International Surgery Journal
*Saricam M. Int Surg J. 2020 Mar;7(3):764-769*
http://www.ijsurgery.com
pISSN 2349-3305 | eISSN 2349-2902

DOI: http://dx.doi.org/10.18203/2349-2902.isj20200819

**Original Research Article**

# F-18 fluorodeoxyglucose positron emission computed tomography in the diagnosis of pleural metastases from breast carcinoma

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**Received:** 28 December 2019
**Accepted:** 10 February 2020

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## ABSTRACT

**Background:** This study aimed to investigate the feasibility of F-18 fluorodeoxyglucose (FDG) positron emission computed tomography (PET/CT) in identifying the pleural invasion of metastatic breast cancers.
**Methods:** A retrospective study was conducted to include 75 patients with untreated breast cancer who had undergone thoracoscopy to drain pleural effusions and to perform pleural biopsies. Whole group of patients were evaluated in terms of age, type of primary breast cancer, macroscopic appearance of pleura during thoracoscopy, maximum standardized FDG uptake value (SUV) reported by PET/CT scan in addition to presence of malignancy detected in pleura and/or pleural effusion.
**Results:** All of 75 patients were female and mean age was 56.12±11.70. Metastatic disease was diagnosed in the pleura of 40 (53.3%) and in the pleural effusion of 43 (57.3%) patients. The sensitivity and specificity of PET/CT in detecting pleural metastases of breast carcinoma was calculated as 88.2% and 96.2% whereas PET/CT demonstrated sensitivity of 91.9% and specificity of 91.3% in identifying malignant pleural effusion. Cut-off values of FDG uptake were 4.25 for pleural metastases and 3.85 for malignant pleural effusions. PET/CT also indicated a false negative rate of 12.5%, a false positive rate of 16.28% and an overall accuracy rate of 85.33% in the diagnosis of pleural metastasis of breast carcinoma.
**Conclusions:** PET/CT reporting an FDG uptake over 4 in the pleura or pleural effusion is beneficial in managing the patients with the suspicion of pleural metastases from breast cancer.

**Keywords:** Breast cancer, Diagnosis, Pleural metastases, PET/CT

## INTRODUCTION

Breast cancer is the most frequently diagnosed malignancy and the leading cause of cancer-related deaths in women.[1-5] It is also of capital importance for physicians considering that distant organ dissemination may be present at the time of diagnosis and even the early-stage disease is predisposed to develop metastases.[2,6]

Surgical resection of primary tumor is the principal practice of treatment for non-metastasizing breast cancers whereas locally advanced disease and distant metastases necessitate chemotherapy, hormonal therapy or radiotherapy following evaluation on a case-by-case basis.[7,8]

Pleural metastasis of breast cancer mostly present as pleural nodularity or thickening frequently with an accompanying malignant pleural effusion.[3,4] Median survival is regarded as 15 months at most following the accumulation of pleural effusion secondary to breast cancer metastasis.[6] As in any other malignancies, a newly diagnosed breast cancer indicates appropriate staging to constitute an accurate treatment algorithm. This study aimed to reveal the efficiency of PET/CT in exposing the pleural invasion of metastatic breast cancers.

## METHODS

Following the approval of Medical Faculty's Ethic Committee, a retrospective study was conducted to investigate 75 patients with untreated breast cancer who had undergone thoracoscopy with intent to drain pleural effusions between 2010 and 2018.

Final diagnosis of a breast carcinoma was established via fine needle aspiration cytology or surgical biopsy and all of the patients presented pleural effusion involving one-third of the affected hemithorax at least and had PET/CT scan in the course of initial admission. Cases with unclear postoperative pathology reports following thoracoscopy and biopsies concluding with non-malignant diseases such as tuberculosis, pleuritis or sarcoidosis were excluded from the study.

All the patients underwent two-port thoracoscopy under general anesthesia. Pleural effusions were completely discharged. Pleural sampling was performed by conducting multiple biopsies from both regions with macroscopically healthy and diseased appearance. Thereafter, all the specimens were examined via cytologic and microbiologic studies.

Whole group of patients were evaluated in terms of age, type of primary breast cancer, macroscopic appearance of pleura during thoracoscopy, maximum standardized fluorodeoxyglucose (FDG) uptake value identified by PET/CT scan in addition to presence of malignancy detected in pleura and/or pleural effusion.

### *Statistical analysis*

In calculating the sample width of this study, power (the test of power) was determined by taking at least 0.80 and type 1 error 0.05. Descriptive statistics for continuous variables in the study were expressed as mean, standard deviation, minimum and maximum; categorical variables were expressed as number (n) and percentage (%). After checking that this data was normally distributed via Shapiro-Wilk and Skewness-Kurtosis tests, parametric tests were applied.

Independent t-test or one-way analysis of variance (ANOVA) were used to compare average of measurements and Pearson correlation parameters were calculated to determine the relation between the measurements. Sensitivity, specificity and cut-off values were calculated via ROC analysis. Chi-square test was employed to reveal the relation between categorical variables. The statistical significance level (α) was taken as 5% and SPSS (IBM SPSS for Windows, ver.24) statistical package program was used for calculations.

## RESULTS

Whole group of 75 patients were female and mean age was 56.12±11.70 (range=29-79) years. The majority of primary breast cancer was invasive ductal carcinoma (70.7%). PET/CT scan did not report a pathological appearance of the pleura in 28 (37.3%) patients while nodularity was observed in 31 (41.3%) cases. Metastatic disease was diagnosed in the pleura of 40 (53.3%) and in the pleural effusion of 43 (57.3%) patients. PET/CT scan did not identify any FDG uptake in any location of thorax in 15 (20%) cases whereas mean FDG uptake value was reported as 4.63±1.74, ranging between 1.2 and 11.3 for the rest of 60 patients (Table 1).

**Table 1: Clinical and radiological features of the patients.**

| Parameters | Subgroups | N | % |
|---|---|---|---|
| **Type of breast cancer** | Invasive ductal carcinoma | 53 | 70.7 |
| | Invasive lobular carcinoma | 9 | 12 |
| | Triple-negative carcinoma | 7 | 9.3 |
| | Inflammatory carcinoma | 6 | 8 |
| **Appearance of pleura** | Normal | 28 | 37.3 |
| | Nodularity | 31 | 41.3 |
| | Diffuse thickening | 16 | 21.4 |
| **Malignancy in pleura** | Absent | 35 | 46.7 |
| | Present | 40 | 53.3 |
| **Malignancy in pleural effusion** | Absent | 32 | 42.7 |
| | Present | 43 | 57.3 |
| **Total** | | 75 | 100 |

In this series, statistical studies presented invasive ductal carcinoma as the most common type of breast cancer and also invasive lobular carcinoma as the most vulnerable to metastasize to pleura ($p<0.05$). All of the patients with invasive lobular carcinoma and positive pleural FDG uptakes in PET/CT developed malignant pleural effusion whereas metastases in pleura were diagnosed in 88.9% of the same patient group.

Analyzes did not reveal a statistically significant difference in type of primary breast cancer relating the ages of patients ($p>0.05$). On the other hand, different types of metastatic breast carcinomas developed dissimilar FDG uptakes in the pleura ($p<0.05$). Mean FDG uptake values were correlative for invasive lobular and inflammatory carcinomas and also for invasive ductal and triple-negative carcinomas (Table 2, Figure 1).

FDG uptake values demonstrated significant differences in all subgroups from the standpoint of pleural appearance ($p<0.05$) and highest uptake value was detected in the patients with pleural nodularity.

Analyzing the relation between values of FDG uptake and malignancy in the pleura and pleural effusion, a significant difference was observed ($p<0.05$). Patients with metastatic

disease in both pleura and pleural effusion had developed higher values of FDG uptake (Table 3).

**Table 2: Comparison of breast cancer types in terms of age and FDG uptake.**

| Parameters | Type of breast carcinoma | N | Mean | Std.Dev. | Min. | Max. | *P value |
|---|---|---|---|---|---|---|---|
| **Age** | Invasive ductal carcinoma | 53 | 55.83 | 12.22 | 29 | 79 | 0.886 |
| | Invasive lobular carcinoma | 9 | 58.67 | 9.73 | 46 | 78 | |
| | Triple-negative carcinoma | 7 | 54.29 | 11.38 | 34 | 68 | |
| | Inflammatory carcinoma | 6 | 57.00 | 12.03 | 35 | 66 | |
| | Total | 75 | 56.12 | 11.69 | 29 | 79 | |
| **FDG uptake value** | Invasive ductal carcinoma | 43 | 4.06 | 1.26 | 1.20 | 7.20 | 0.001 |
| | Invasive lobular carcinoma | 9 | 6.68 | 1.96 | 4.10 | 11.30 | |
| | Triple-negative carcinoma | 2 | 3.30 | 1.41 | 2.30 | 4.30 | |
| | Inflammatory carcinoma | 6 | 5.98 | 1.50 | 4.60 | 8.80 | |
| | Total | 60 | 4.62 | 1.73 | 1.20 | 11.30 | |

*ANOVA test, Std. dev: Standard deviation, Min: Minimum, Max: Maximum.

**Table 3: Relation of metastases in pleura and FDG uptake values.**

| | Variables | Parameters | N | Mean | Std.Dev. | Min. | Max. | P value |
|---|---|---|---|---|---|---|---|---|
| **FDG uptake** | Pleural Appearence | Normal | 19 | 3.05 | 0.66 | 1.20 | 3.80 | 0.001* |
| | | Nodularity | 25 | 5.96 | 1.59 | 3.90 | 11.30 | |
| | | Diffuse thickening | 16 | 4.40 | 1.05 | 2.30 | 6.80 | |
| | | Total | 60 | 4.62 | 1.73 | 1.20 | 11.30 | |
| | Malignancy in Pleura | Absent | 26 | 3.25 | 0.74 | 1.20 | 4.30 | 0.001** |
| | | Present | 34 | 5.67 | 1.54 | 3.70 | 11.30 | |
| | | Total | 60 | 4.62 | 1.73 | 1.20 | 11.30 | |
| | Malignancy in Pleural Effusion | Absent | 23 | 3.28 | 0.85 | 1.20 | 5.50 | 0.001** |
| | | Present | 37 | 5.45 | 1.62 | 2.30 | 11.30 | |
| | | Total | 60 | 4.62 | 1.73 | 1.20 | 11.30 | |

*ANOVA test, **Independent T-test, Std. dev: Standard deviation, Min: Minimum, Max: Maximum.

**Table 4: Correlation of macroscopic appearance of pleura and malignancies.**

| Appearance | | | P value* |
|---|---|---|---|
| **Malignancy in pleura** | | | |
| Appearance | Absent | Present | 0.001 |
| Normal (n/%) | 28/100 | 0/0 | |
| Nodularity (n/%) | 0/0 | 31/100 | |
| Diffuse thickening (n/%) | 7/43.8 | 9/56.3 | |
| Total | 35/46.7 | 40/53.3 | |
| **Malignancy in pleural effusion** | | | |
| Appearance | Absent | Present | 0.001 |
| Normal (n/%) | 28/100 | 0/0 | |
| Nodularity (n/%) | 0/0 | 31/100 | |
| Diffuse thickening (n/%) | 4/25% | 12/75 | |
| Total | 32/42.7 | 43/57.3 | |

*Chi-square test.

Likewise, abnormal pleural appearance demonstrated high incidence of malignancy in pleura ($p<0.05$). Particularly, nodular lesions of the pleura definitely pointed out the metastatic disease while a macroscopically healthy pleura beared no risk of malignancy (Table 4).

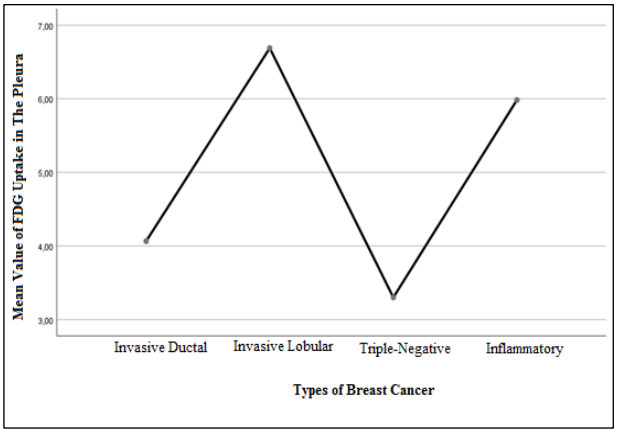


**Figure 1: FDG uptakes in the pleura in relation to types of breast carcinomas.**

The sensitivity and specificity of PET/CT in detecting pleural metastases of breast carcinoma was calculated as 88.2% and 96.2%, respectively. Moreover, as a diagnostic tool for malignant pleural effusion, PET/CT demonstrated sensitivity of 91.9% and specificity of 91.3%. Cut-off values of FDG uptake were 4.25 for pleural metastases and 3.85 for malignant pleural effusions (Table 5 and Figure 2).

**Table 5: Results of ROC analysis.**

| Value of FDG uptake | Area under curve | Standard error | P value | Cut-off value | Sensitivity | Specificity |
|---|---|---|---|---|---|---|
| **Malignancy in pleura** | 0.972 | 0.017 | 0.00 | 4.250 | 0.882 | 0.962 |
| **Malignancy in pleural effusion** | 0.932 | 0.037 | 0.00 | 3.850 | 0.919 | 0.913 |

As a diagnostic tool for pleural metastases, PET/CT presented a false negative rate of 12.5% and a false positive rate of 16.28%. Rates were calculated as 80% and 90% for positive and negative prediction, respectively. PET/CT also indicated an overall accuracy rate of 85.33% and confidence interval of 0.95%.

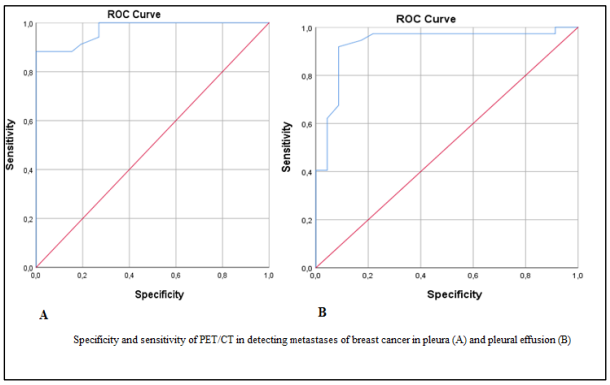


**Figure 2: Specificity and sensitivity of PET/CT in detecting pleural metastases of breast cancer.**

None of the patients suffered surgical complications while all the cases were discharged between 2 and 4 days following thoracoscopy.

## DISCUSSION

The findings of this study clearly show that PET/CT is a sensitive and a reliable imaging method for detecting pleural metastasis of breast carcinoma.

The patients with primary breast cancer present metastasis at the time of diagnosis at a rate as high as 10%. Moreover, up to 50% of the remaining group of cases will eventually develop metastatic disease which distinctly decreases the survival time and deteriorates the quality of life.[6-11]

The most common metastatic targets of breast cancer are lungs, bones and liver. Almost 60% of the patients with advanced breast cancer suffer lung and bone metastasis.[9, 12,13] Pleural metastasis from breast cancer may occur at the time of diagnosis or during the following few years and commonly present with remitting malignant pleural effusions.[14] Diagnosis of pleural metastasis is essential considering that the most common pleural malignancy is the metastatic involvement in which high incidence causative primary diseases are bronchogenic carcinoma, breast carcinoma and lymphoma.[15,16]

PET/CT scan is an efficient imaging method for initial staging, assessment of treatment response and evaluation of recurrence by quantitating FDG avidity of cancer with standardized uptake value. Limited by low sensitivity to detect breast cancers smaller than 1 cm and lobular carcinomas, PET/CT still has efficacy superior to convential imaging for the locoregional spread and distant metastasis.[15-18] Moreover, PET/CT is considered to be more valuable in diagnosing skeletal metastasis compared with bone scintigraphy and predicting recurrence.[18-24]

This study distinctly states that absence of FDG uptake in pleura or pleural effusion minimizes the risk of metastasis regarding that none of 15 patients with no avidity in PET/CT were diagnosed with a pleural malignancy.

Recent studies announced that PET/CT had demonstrated sensitivity ranging widely between 75% and 93%, also specificity between 88% and 96% in the identification of malignant pleural effusions.[20-22,25-29] This big difference may result from 60% mean sensitivity rate of pleural fluid cytology depending on the primary tumor, sample preparation and experience of the cytologist.[30] A review of 14 studies comprising 407 patients with malignant disease reported that PET/CT imaging had a sensitivity of 81% and specificity of 74% concluding that there was no basis for the inclusion of PET/CT in the diagnosis of malignant effusion.[31] However, PET/CT indicating sensitivity of 91.9% and specificity of 91.3% in defining malignant pleural effusions in this study was proven to be a reliable diagnostic tool.

Meta-analyses in the literature reported a sensitivity between 76% and 95%, also a specificity between 67% and 82% for PET/CT in the differentiation of malignant and benign pleural lesions.[32] Introducing the potential false-negative and false-positive findings, most of the studies advocated that PET/CT could be of use in evaluating prognosis and response to the treatment in addition to localizing the optimal site for pleural biopsy for potential malignancy rather than utilization in diagnostic objectives.[30-32] On the contrary, PET/CT with a sensitivity of 88.2% and specificity of 96.2% appears to be valuable in identifying pleural malignancies when compared with the rates in the recent papers.

Other findings of this study clarified the relation between the macroscopic appearance of the pleura in thoracoscopy and the existence of malignancy. All of the nodular pleural lesions were diagnosed with cancer whereas 56.3% of the patients with diffuse pleural thickening ended up as malignancy and visibly healthy pleura was completely reported as disease-free. Likewise, mean value of FDG uptake of the nodular lesions was significantly higher than diffuse thickening of the pleura. Unfortunately, recent literature does not contain any data to compare these findings.

Presenting 12.5% of false-negative and 16.28% of false-positive results with an overall accuracy rate of 85.33%, PET/CT provides dependable findings to guide physicians in the diagnosis of pleural metastases from breast cancer. Thoracoscopy is also a minimally invasive approach with low complication rates and significantly contributes to the diagnosis of malignancies.

The principal limitation of this study was the retrospective design conducted as a single-centered workup. Also, the study group included the patients who had suited to go under general anesthesia for thoracoscopy and also had developed sizeable amounts of pleural effusion. Larger cohorts of patients varying in types of breast cancer are required to confirm the results.

## CONCLUSION

PET/CT is beneficial in managing the patients with the suspicion of pleural metastases from breast cancer. Regarding that diagnosis of a metastatic disease will alter the whole treatment modality, cases who develop an FDG uptake over 4 in the pleura or pleural effusion shall be examined more closely.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: The study was approved by the Institutional Ethics Committee*

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**Cite this article as:** Saricam M. F-18 fluorodeoxyglucose positron emission computed tomography in the diagnosis of pleural metastases from breast carcinoma. Int Surg J 2020;7:764-9.