone high gray level emphasis, ZLNU: Zone length non-uniformity, ZP: Zone percentage, NGLDM: Neighborhood gray level different matrix

Discussion

Staging is not the only parameter that can guide therapy in breast cancer. Intratumoral heterogeneity is a challenging issue in the management of breast cancer. Various types of genetic alterations, receptor expressions, and sensitivity to certain hormones highly affect the biological behavior and the clinical course of the disease. Classification and

Table 2. Demographic characteristics of the patients

		Mean ± SD (minimum-maximum)
Age		55.83±13.37 (26-88)
Tumor size		39.92±22.83 (7-140 mm)
		Number of patients (%)
Stage	**IIA**	65 (43%)
	IIB	61 (40%)
	IIIA	14 (9%)
	IIIB	-
	IIIC	13 (8%)
Histopathology	**Ductal**	127 (83%)
	Lobular	12 (8%)
	Mucinous	3 (2%)
	Others	11 (7%)
	Micropapillary	1 (0.6%)
	Tubular + cribriform	1 (0.6%)
	Ductal + micropapillary	4 (2.6%)
	Ductal + micropapillary	4 (2.6%)
	Ductal + cribriform	1 (0.6%)
	Ductal + mucinous	
Hormone receptor status	**Positive**	116 (76%)
	Negative	37 (24%)

SD: Standard deviation

Table 3. Descriptives for hormone receptor status

Variables	HR status				
	Negative (n=37)		Positive (n=116)		
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	p value
SUV_{mean}	6.73±4.36	6.09 (0.97-24.46)	5.20±3.32	4.44 (1.16-20.67)	0.027
SUV_{max}	11.55±7.42	10.58 (3.30-44.23)	8.63±5.23	7.11 (1.46-29.20)	0.006
SUV_{peak}	8.37±6.81	7.46 (0.00-37.44)	5.72±4.86	4.66 (0.00-26.08)	0.012
TLG	86.54±113.38	38.66 (2.79-462.25)	48.45±77.18	22.74 (1.71-599.65)	0.104
MTV	23.26±70.19	5.66 (0.51-419.68)	8.57±9.92	5.89 (0.83-64.81)	0.548
GLZLM LZE	1928.13±7411.88	5.85 (0.00-33375.38)	201.24±780.95	11.24 (0.00-6851.30)	0.196
GLRLM GLNU	50.55±136.04	9.33 (0.00-718.89)	21.39±31.95	12.94 (0.00-215.10)	0.656

HR: Hormone receptor, SD: Standard deviation, min: Minimum, max: Maximum, SUV: Standardized uptake value, TLG: Total lesion glycolysis, MTV: Metabolic tumor volume, GLZLM: Gray level zone length matrix, LZE: Level zone emphasis, GLRLM: Gray level run-length matrix, GLNU: Gray level non-uniformity

Table 4. Cut-off values for the SUV_{mean}, SUV_{max}, and SUV_{peak} in the prediction of hormone receptor status

Variables	Area	Standard error	p value	95% confidence interval		Sensitivity	Specificity	Cut-off value
				Lower bound	Upper bound			
SUV_{mean}	0.623	0.053	0.027	0.518	0.727	0.617	0.611	4.935
SUV_{max}	0.651	0.050	0.006	0.553	0.748	0.635	0.667	8.355
SUV_{peak}	0.638	0.053	0.012	0.534	0.743	0.6262	0.639	6.025

SUV: Standardized uptake value, max: Maximum

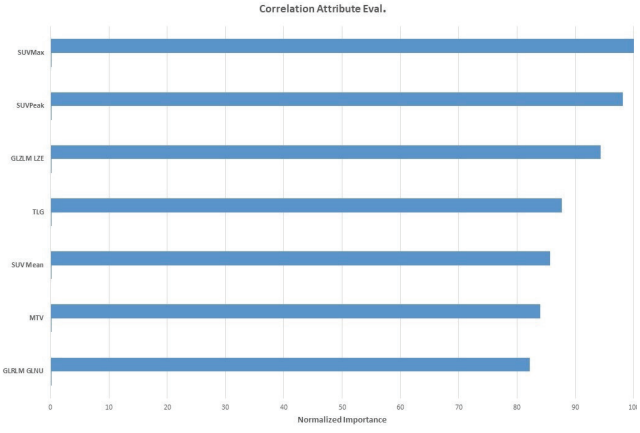

Figure 1. Variable importance for hormone receptor positivity

prognosis estimation is thus difficult because many factors are needed to consider. Breast cancers are dependent on estrogen and progesterone for growth; thus, receptor modulators and receptor downregulators are also used in the therapeutic management of disease other than conventional chemotherapy. ER and PR positivity is known as the most important prognostic factor in breast cancer. Hormonal therapy has been shown to be beneficial in overall survival and progression-free survival (13).

Imaging at diagnosis primarily aimed to correct cancer staging. However, in heterogeneous tumors like breast cancer, tumor size, local invasion, or disease extent is not enough for prognosis estimation and treatment decision. Any radiological or functional image obtained is actually more valuable than the reconstructed image, as huge amounts of processable data are hidden. Texture analysis include the parameters derived from the first-, second-, and higher-order statistics reflecting the entropy, skewness, curtosis, etc. (14). The radiomics parameters calculated from ^{18}F-FDG PET/CT have been reported to be related with molecular characteristics and outcome results in breast cancer (15).

SUV reflects the cellular content of the selected tumoral tissue. SUV_{max} is the most widely used parameter for the absolute quantification of activity concentration of the tumoral tissue in a selected voxel in proportion to the injected activity (16). SUV calculation assumes that the injected radiopharmaceutical is evenly distributed throughout the body. Thus, it is affected by various factors such as partial volume effect, motion, time interval between injection and acquisition, and reconstruction method (16,17,18). This is why the use of volumetric parameters like MTV and TLG has been recommended, which represent the tumoral load closest to real in a given tumoral lesion. Thus, they have been advocated to be more successful in estimating disease severity in various cancers, including breast cancer (19). However, in this study, we examined PET metabolic

Table 5. Binary logistic regression results for predicting hormone receptor status

Variables (reference)	β	SE	p value	OR	95% CI for OR	
					Lower bound	Upper bound
SUV_{max}	0.077	0.032	0.017	1.080	1.014	1.150
SUV_{peak}	0.082	0.035	0.018	1.086	1.014	1.163
GLZLM LZE	0.001	0.001	0.161	1.001	0.999	1.001
TLG	0.004	0.002	0.037	1.004	1.000	1.008
SUV_{mean}	0.106	0.050	0.035	1.112	1.007	1.227
MTV	0.020	0.014	0.165	1.020	0.992	1.048
GLRLM GLNU	0.005	0.003	0.103	1.005	0.999	1.011

β: Beta coefficient, SE: Standard error of mean, OR: Odds ratio, CI: Confidence interval, SUV: Standardized uptake value, max: Maximum, GLZLM: Gray level zone length matrix, LZE: Level zone emphasis, TLG: Total lesion glycolysis, MTV: Metabolic tumor volume, GLRLM: Gray level run-length matrix, GLNU: Gray level non-uniformity

Table 6. Comparison of the performance of data-mining methods

Methods	Accuracy	F-measure	Precision	Recall	PRC area
Support vector machine	0.762	0.659	0.581	0.761	0.629
Logistic regression	0.762	0.690	0.709	0.760	0.652
Multilayer perceptron	0.748	0.663	0.643	0.745	0.655

PRC: Precision-recall curve

and radiomic features of the primary breast lesion only and investigated its relationship with the hormonal status of the tumor. All SUV parameters, including maximum, peak, and mean SUV were factors related with HR status. Interestingly, and in contrast to previously mentioned hypothesis that volumetric parameters are more reliable, MTV was not significant. However, TLG, the calculated product of MTV and SUV_{mean} of the target lesion, was also significantly related with the HR status in patients with breast cancer. We attributed the difference between the significance level of MTV and TLG to the fact that TLG is eventually a derivative of SUV already. These results are compatible with those of a previous study (20). A study on patients with breast cancer who have undergone positron emission mammography (PEM) deserves attention because the authors presented PET data dedicated to breast. In contrast to many other studies, they proposed that volumetric data are not of significant importance and SUV is predictive of hormonal status of the tumor (4).

The dataset contains many radiomics features. Thus, according to WEKA and binary logistic regression analysis, among radiomics parameters, only GLZLM LZE and GLRLM GLNU were included. GLZLM reflects the size of the homogenous zones for each gray level in three dimensions, and LZE is the distribution of the long homogenous zones in an image. GLRLM is used for the size of homogenous runs for each gray level in three dimensions, and GLNU measures the similarity of values of the gray level. In this study, none of the radiomics parameters were significant in predicting HR status. However, previous reports on radiomics and molecular characteristics of primary breast cancer have mostly studied multiple histopathological and clinical parameters including the tumor type (ductal/lobular), tumor size, Her-2 status, Ki-67 index, and TNM stage along with the HR status. Binary logistic regression analysis and risk estimation were the primary endpoints in these studies. However, in the present study, we used data-mining method, a higher-order and more complicated statistical method than methods used in previous studies. After determining the variables indicative of HR status by binary logistic regression analysis, we created a data-mining model that can accurately select patients with positive HR status using data obtained from ^{18}F-FDG PET/CT by utilizing the least number of features. Attempts to define quantitative features indicative of an event or characteristic of a lesion in radiological studies all serve as preliminary studies for modeling methods to be used in artificial intelligence. Studies have used various radiomics features to define HR status. However, if a program is created to determine histopathological characteristics of tumor based on ^{18}F-FDG PET/CT study for disease staging, only a few features will be needed to create a model (21). This is why we moved one step forward in statistics compared with previous studies. We investigated the importance level of variables determined by logistic regression and generated the best model for the prediction of HR status of primary breast cancer lesions using data from ^{18}F-FDG PET/CT performed for staging. In addition to risk estimation

calculated by binary logistic regression, the proposed PET radiomics model including metabolic parameters can also distinguish hormone-positive from hormone-negative breast cancer with a prediction accuracy of 76%. Because data-mining methods necessitate an incredible amount of data to be processed statistically, only HR status was examined under the scope of this study.

Despite the high-level statistics conducted in a large patient population for the estimation of a very specific condition in this study, there are a few limitations necessary to mention. First, the hormone-negative group was relatively small compared with the hormone-positive group. If a greater number of patients could be included, some radiomics parameters would have been significant together with metabolic parameters. We had to exclude many patients because of faint ^{18}F-FDG uptake and/or small breast tumors. If the same patients could be scanned with PEM or with PET/magnetic resonance (MR), some lesions may have been clarified, and these patients could have been enrolled in the study. However, PET/CT is the standard of choice in staging breast cancer because it provides data of the M status of the disease (22). PEM or PET/MR is rather used for further evaluation of local invasion or involvement of axillary lymph nodes. Radiomics data of PEM or PET/MR would also be certainly very valuable in predicting histopathological characteristics of primary breast cancer.

Conclusion

In addition to the relatively limited number of patients in this study, radiomics parameters cannot predict HR status of primary breast cancer. SUV levels of the HR-negative group were significantly higher than those in the HR-positive group. To clarify the role of metabolic and radiomics parameters in predicting HR status in breast cancer, further studies with a larger number of patients are needed.

Ethics

Ethics Committee Approval: Ankara University Human Research Ethics Committee approval was obtained (ethical approval no: I1-43-21).

Informed Consent: Was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ç.S., M.A., Design: Ç.S., M.A., S.D.S., E.Ö., Data Collection or Processing: P.G., Ç.S., A.K., Analysis or Interpretation: B.B., Ç.S., Literature Search: M.A., Ç.S., Writing: M.A.

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References

1. Harvey JM, Clark GM, Osborne CK, Allred DC. Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. J Clin Oncol 1999;17:1474-1481.
2. Yoon HJ, Kim Y, Kim BS. Intratumoral metabolic heterogeneity predicts invasive components in breast ductal carcinoma in situ. Eur Radiol 2015;25:3648-3658.
3. Garcia-Vicente AM, Pérez-Beteta J, Pérez-García VM, Molina D, Jiménez-Londoño GA, Soriano-Castrejón A, Martínez-González A. Metabolic tumor burden assessed by dual time point [18F]FDG PET/CT in locally advanced breast cancer: relation with tumor biology. Mol Imaging Biol 2017;19:636-644.
4. Moscoso A, Ruibal Á, Domínguez-Prado I, Fernández-Ferreiro A, Herranz M, Albaina L, Argibay S, Silva-Rodríguez J, Pardo-Montero J, Aguiar P. Texture analysis of high-resolution dedicated breast 18 F-FDG PET images correlates with immunohistochemical factors and subtype of breast cancer. Eur J Nucl Med Mol Imaging 2018;45:196-206.
5. Ha S, Park S, Bang JI, Kim EK, Lee HY. Metabolic radiomics for pretreatment 18F-FDG PET/CT to characterize locally advanced breast cancer: histopathologic characteristics, response to neoadjuvant chemotherapy, and prognosis. Sci Rep 2017;7:1556.
6. Antunovic L, Gallivanone F, Sollini M, Sagona A, Invento A, Manfrinato G, Kirienko M, Tinterri C, Chiti A, Castiglioni I. [18F]FDG PET/CT features for the molecular characterization of primary breast tumors. Eur J Nucl Med Mol Imaging 2017;44:1945-1954.
7. Acar E, Turgut B, Yiğit S, Kaya G. Comparison of the volumetric and radiomics findings of 18F-FDG PET/CT images with immunohistochemical prognostic factors in local/locally advanced breast cancer. Nucl Med Commun 2019;40:764-772.
8. Molina-García D, García-Vicente AM, Pérez-Beteta J, Amo-Salas M, Martínez-González A, Tello-Galán MJ, Soriano-Castrejón Á, Pérez-García VM. Intratumoral heterogeneity in 18F-FDG PET/CT by textural analysis in breast cancer as a predictive and prognostic subrogate. Ann Nucl Med 2018;32:379-388.
9. Lambin P, Rios-Velazquez E, Leijenaar R, Carvalho S, van Stiphout RG, Granton P, Zegers CM, Gillies R, Boellard R, Dekker A, Aerts HJ. Radiomics: extracting more information from medical images using advanced feature analysis. Eur J Cancer 2012;48:441-446.
10. Gillies RJ, Kinahan PE, Hricak H. Radiomics: images are more than pictures, they are data. Radiology 2016;278:563-577.
11. Allison KH, Hammond MEH, Dowsett M, McKernin SE, Carey LA, Fitzgibbons PL, Hayes DF, Lakhani SR, Chavez-MacGregor M, Perlmutter J, Perou CM, Regan MM, Rimm DL, Symmans WF, Torlakovic EE, Varella L, Viale G, Weisberg TF, McShane LM, Wolff AC. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP guideline update. J Clin Oncol 2020;38:1346-1366.
12. Røge R, Nielsen S, Riber-Hansen R, Vyberg M. Ki-67 proliferation index in breast cancer as a function of assessment method: a NordiQC experience. Appl Immunohistochem Mol Morphol 2021;29:99-104.
13. Pertschuk LP, Kim DS, Nayer K, Feldman JG, Eisenberg KB, Carter AC, Rong ZT, Thelmo WL, Fleisher J, Greene GL. Immunocytochemical estrogen and progestin receptor assays in breast cancer with monoclonal antibodies. Histopathologic, demographic, and biochemical correlations and relationship to endocrine response and survival. Cancer 1990;66:1663-1670.
14. Mayerhoefer ME, Materka A, Langs G, Häggström I, Szczypiński P, Gibbs P, Cook G. Introduction to radiomics. J Nucl Med 2020;61:488-495.
15. Lemarignier C, Martineau A, Teixeira L, Vercellino L, Espié M, Merlet P, Groheux D. Correlation between tumour characteristics, SUV measurements, metabolic tumour volume, TLG and textural features assessed with 18F-FDG PET in a large cohort of oestrogen

receptor-positive breast cancer patients. Eur J Nucl Med Mol Imaging 2017;44:1145-1154.

16. Thie JA. Understanding the standardized uptake value, its methods, and implications for usage. J Nucl Med 2004;45:1431-1434.
17. Nakamoto Y, Zasadny KR, Minn H, Wahl RL. Reproducibility of common semi-quantitative parameters for evaluating lung cancer glucose metabolism with positron emission tomography using 2-deoxy-2-[18F] fluoro-D-glucose. Mol Imaging Biol 2002;4:171-178.
18. Keyes JW Jr. SUV: standard uptake or silly useless value? J Nucl Med 1995;36:1836-1839.
19. Moon SH, Hyun SH, Choi JY. Prognostic significance of volume-based PET parameters in cancer patients. Korean J Radiol 2013;14:1-12.
20. Sollini M, Cozzi L, Ninatti G, Antunovic L, Cavinato L, Chiti A, Kirienko M. PET/CT radiomics in breast cancer: mind the step. Methods 2021;188:122-132.
21. Hua J, Xiong Z, Lowey J, Suh E, Dougherty ER. Optimal number of features as a function of sample size for various classification rules. Bioinformatics 2005;21:1509-1515.
22. AJCC (American Joint Committee on Cancer) Cancer Staging Manual; 8th edition, 3rd printing, Amin MB, Edge SB, Greene FL, et al (Eds), Springer, Chicago 2018.