

## Original Article

# Breast Incidental Lesions at 18 F FDG PET/CT: Diagnostic Performance of PET-derived Metabolic Parameters

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## Abstract

**Background:** Breast incidental lesion at 18 F FDG PET/CT are occasionally encountered in cancer patients, which may represent a second primary malignancy. The aim of the present study was to investigate the diagnostic performance of PET metabolic parameters to characterize breast incidentaloma.

**Materials and Methods:** All the images of patients with cancers other than breast with breast incidental lesion underwent PET/CT scan at Masih Daneshvari Hospital between May 2012 and May 2016 were retrieved and reviewed. SUVmax, SUVmean, MTV and TLG in addition to associated morphologic features on CT and demographics were recorded and correlated with final diagnosis defined by histopathologic confirmation or an at least 1-year clinical formal follow up.

**Results:** Of a total 58 from 51 patients (51/5029, 1.01%), 10 (19.60%) were histopathologically verified as second primary breast cancers. There was a statistically significant difference in SUVmax, SUVmean, MTV and TLG between benign and malignant group (1.64 vs. 5.32 (p=0.009), 1.34 vs. 3.69 (p=0.027), 0.96 vs. 2.62 (p=0.035), 1.54 vs 8.89 (p=0.006). Using cut off 2, 1.35, 1.16 and 1.75, sensitivity and specificity of SUVmax, SUVmean, MTV and TLG were calculated as 77% and 62%, 92% and 66.5%, 77% and 75% 77% and 67%, respectively.

**Conclusion:** Despite a significantly higher value in malignant breast incidental lesion, PET-derivative metabolic parameters provided only modest sensitivity and specificity and hence may not be considered as the sole criteria for risk stratification in this clinical setting.

**Keywords:** diagnostic performance, metabolic parameters, 18 F FDG PET/CT, breast incidental lesion

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## Introduction

Breast incidental lesions are occasionally encountered at 18 F FDG PET/CT scan harboring malignancy in up to 57% of cases<sup>1</sup>. Accurate risk stratification of

breast incidentaloma may prompt further diagnostic work up to avoid delayed urgent treatment. Recent investigations have provided evidence for PET-derived metabolic parameters as reliable prognostic indicators in various malignancies. SUVmax as the

most validated semi quantitative PET-based measures play a major role in the diagnostic algorithm of solitary pulmonary nodule with an excellent diagnostic performance (sensitive=97%, specific=85%, positive predictive value=93%, negative predictive value=92%, accuracy=93%)<sup>2</sup>; However, diagnostic applications of these parameters still needs to be verified in routine practice in most clinical settings. Few publications have investigated the potential role of metabolic parameters in differentiation of malignant from benign conditions identified at 18 F FDG PET/CT. One study provided evidence for SUVmax and TLG as a useful predictor of malignancy in intermediate and high-risk adrenal incidentaloma<sup>3</sup>. Another study demonstrated that PET metabolic parameters offer the potential to accurately identify malignant mediastinal tumor<sup>4</sup>. Evidence of ovarian tumoral lesions was also encouraging<sup>5</sup>. Many studies have been reported the prevalence and clinical significance of the breast incidental lesion at 18 F FDG PET/CT<sup>1,6-8</sup>; however, few have been investigated the potential value of metabolic parameters for characterization and risk stratification of breast incidental lesion<sup>1,8</sup>. To the best of our knowledge, there is little evidence of potential diagnostic value of volumetric PET-derivative metabolic parameters in breast incidentaloma. The aim of the present study was to investigate the diagnostic performance of SUVmax, SUVmean, MTV and TLG in association with other demographics, underlying cancer related characteristics and CT-associated morphologic features in breast incidentaloma in patients with non-breast cancers.

## Methods

The Institutional Review Board at Shahid Beheshti University of Medical Science approved this retrospective study and waived the need for informed consent.

**Patients:** Of a total 5826 cancer patients investigated by<sup>18</sup> F FDG-PET/CT at Masih Daneshvari Hospital, as a tertiary teaching center of PET/CT, from May 2012 to May 2016, 5029 patients were identified to have non-breast cancer. A retrospective review of PET reports revealed 72 breast incidental lesions in 68 patients for further analysis. Of these, 10 patients

lost to complete clinical formal follow up and 3 were not candidates for histopathologic examination due to advanced primary cancer and hence were excluded from the study. Lesions with a mean diameter below the PET resolution (7mm) were also excluded due to the negative impact of partial volume effect on the accuracy of PET-derived metabolic information (n=4). Finally, a total of 51 patients with 56 lesions constituted the study cohort. Demographics and primary cancer characteristics, including age, gender and type of primary cancer were recorded for each patient.

### **Imaging Acquisition and FDG-PET/CT acquisition protocol:**

Whole body F-18 FDG PET/CT was performed using an integrated FDG-PET/CT scanner (GE 690 Discovery, 64 Slice, Time of Flight). Fasting period was considered at least 8hr. Blood glucose level was below 150 mg/dl at the time of radiotracer injection. Sixty minutes ( $\pm 10\%$ ) after 4.6MBq/Kg (0.12 mCi/Kg) IV administration of 2-deoxy- 2-[ 18 F]fluoro -D-glucose (F FDG)<sup>18</sup>, CT acquisition commenced craniocaudally in supine position from vertex to mid-thigh (or to toe as indicated) with a multidetector CT scanner and the following parameters: 50-120 auto mAs tube current, 120 kV, noise factor 19, 2.5 mm thickness, tidal breathing. Thirty minutes before imaging acquisition, 40cc meglumin 76% (containing 370mg Iodine /cc) in 1500 water was administered as oral contrast. The PET data were then collected in the reverse direction immediately after CT acquisition at 3 minutes per bed position. The PET raw data were corrected for attenuation, dead time, random and scatter coincidence, and subsequently reconstructed by iterative method and HD (high definition) technique.

**Image interpretation FDG PET/CT:** All PET images' data set of eligible cohort were retrieved and reviewed at volume share AW 4.5 (Advantage Windows: GE, 690) by a team comprised of an experienced radiologist and a nuclear physician reached in consensus for visual interpretation of abnormal breast findings. Abnormal increased 18F FDG uptake in the breast more than background activity of surrounding normal tissue on AC and Non-AC PET images and/or abnormal soft tissue density including nodule, skin thickening or ill-defined soft tissue density on CT images were considered as breast

incidental finding. The greatest axial diameter of the CT corresponding abnormality was measured (in mm). The intensity of FDG uptake was categorized as mild (equal or less than mediastinal blood pool activity), moderate (more than a mediastinal blood pool and equal or less than liver activity) and severe (markedly more than liver activity) for descriptive purposes. To define as a dichotomous diagnostic test, lesion intensity of 18F FDG was reclassified as non to moderate uptake and intense uptake, representative of benign and malignancy, respectively.

Metabolic parameters were calculated semi automatically on PETVCAR AW 4.5. A volume of interest was drawn on the metabolically active breast lesion.  $SUV_{max}$ , as the most validated easily obtainable PET Semiquantitative metabolic parameters were then measured and recorded.

**Standard of reference:** All breast incidental lesions were finally verified as benign or malignant according to the histological findings or oncologist decision making based on a at least 1-year clinical formal follow up including routine clinical examination and serial breast US and mammography as well as follow up PET/CT whenever available as the standard of reference. Tissue biopsy was obtained in 20 patients (43.13%) (Fine needle, n=12, excisional biopsy, n=8)

immediately after baseline breast imaging and the 36 remaining (56.86%) underwent clinical formal follow up (median follow up duration=24.18 months). Two patients developed histologically-proven malignant lesions 9 and 6 months after the benign baseline US examinations categorized as BI-RDAS II and BI-RADS III, respectively. Thirty four lesions revealed no further evidence of malignant nature by the end of the study and thus considered as a benign lesion in 29 patients.

**Statistical analysis:** Normally and non-normally distributed variables were analyzed by parametric and nonparametric tests, respectively. Continuous and categorical variables were described as mean $\pm$ SD and frequency and compared between benign and malignant groups using Mann-Whitney U-test and the Fisher exact test with linear-by-linear association, respectively. Receiver operating characteristic (ROC) curves were performed to investigate the diagnostic characteristics of the SUVmax, SUVmean, MTV and TLG for identification of malignancy based on the appropriate cutoff. All statistical analysis was performed using SPSS version 23.

## Results

Fifty one out of 5029 patients (1.01%) with a total of

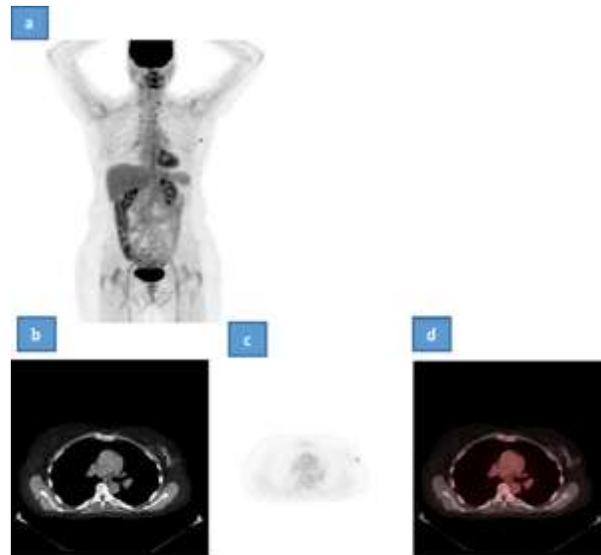
**Table 1:** Quantitative metabolic parameters of PET-detected breast incidental lesions.

Metabolic Parameters	SUV*max, mean ( $\pm$ SD)	SUV*mean mean ( $\pm$ SD)	MTV** mean ( $\pm$ SD)	TLG*** mean ( $\pm$ SD)
Benign Lesions	1.64 ( $\pm$ 1.01)	1.34 ( $\pm$ 0.9)	0.96 ( $\pm$ 0.6)	1.54 ( $\pm$ 1.12)
Fibroadenoma	4.64 ( $\pm$ 2.44)	3.37 ( $\pm$ 2.14)	1.29 ( $\pm$ .80)	4.17 ( $\pm$ 3.22)
Not otherwise specified	2.36 ( $\pm$ 1.13)	1.8 ( $\pm$ .92)	1.28 ( $\pm$ 1.77)	2.98 ( $\pm$ 1.99)
Malignant Lesion	5.32 ( $\pm$ 2.23)	3.69 ( $\pm$ 1.67)	2.62 ( $\pm$ 1.61)	8.89 ( $\pm$ 5.34)
Invasive Ductal Carcinoma	6.76 ( $\pm$ 4.36)	4.66 ( $\pm$ 2.67)	2.52 ( $\pm$ 2.75)	10.89 ( $\pm$ 12.16)
Invasive lobular carcinoma	1.26 ( $\pm$ 1.13)	.93 ( $\pm$ .80)	3.1 ( $\pm$ 5.16)	4.34 ( $\pm$ 7.23)
Lymphoma	8.8	6.1	1.78	10.8

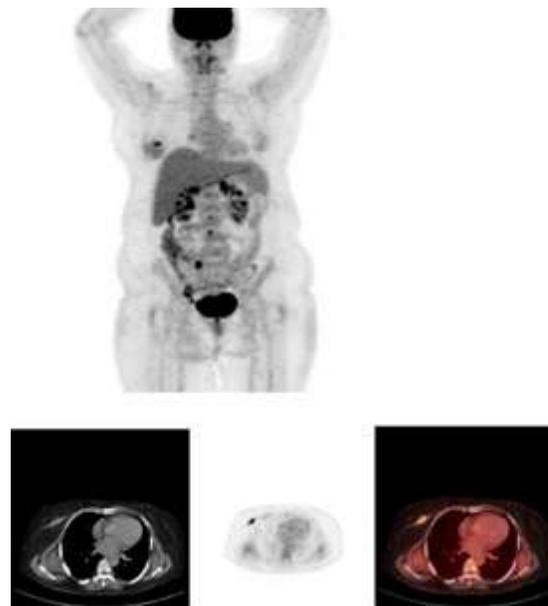
\*SUV= Maximum Uptake Value

\*\*MTV=Metabolic Tumor Volume

\*\*\*TLG=Total Lesion Glycolysis



**Figure 1.** Invasive ductal carcinoma incidentally detected in a 66 Y/O women with endometrial cancer being work up for subsequent treatment strategy. MIP (a), PET, NECT and fused PET/CT in axial view (b-d) demonstrated a small focus of intense F-18 FDG uptake corresponding with a small sized irregular isodense nodule in left breast.



**Figure 2.** Fibroadenoma incidentally detected in a 68 Y/O women with ovarian cancer being work up for subsequent treatment strategy. MIP (a), PET, NECT and fused PET/CT in axial view (b-d) demonstrated focal intense F-18 FDG uptake corresponding with a calcified irregular isodense soft tissue density in right breast.

56 lesions were identified to have breast incidental lesions (48 female (94.1%), 3 male (5.9%), mean age:  $49.18 \pm 14.31$ , age range: 17-71 years old). The prevalence of the underlying cancers were as the following: Lymphoma (HD and NHL): 15 (29.4%), Genitourinary: 15 (29.5%), GI (esophageal, gastric

and colon cancer) 9 (17.7%), lung cancer 5 (9.8%), head and neck cancer 2 (3.9%), osteosarcoma 1 (1.9%), chondrosarcoma 1 (1.9%), non-melanoma skin tumor 1 (1.9%), plasmacytoma 1 (2%) and papillary thyroid carcinoma 1 (2%).

Of a total 56 lesions, 47 (83.92%) in 41 patients

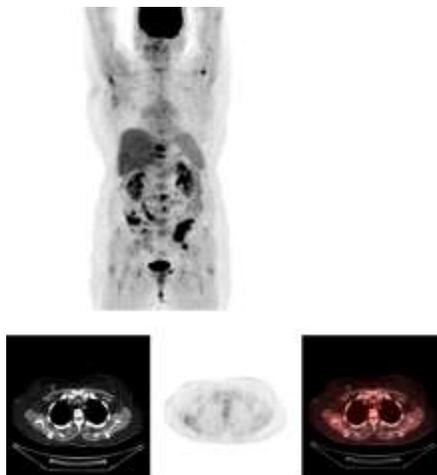


Figure 3. Invasive lobular carcinoma incidentally detected in a 57 Y/O women with colon cancer being work up for subsequent treatment strategy. MIP (a), PET, NECT and fused PET/CT in axial view (b-d) demonstrated a partially calcified irregular mass in right breast with no discernible metabolic activity.

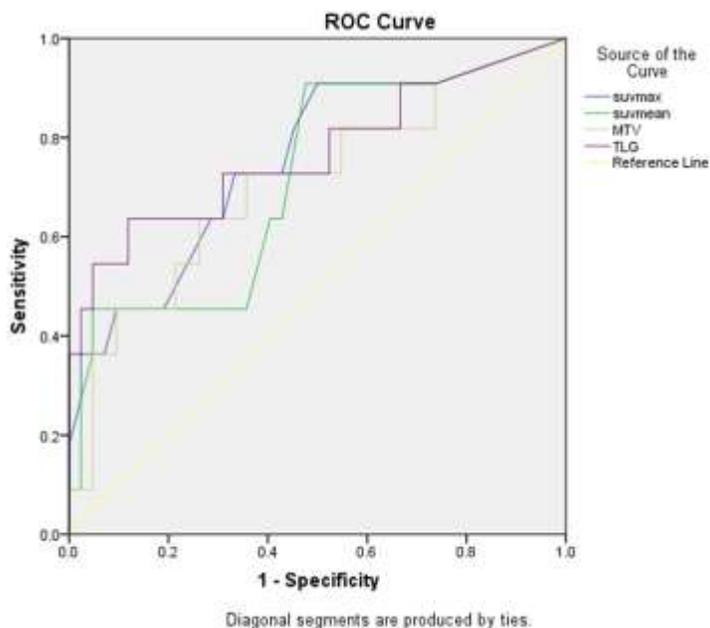


Figure 4. ROC curves for PET-metabolic parameters for the detection of malignant lesion in patients breast incidental lesions at 18F FDG PET/CT.

ultimately proved to be of benign origin, 12 (25.53%) by histopathologic confirmation (fibrocystic change [n=5], fibroadenoma [n=4], intraductal papilloma [n=3]) and 36 (74.46%) by a mean duration of 24.18 month clinical formal follow up. Among 10 histologically-verified malignant lesions (19.6%), 3 subtypes were classified: invasive ductal carcinoma (n=6), invasive lobular carcinoma (n=3) and lymphoma (n=1).

There was no statistically significant difference between benign and malignant groups regarding mean age (49.25 years old [17-77] vs 48.88 years old [30-66], p=0.9) and gender (benign lesions: 39 female [95.12%] vs 2 male [4.78%], malignant lesion: female 9 [90%], male 1 [10%], p=0.53). Genitourinary malignancies constituted the vast majority of primary cancers in the malignant group (n=6/9, 60%) which was more prevalent compared to the benign cohort

(9/41, 21.95%) though not statistically significant ( $p=0.10$ ).

CT corresponding features showed significant difference between study groups. Nodule was demonstrated as the unique associated morphological abnormality of malignant lesions which was significantly more prevalent compared to benign group (60.5%) ( $p=0.04$ ). There was a trend toward a greater mean diameter of malignant nodules, however, the difference did not approach a statistical significance (14.37 vs. 19.61 mm,  $p=0.060$ ). Other structural abnormalities in benign group were ill-defined soft tissue density ( $n=12$ , 31.6%) and skin thickening ( $n=3$ , 7.9%).

Regarding the anatomic location, most benign and malignant lesions were found in UUQ (61.5% vs. 80%), followed by UIQ (20.5% vs. 10%), LOQ (5.1% vs. 10%) and LIQ (12.8% vs. 0), respectively. The laterality distribution pattern was found to be as the following: 25 (49%) on the right, 21 (41.17%) on the left and 5 (9.8%) bilateral. Most malignant lesions were found in right breast (70% vs 30%) while benign lesions showed equal distribution between right and left side (right side:  $n=18$  [43.3%], left side:  $n=18$  [43.3%]).

In the context of metabolic criteria, the intensity pattern of FDG uptake significantly differed between benign and malignant groups ( $P=0.000$ ). Two out of 41 benign lesions (4.8%) vs. 6 out of 10 (60%) malignant lesions demonstrated severe FDG uptake, the difference of which proved to be statistically significant ( $p=0.000$ ). Sizable lesions ( $>7$ mm) with no discernible metabolic activity were found in 11 benign lesions (26.8%) and 1 pathologically-diagnosed malignant lesion (10%).

Focal pattern of FDG uptake was found in 28/41 (75.7%) of benign lesions and 10/10 (100%) of malignant lesions ( $p$  value=0.05).

On the basis of histologic subtypes, metabolic characteristics of invasive ductal carcinoma (Figure 1) and 3 histologically-proven fibroadenoma (Figure 2) did not show significant differences ( $p$  value for intensity of  $^{18}\text{F}$  FDG uptake, SUVmax were 0.1 and 0.42, respectively). In addition, no significant difference was found between metabolic features of invasive lobular carcinoma (Figure 3) and not otherwise specified benign lesions ( $p$  value for

intensity uptake and SUVmax were 0.1 and 0.91, respectively).

All PET metabolic parameters including SUVmax, SUVmean, MTV and TLG demonstrated statistically significant difference between benign and malignant groups Table 1 summarized metabolic characteristics of breast incidental lesion in benign and malignant groups as well as on a per histologic types. There was no statistically significant difference between metabolic parameters of invasive ductal carcinoma and fibroadenoma ( $p$  value for SUVmax, SUVmean, MTV and TLG were 0.52, 0.40, 0.46, 0.25, respectively). In addition, no significant difference was found between invasive lobular carcinoma and benign lesions other than fibroadenoma ( $p$  value for SUVmax, SUVmean, MTV and TLG were 0.91, 0.75, 0.75, 0.79, respectively). Figure 4 demonstrated the area under the ROC curve as 0.78 ( $p=.003$ ) for SUVmax, 0.75 ( $p=.006$ ) for SUVmean, 0.75 ( $p=.005$ ) for MTV and 0.8 ( $p=.001$ ) for TLG. The sensitivity and specificity for detection of malignant lesion using SUVmax of 2 were 77% and 62.5%, SUVmean of 1.35 were 92% and 52.5%, MTV of 1.16 were 77 and 75% and TLG of 1.75 were 77 and 67%, respectively.

## Discussion

Current study revealed that PET-derivative metabolic parameters showed significantly higher values in the malignant lesion compared to benign ones, though the diagnostic performance seemed to be modest. Most researches have focused on the prognostic implications of PET metabolic parameters<sup>9-13</sup> but evidence on their diagnostic performance, particularly of volumetric measures including MTV and TLG for detection of malignancy is scarce. The results of one study<sup>4</sup> demonstrated that in mediastinal tumor SUVmax=4.2 has a sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 78.2%, 86.2%, 82.6%, 81.8% and of 83.3% to identify malignancy, respectively. Volumetric metabolic parameters showed a better performance since MTV of 22.3 and TLG of 79.9 revealed sensitivity, specificity, accuracy, positive predictive value and negative predictive value of 82.6%, 96.6%, 90.4%, 95%, and 87.5%, respectively to distinguish benign from malignant mediastinal tumor. In this study, metabolic parameters of thymic

carcinoma demonstrated significantly higher values in comparison with thymoma and hence it was concluded that PET-derivative metabolic parameters may be considered as an accurate predictor of malignancy in mediastinal tumor. In another study on adrenal incidentaloma<sup>3</sup> malignant lesions demonstrated significantly higher values of metabolic parameters when compared to benign lesions. Using a cutoff of 12, TLG showed a sensitivity and specificity of 92.1% and 78.6%, respectively. The author concluded that TLG may be a reliable indicator of malignancy in adrenal incidentaloma. One study demonstrated that mean SUVmax, SUVmean and TLG of malignant ovarian masses are significantly higher than benign lesions (7.55 and 4.17,  $p < 0.001$ , 4.5 and 2.5,  $p < 0.001$ , 302.196 and 130.458,  $p = 0.035$ ) and hence, concluded that metabolic indices at 18F FDG PET/CT in association with visual interpretation criteria may be useful to detect malignant ovarian lesion<sup>5</sup>. However, in an attempted to differentiate borderline ovarian tumors and stage 1 malignant ovarian tumor<sup>14</sup>, one study suggested that cystic portion of malignant ovarian tumor may negatively influence on the ability of volumetric measures, including MTV and TLG to predict malignancy and recommended that mean SUVmax should be considered as the most reliable discriminator of malignancy in this clinical setting ( $2.9 \pm 1.5$  vs.  $6.6 \pm 2.9$ ,  $p = 0.02$ ) with a high sensitivity and specificity (using a cutoff of 3.7, 83.3% and 85.7%, respectively). On the contrary, researches on diagnostic performance of SUVmax to differentiate benign and malignant breast incidental lesion was discouraging. A recent study on 60 patients with breast incidentaloma revealed that using a cutoff of 2.3, SUVmax had a sensitivity and specificity of 61.3% and 76.3%, respectively to identify malignant lesion<sup>6</sup>. In another study of 48 patients, including 62.5% benign lesions and 37.5% malignant lesions, the optimal cutoff for SUVmax was found to be 2<sup>7</sup>. One research on 91 breast incidental lesions (70.3% benign and 29.7% malignant lesions) demonstrated a significant difference in median SUVmax of benign and malignant lesions, but with a significant overlap in the range of SUVmax between benign and malignant groups (1.3-16 vs. 1-5.7, respectively) and hence concluded that SUVmax should not be

considered as a reliable index to differentiate benign from malignant breast incidentaloma<sup>8</sup>. In one research SUVmax between benign and malignant lesions showed a borderline significant difference (0.054)<sup>1</sup>. In line with literature, the results obtained in the current study showed a significant difference in all PET-derivative metabolic parameters between benign and malignant lesions; however, the overall diagnostic performance was suboptimal. This can be explained by the distinct metabolic characteristics of fibroadenoma which may demonstrate a high level of metabolic activity and consequently mimic invasive ductal carcinoma. Regarding low cellular density and infiltrative growth pattern, invasive lobular carcinoma may be considered as a potential source of false negative and relatively low sensitivity of PET/CT to evaluate breast incidental lesion. Such finding are compatible with the results of previous studies, which demonstrated a significant overlap between metabolic characteristics of benign and malignant breast diseases<sup>15,16</sup>.

There are some drawbacks in the present study. Histopathologic confirmation was not available for all breast incidental lesions. Sonographic/mammographic assessment of breast incidentaloma was performed outside the clinic. Small sized cohort preclude precise characterization of metabolic features in each histological subtype.

## Conclusion

PET-derivative metabolic parameters showed significantly higher value in malignant lesion compared to benign disease, however, due to the distinct metabolic features of invasive lobular carcinoma and fibroadenoma, as the major potential sources of falsely negative malignant lesion and falsely positive, benign ones at 18 F FDG PET/CT, metabolic measures do not serve as a reliable indicator for risk stratification of breast incidental lesion.

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