Quantitative assessment of volume-based metabolic parameters in early-stage invasive ductal breast cancer: Impact of different standardized uptake value thresholds on prognostic factors – A comprehensive analysis

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Abstract

Objective: This study compares volume-based metabolic parameters in early-stage invasive ductal breast cancer using different standardized uptake value (SUV) thresholds and examines their association with immunohistochemical factors. **Subjects and Methods:** A retrospective analysis included 135 patients with early-stage invasive ductal breast cancer who underwent preoperative fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) scans. Metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were derived using absolute SUV threshold methods and fixed % maximum tumor SUV threshold methods. Associations with immunohistochemical factors were explored, and receiver operating characteristic curves were generated. **Results:** Metabolic tumor volume 2.5 and TLG 2.5 showed stronger correlations with maximum tumor SUV values. Metabolic tumor volume 2.0 and TLG 2.0 had superior area under the curve (AUC) values in predicting estrogen and progesterone receptor negativity. Metabolic tumor volume 2.0 and TLG 2.0 were superior in distinguishing low and high-grade tumors. **Conclusion:** Absolute SUV threshold methods with a threshold of 2.0 are recommended for calculating volume-based metabolic parameters due to their strong correlation with immunohistochemical factors in invasive ductal breast cancer.

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Introduction

Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) has demonstrated significant benefits, providing valuable insights into the metabolism, diagnosis, and prediction of the development and outcome of breast cancer (BC) [1, 2]. Fluorine-18-FDG refers to fluorodeoxyglucose, a radiopharmaceutical compound used in PET scans to detect and visualize metabolic activity in the body PET/CT imaging functions as a noninvasive diagnostic tool that provides tomographic pictures and allows for the measurement of quantitative parameters associated with the metabolic activity of specific tissues. The often used quantitative metric is the maximum standardized uptake value (SUVmax), which represents the voxel value with the highest intensity of ^{18}F-FDG uptake in the tumor. Maximum SUV is preferred for its simplicity and high reproducibility. Nevertheless, it can be impacted by variables such as glucose concentrations, body mass, time elapsed after injection, dimensions of the region of interest (ROI), and resolution of the scanner. Furthermore, this metric has constraints in accurately representing the glucose metabolic rate of tumors, such as vulnerability to interference, the impact of partial volume, and the level of detail in the image [3-5]. Therefore, further exploration of alternative metabolic parameters is warranted. Numerous studies have investigated the use of metabolic tumor volume (MTV) as an index for predicting prognosis and assessing response [2, 6-11]. These studies have examined MTV either by itself or in conjunction with the mean SUV (SUVmean) in order to compute the total lesion glycolysis (TLG), which is defined as the product of MTV multiplied by SUVmean.

Quantitative analysis of glycolytic tumor volume measurements typically involves delineating tumor boundaries and employing various tumor segmentation methods [3, 12, 13]. Various methods have been proposed for calculating volume-based metabolic parameters (VBMP), but a consensus on the choice of standard methods and SUV thres-

holds for VBMP calculations is lacking in the literature. In this context, we compared VBMP obtained using two different delineation methods: the absolute SUV threshold method (ASTM) (2.0, 2.5) and the fixed % SUVmax threshold method (FSTM) (42%-50%). The selection of fixed threshold values, specifically 42% and 50%, was based on fundamental factors such as standardization, statistical significance, empirical evidence, contextual relevance, and exploratory analysis, as well as their established use in prior research as benchmarks for decision-making [10, 12, 13]. These thresholds facilitate comparisons across studies and enhance the interpretability of results, ensuring alignment with industry standards and providing a basis for further analysis. We examined the relationship between VBMP and immunohistochemical factors (IHCF) in a group of patients diagnosed with early-stage invasive ductal breast cancer (IDBC).

Subjects and Methods

From January 2020 to January 2024, we conducted a retrospective analysis of patients who were diagnosed with IDBC at the Nuclear Medicine Department of our Institution. Ethical was secured from the Ethics Committee of the Faculty of Medicine at Karatay University. (Approval no:83946, Dated:29-04-2024). Each patient provided informed written consent to participate in the study and for publication of study results. The review included patients who had undergone ^{18}F-FDG PET/CT imaging for staging purposes. Inclusion criteria comprised patients in the early stages (I–IIIB) who had not undergone any treatment. Exclusion criteria encompassed individuals with a history of surgery or prior treatment (chemotherapy, radiotherapy, hormone therapy), those showing no ^{18}F-FDG uptake in the primary tumor area, and individuals diagnosed with another cancer prior to breast cancer. Furthermore, only individuals with a lesion diameter above 15mm were included in order to reduce the impact of partial volume effect on ^{18}F-FDG uptake.

The patient flowchart, detailing the participant selection process for the study, is presented in Figure 1.

Every patient strictly followed a fasting period of at least 6 hours, and their blood glucose levels had to be below 180 mg/dL prior to conducting any exams. The Siemens Biograph LSO 16 PET/CT device was utilized for imaging purposes. The scans had a median duration of 61 minutes, ranging from 56 to 70 minutes. They started following the intravenous administration of ^{18}F-FDG, with a dose ranging from 236.4 to 458.6 MBq (6.4-12.4mCi), based on body weight (3.7MBq/kg). Computed tomography acquisition employed a 4-slice spiral CT with a slice thickness of 5mm (120-150kV, 80mA). After the transmission scan, a three-dimensional PET acquisition was conducted across 6 to 8 sessions, with each session lasting 3 minutes. The acquisition was done in a bed posture. Computed tomography scans played a crucial role in correcting the attenuation of PET/CT data.

Two experienced nuclear medicine experts independently conducted double-blind measurements. Consistency analysis was executed on the determined measurements, and ultimately, the average value was utilized in the statistical analysis. Regions with increased metabolism, indicative of active tumor foci, were identified. The pixel inside the ROI that had the greatest ^{18}F-FDG uptake was identified as the SUVmax.

To evaluate the volume-based PET/CT parameters, we used specialized software (TrueD, Syngo Via, Siemens Medi-

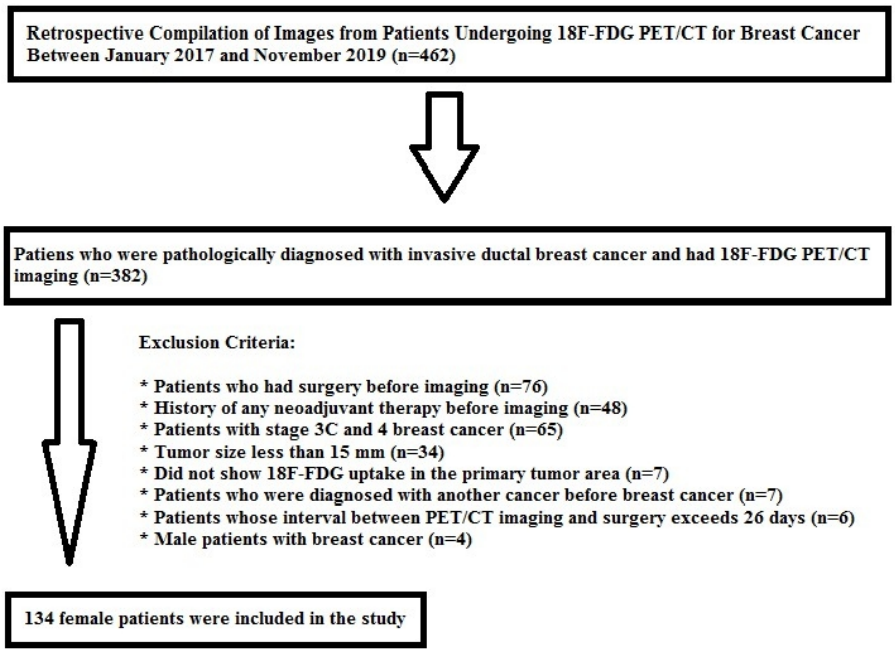

Figure 1. The patient flowchart.

cal Solutions, Chicago, IL) to create a 3D volume of interest (VOI) around the primary tumor lesion.

Two delineation methods were employed for calculating VBMP:

1. The ASTM Method: This process entails delineating the tumor zone as an area with a value exceeding a preset threshold, such as a standardized uptake value (SUV) of 2.0 or 2.5.
2. The FSTM Method: This procedure defines the tumor area with an SUV higher than a certain proportion of SUVmax (42%-50%) within the tumor. The product of the mean SUV and MTV values, determined independently by each method, was defined as TLG.

The patients received surgery prior to any targeted treatment for IDBC, with a median time frame of 17 (10-26) days following ^{18}F-FDG PET/CT imaging. In these patients, IHCF were evaluated by obtaining surgical samples and PET/CT images.

The nuclear grade was determined by analyzing 5mm slices of tumor tissue that had been preserved in formalin and embedded in paraffin. Subsequently, these sections were stained with hematoxylin and eosin. Tumors categorized as Grade I and II were labeled as low-grade, whereas Grade III tumors were classified as high-grade. Estrogen receptor (ER) and progesterone receptor (PR) positivity were defined if tumors exhibited moderate or high positivity (2 or 3+) in at least 10% of the tumor cells, assessed using ER and PR antibodies. A positive HER-2 status was determined if there was a membrane immunostaining of 3+ or 2+ with the presence of HER-2 gene amplification as confirmed by fluorescence in-situ hybridization analysis. The evaluation of Ki-67 expression involved measuring the proportion of cells that had positive nuclear staining, in accordance with the guidelines provided by the International Ki-67 in breast cancer working group [14]. Tumors exhibiting a Ki-67 proliferation index equal to or greater than 14 were categorized as highly proliferative, whereas those with a value below 14 were classed as low proliferative. Histopathological staging utilized the Scarff-Bloom-Richardson classification system [15]. Molecular subtypes of BC were defined based on the recommendations of the 12th International Breast Conference, dividing them into two groups: luminal and non-luminal. In the luminal group, subtypes included luminal A (lum A), luminal B negative [lum B(-)], and luminal B positive [lum B (+)]. In the non-luminal group, subtypes comprised HER-2 positive [HER-2 (+)] and triple negative (TN). Pathological prognostic staging followed the guidelines reported in the American Joint Committee on Cancer, 8th edition [16].

IBM SPSS Statistics for Windows (version 25, IBM Corp., Armonk, NY) was used for the statistical analyses. The Kolmogorov-Smirnov method was used to evaluate the continuous variables' distribution's normality. Continuous data were reported as medians or means, if deemed suitable. Categorical data were reported as frequencies and percentages. Non-parametric tests were employed to compare continuous variables. Two-group comparisons of continuous variables were assessed using Mann-Whitney U tests. The Kruskal-Wallis H test was employed for comparing multiple groups of continuous variables that did not exhibit normal distribution. The discriminatory power of the test was evaluated by measuring the area under the curve (AUC) using ROC analysis for variables that do not follow a normal distribution. Spearman's correlation test was employed to evaluate the link between continuous variables. A P-value below 0.05 was deemed statistically significant.

Results

This study included a cohort of 134 patients diagnosed with early-stage IDBC. The patients had a median age of 52.28 years, with an age range of 30 to 79 years.

Table 1 presents the overall traits of the patients enrolled in the study.

Table 1. *Patients characteristics.*

	N	(%)
T stage		
T1	54	40.3
T2	80	59.7
Lymph node involvement		
Negative	62	46.3
Positive	72	53.7
Grade status		
Low grade	86	64.2
High grade	48	35.8
Ki-67 proliferative index		
Low	42	31.3
High	92	68.7
ER status		
Negative	20	14.9
Positive	114	85.1
PR status		
Negative	28	20.9
Positive	106	79.1
HER-2 status		
Negative	97	72.4
Positive	37	27.6
Molecular subtypes		
Non-luminal group	20	14.9
Luminal group	114	85.1

ER, Estrogen Receptor; HER-2, Human Epidermal Growth Factor Receptor 2; PR, Progesterone Receptor.

Figures 2 and 3 illustrate the metabolic tumor volumes obtained from the same patient using different SUV thresholds.

The mean (SD) diameter of the tumors was 2.54 (0.93) cm. Tumor staging revealed that 54 (40.3%) patients had T1 tumors, while 80 (59.70%) patients had T2 tumors. Differences in T stages were observed with SUVmax and all VBMP (P-value: <0.001, for both). However, The highest values of the AUC were observed for MTV 2.0 and TLG 50% (AUC values: 0.877 and 0.865, respectively). A total of seventy-two patients, accounting for 67.59% of the sample, were found to have axillary lymph node metastases. There was no statistically significant difference observed between lymph node involvement and any VBMP. Out of the patients, 67 (50.0%) were diagnosed with stage IA, 33 (24.6%) with stage IB, 13 (9.7%) with stage IIA, 8 (6.0%) with stage IIB, 9 (6.7%) with stage IIIA, and 4 (3.0%) with stage IIIB. There was a notable disparity among all VBMP in the stage group.

Histopathological analysis revealed that 17 patients (12.7%) had grade I tumors, 69 (51.5%) had grade II tumors, and 48 (35.8%) had grade III tumors. Median values of VBMP, except MTV 42% and MTV 50%, were significantly higher in high-grade tumors. Although MTV 2.0 and MTV 2.5 showed similar values in distinguishing low-grade and high-grade tumors, a relatively superior AUC value was observed in MTV 2.0 (AUC value: 0.685 and 0.684). Similarly, although TLG 2.0 and TLG 2.5 showed similar values in distinguishing low-grade and high-grade tumors, a relatively superior AUC value was observed in TLG 2.0 (AUC value: 0.704 and 0.697).

Fourty-two (31.3%) patients had a Ki-67 index less than 14%. Although MTV 2.0 and MTV 2.5 showed similar values in distinguishing tumors with a Ki-67 index below and above 14%, a relatively superior AUC value was observed in MTV 2.5 (AUC value: 0.664 and 0.668). Similarly, although TLG 2.0 and TLG 2.5 showed similar values in distinguishing tumors with a Ki-67 index below and above 14%, a relatively superior AUC value was observed in TLG 2.5 (AUC value: 0.683 and 0.693).

The positivity rates for ER, PR, and HER-2 statuses were 114 (85.1%), 106 (79.1%), and 37 (27.6%) correspondingly. The distribution of molecular subtypes was as follows: 33 (24.6%) luminal A (lum A), 53 (39.6%) luminal B negative [lum B(-)], 28 (20.9%) luminal B positive [lum B (+)], 9 (6.7%) HER-2 positive [HER-2 (+)], and 11 (8.2%) triple negative (TN).

In ER status a significant difference was observed between

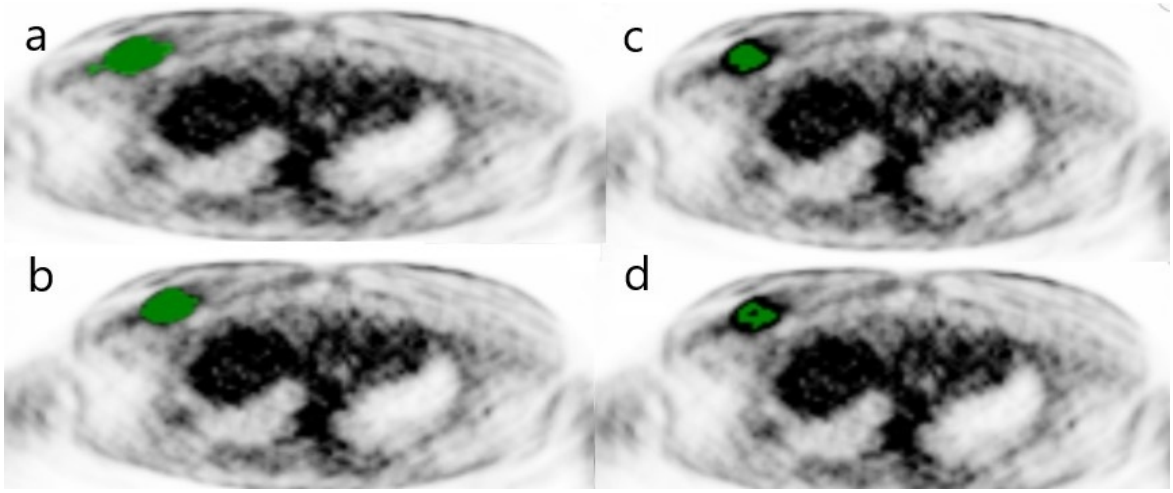

Figure 2. Shows the metabolic tumor volumes obtained from the same patient using different SUV thresholds. a, MTV 2.0; b, MTV 2.5; c, MTV 42%; d, MTV 50%.

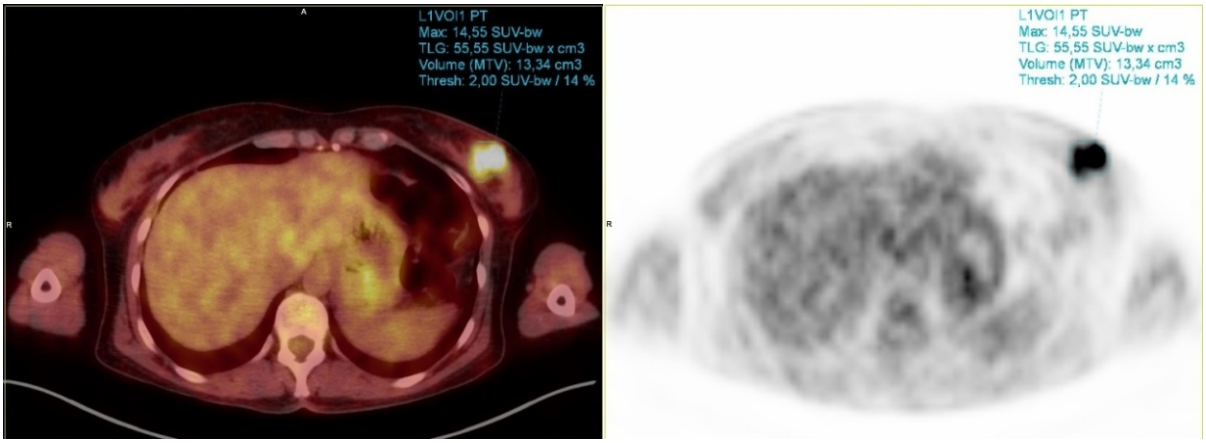

Figure 3. Positron emission tomogrpahy/CT fusion and PET-only images showing SUVmax, MTV 2.0 and TLG measurements in ER-positive, PR-positive, and HER2-positive breast cancer.

all VBMP, except MTV 42% and MTV 50%. Although MTV 2.0 and MTV 2.5 showed similar values in predicting ER receptor status, a relatively superior AUC value was observed in MTV 2.0 (AUC value: 0.751 and 0.743). Similarly, although TLG 2.0 and TLG 2.5 showed similar values in predicting ER receptor status, a relatively superior AUC value was observed in TLG 2.0 (AUC value: 0.772 and 0.764).

In PR status a significant difference was observed between all VBMP, except MTV 42%, TLG 42%, MTV 50%, and TLG 50%. Although MTV 2.0 and MTV 2.5 showed similar values in predicting PR receptor status, a relatively superior AUC value was observed in MTV 2.0 (AUC value: 0.632 and 0.627). Similarly, although TLG 2.0 and TLG 2.5 showed similar values in predicting PR receptor status, a relatively superior AUC value was observed in TLG 2.0 (AUC value: 0.651 and 0.648).

No significant association was found for any of the VBMP in predicting HER-2 receptor status.

The relationship between IHCF and VBMP in IDBC is presented in Table 2.

The highest correlation with SUVmax was found in MTV 2.5 in MTV types and TLG 2.5 in TLG types (r values: 0.829 and 0.891, respectively, both P-value: <0.001). Whereas, MTV 42% had the lowest correlation with SUVmax in MTV types (r value: 0.247, P-value: 0.004).

The relationship between SUVmax and VBMP is presented in Table 3.

Table 2. *The relationship between immunohistochemical factors and area under the curve values for volume-based metabolic parameters in invasive ductal breast cancer.*

	SUVmax	MTV 2.0	MTV 2.5	MTV 42%	MTV 50%	TLG 2.0	TLG 2.5	TLG 42%	TLG 50%
T stage	0.731	0.877	0.848	0.820	0.827	0.860	0.833	0.862	0.865
P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Grade	0.730	0.685	0.684	0.555	0.560	0.704	0.697	0.671	0.671
P value	<0.001	<0.001	<0.001	0.288	0.248	<0.001	<0.001	0.001	0.001
Ki-67 Index	0.708	0.664	0.678	0.549	0.569	0.683	0.693	0.673	0.675
P value	<0.001	0.002	0.001	0.368	0.201	0.001	<0.001	0.001	0.001
ER status	0.785	0.751	0.743	0.595	0.612	0.772	0.764	0.725	0.729
P value	<0.001	<0.001	0.001	0.175	0.112	<0.001	<0.001	0.001	0.001
PR status	0.690	0.632	0.627	0.525	0.530	0.651	0.648	0.616	0.615
P value	0.001	0.032	0.040	0.679	0.628	0.014	0.016	0.061	0.061
HER-2 status	0.599	0.572	0.569	0.492	0.483	0.583	0.574	0.548	0.545
P value	0.077	0.200	0.215	0.889	0.767	0.140	0.186	0.393	0.426

The underlined text denotes results that are not statistically significant. T, tumor; ER, Estrogen Receptor; PR, Progesterone Receptor; HER-2, Human Epidermal Growth Factor Receptor 2; AUC, Area Under the Curve; SUVmax, maximum standardized uptake value; MTV, Metabolic tumor volume; TLG, total lesion glycolysis. This table displays the AUC values that indicate the performance of various volume-based metabolic parameters (SUVmax, MTV, TLG) in relation to immunohistochemical markers such as T stage, Grade, Ki-67 Index, ER status, PR status, and HER-2 status. Higher AUC values suggest a stronger association between these factors and the metabolic parameters.

Table 3. *The relationship between SUVmax and area under the curve values for volume-based metabolic parameters.*

	MTV 2.0	MTV 2.5	MTV 42%	MTV 50%	TLG 2.0	TLG 2.5	TLG 42%	TLG 50%
Correlation Coefficient	0.769	0.829	0.247	0.267	0.853	0.891	0.742	0.741
P value	<0.001	<0.001	0.004	0.002	<0.001	<0.001	<0.001	<0.001

MTV, metabolic tumor volume; TLG, total lesion glycolysis. The correlation coefficients indicate the strength of the relationship between SUVmax and the Area Under the Curve (AUC) values for the specified volume-based metabolic parameters (MTV and TLG). P values indicate the statistical significance of these correlations.

Discussion

The constraints of SUVmax, which only captures data from a single voxel (usually <0.1mL), render it susceptible to statistical noise present in images [7]. In contrast, MTV and TLG have gained recent prominence as indicators of overall glucose metabolism in tumors, proving to be promising prognostic factors in various solid tumors, including lung, head-and-neck, and breast cancer [11, 17, 18]. Some studies even suggest that MTV and TLG might provide a better reflection of tumor metabolism concerning IHCF compared to SUVmax [9].

However, the calculation of MTV and TLG involves the challenging task of tumor contouring on PET images. Numerous methods, including manual contouring, ASTM, and FSTM, have been proposed for this purpose [3, 19]. The choice of the optimal SUV threshold method remains a subject of debate. While the SUVmax demonstrates strong consistency among and across operators, the consistency of MTV and TLG still has to be thoroughly evaluated. A study focusing on lung cancer with ^{18}F-FDG PET/CT demonstrated that MTV 2.5 offered the best predictive value for local recurrence and disease-free survival [12].

The relationship between VBMP and IHCF can vary, as observed by Kajary et al. (2015) [9]. Similarly, in our study, SUVmax seemed to more reliably reflect tumor metabolism compared to VBMP. These findings diverged from those repor-ted by Kaida and colleagues (2013) [10]. Kajary et al. (2015) proposed that these differences might be attributed to the use of different SUV thresholds [9]. Our study found that when assessing the therapeutic usefulness of VBMP, the metrics MTV 2.0 and TLG 2.0 showed a stronger correlation with IHCF compared to other VBMP.

In a study conducted by Cheebsumon et al. (2011), it was observed that volumes determined using higher thresholds (41%-70% of the highest voxel value) were smaller, leading to an underestimating of the volumes [20]. In contrast, they suggested that a smaller threshold (25% of the maximum voxel value) provided the best fit between measured and true volumes, with minimal impact from lesion features or metabolic heterogeneity [21]. This discrepancy highlights the lack of consensus on the fixed threshold value to use. Thresholding, however, is highly vulnerable to noise and changes in contrast, resulting in inconsistent assessment of the volume of interest (VOI), as demonstrated in a separate study [22]. In line with this, our study observed that using fixed threshold values of 42% and 50%, which were relatively higher, was insufficient to differentiate many IHCF. While these methods are assumed to accurately determine metabolic tumor volumes under specific imaging conditions, tumors are inherently heterogeneous and irregularly shaped. Hatt et al. (2010) developed an algorithm termed "fuzzy locally adaptive Bayesian" to evaluate lesions with heterogeneous uptake and irregular forms, suggesting its ability to more accurately define the metabolic volume of such lesions where threshold-based methods fail [23]. Despite the use of fixed or absolute threshold values in the literature for calculating VBMP, there is no consensus on the preferred method.

To ensure a reliable comparison among VBMP, it is essential to acquire images using consistent analyses and imaging protocols. In our study, all images were captured using a single device, and uniform imaging and analysis protocols were consistently employed to measure SUVmax and four different types of VBMP across all patients.

Another strength of this study lies in its focus on patients with early-stage BC, where lesions were excised without prior treatment, providing an optimal study design to evaluate the usefulness of VBMP.

The current study has some limitations, including its retrospective methodology, the relatively small sample size, and the fact that it was conducted in a single institution. The methods evaluated in this study, assumed to accurately determine metabolic tumor volumes under specific imaging conditions, may not precisely define the metabolic volume of heterogeneous and irregularly shaped tumors. Additionally, findings from this study may not be extrapolated to patients with advanced-stage IDBC.

In conclusion, our study highlights the significance of exploring alternative metabolic parameters beyond SUVmax in ^{18}F-FDG PET/CT imaging for early-stage IDBC. While SUVmax remains a widely used metric, its limitations necessitate the consideration of VBMP such as MTV and TLG. Our comparison of two delineation methods, ASTM and FSTM, underscores the need for standardized approaches in calculating VBMP, as different methods may yield varying results. The associations between VBMP and IHCF emphasize the potential of these parameters in providing valuable insights into the biological characteristics of breast tumors. In our research aimed at determining the most effective method for metabolic tumor volume calculation based on relationships with IHFC, we found that calculations using ASTM 2.0 and 2.5 thresholds provided a closer relationship than FSTM calculations using 42% and 50% thresholds. Between these two thresholds, the calculation using 2.0 threshold had the closest relationship.

The authors declare that they have no conflicts of interest.

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