Original Article

Metachronous Second Primary Malignancies in Known Breast Cancer Patients on 18F-Fluoro-2-Deoxyglucose Positron Emission Tomography–Computerized Tomography in a Tertiary Care Center

Abstract

Introduction: Breast cancer is the most common malignancy among women all over the world, which accounts to 25% of all cancers. In known cases of breast cancer, the risk of developing another denovo malignancy is more when compared to low risk groups, which might be due to common environmental risk factors, treatment induced risk factors, Genetic susceptibility for mutations, presence of cancer syndromes or better detection due to close surveillance. **Objective:** To study the profile of Metachronous 2nd primary malignancies suspected on 18F-FDG PET CT in known Breast cancer patients. In this Retrospective study from January 2014 to April 2018, all the consecutive patients with known Breast cancer, who were referred to Nuclear Medicine department for 18F- FDG PET CT for follow up evaluation were included. Suspected 2nd primary malignancies were correlated with Histopathological examination (HPE). **Results:** During the study period, a total of 233 Breast cancer patients (all are females), with a mean age of 54.2+13.4 years were studied. On 18F-FDG PET CT scan, suspicion for 2nd primary malignancy was observed in 37 patients. HPE was done in 28/37 patients at the site of suspected lesions. 15/28 were positive for second malignancy, and remaining 13/28 were either a benign pathology or a part of metastatic disease from the primary breast cancer. The sites of 2nd primary malignancies included Contralateral breast in 8/15 (53.3%), Ovary in 2/15 (13.3%), Endometrium in 2/15 (13.3%), Lung in 1/15 (6.6%), Stomach in 1/15 (6.6%) and Urinary bladder in 1/15 (6.6%) patients respectively. The incidence of metachronous 2nd primaries in breast cancer is 67.3 per 1000 breast cancer patients. **Conclusion:** Metachronous second primary cancers in breast cancer patients are not very rare. A high imaging suspicion on 18F-FDG PET CT helps in early detection of 2nd primary cancer, thereby facilitating early and appropriate management.

Keywords: *Breast cancer, fluoro-2-deoxyglucose positron emission tomography–computerized tomography, metachronous primary*

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Introduction

Breast cancer is the most common malignancy among women all over the world, accounting for 25% of all cancers.[1] Owing to increased awareness, early diagnosis, and prompt treatment, very good survival is seen in breast cancer patients nowadays. As a result, the probability of developing and detecting a second primary cancer has also increased.[2-4]

A second primary cancer can be either synchronous or metachronous. Synchronous primaries are cancers occurring at the same time or within 6 months of diagnosis of first primary cancer. Metachronous primaries are cancers developing after 6 months of diagnosis of the first primary.[5,6]

According to Warren and Gates criteria, the diagnosis of a second primary malignancy (SPM) should satisfy the following criteria: (a) each tumor should present a definite picture of malignancy, (b) each tumor should be histologically distinct, and (c) the possibility of one being the metastasis of the other must be excluded.[7]

As per the published data on SPMs, one of the most common cancers associated with second primaries is breast cancer.[8-10] Hence, it is worth studying the profile and characteristics of SPMs in breast cancers. In known cases of breast cancer, the risk of developing another *de novo* malignancy was reported to be 1%–18% according to the published literature.[11] High-risk groups for the occurrence of second primaries are those with a positive

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family history, presence of mutations (BRCA1, BRCA2, PTEN, and TP53), and elderly women.[5,6]

Factors affecting the development of an SPM may include common environmental risk factors, treatment-related risk factors, genetic susceptibility for mutations, presence of cancer syndromes (Cowden syndrome, Li–Fraumeni syndrome, and hereditary breast and ovarian cancer syndrome), and better detection due to close surveillance.[5,6]

Objective

The objective was to study the role of 18F-fluoro-2-deoxyglucose (FDG) positron emission tomography–computerized tomography (PET-CT) in the detection of metachronous SPMs and determination of the incidence of metachronous SPMs in known breast cancer patients.

Materials and Methods

In this retrospective study, all the consecutive patients with histologically proven breast cancer, referred for 18F-FDG PET-CT from January 2014 to April 2018, were included. Various recorded details such as age, sex, age at diagnosis of each tumor, whether synchronous/metachronous, site of origin, histopathology, clinical stage at detection, clinical course, treatment given, and disease-free survival were retrieved and analyzed.

18F-fluoro-2-deoxyglucose positron emission tomography–computerized tomography scan

All patients were injected 259–370 MBq (8–10 mCi, 0.14–0.20 mCi/kg) of 18F-FDG intravenously. 18F-FDG PET-CT whole-body scans were performed from skull to mid-thigh, 60 min after 18F-FDG injection using Biograph-6, LSO, PET-CT scanner by SIEMENS. In cases of ambiguity, a delayed scan involving the suspected primary site was performed approximately 120 min (at 2 h) after 18F-FDG injection. Images were analyzed and interpreted qualitatively and semiquantitatively by means of maximum standardized uptake value (SUV).

Histopathological examination correlation

All the cases suspected for SPMs on 18F-FDG PET/CT were followed up and correlated with histopathological examination (HPE) reports, and the profile of metachronous SPMs was studied. The time interval to differentiate between synchronous and metachronous was taken as 6 months as reported by several authors.[9,12-17]

In case of synchronous bilateral breast cancer, disparity in receptor status without any demonstrable metastatic disease was considered. In case of metachronous contralateral breast cancer, a time gap of 5 years and/or disparity in receptor status without any demonstrable metastatic disease was considered.[9]

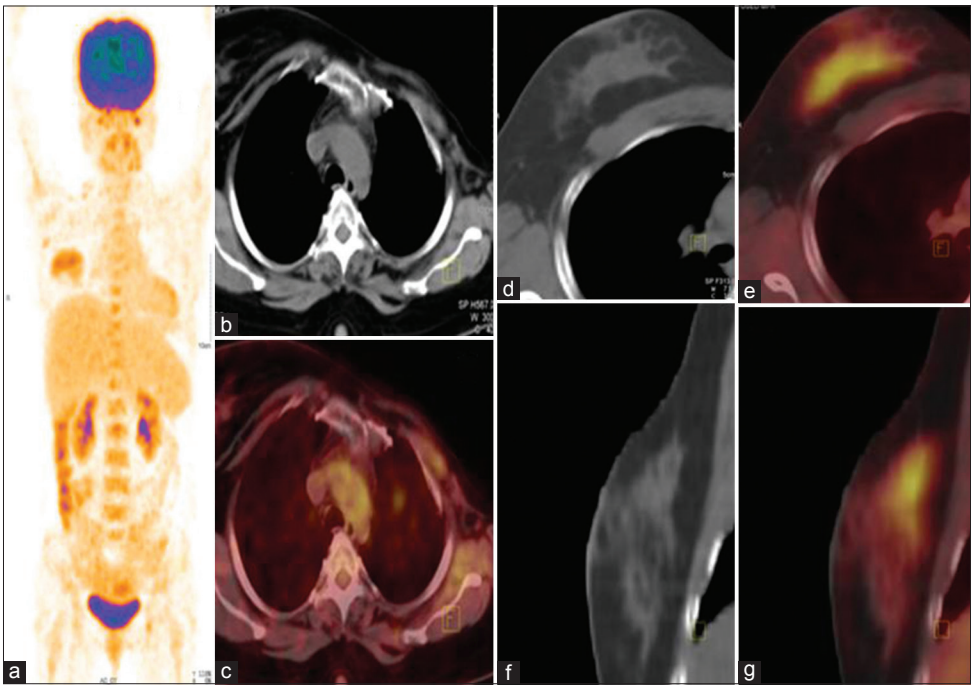

Figure 1: Representative case for true-positive 1: A 39-year-old female, a known case of carcinoma left breast (ER and PR positive, and Her-2neu negative), postneoadjuvant chemotherapy, left modified radical mastectomy, and four cycles of chemotherapy with AC regimen, on regular follow-up, was diagnosed with a metabolically active soft-tissue density lesion in the right breast. (a) MIP image, (b-g) computerized tomography and positron emission tomography–computerized tomography-fused images of the right breast. Positron emission tomography–computerized tomography-based ultrasound-guided biopsy was taken from the lesion, which came out to be infiltrating duct cell carcinoma (triple-positive)

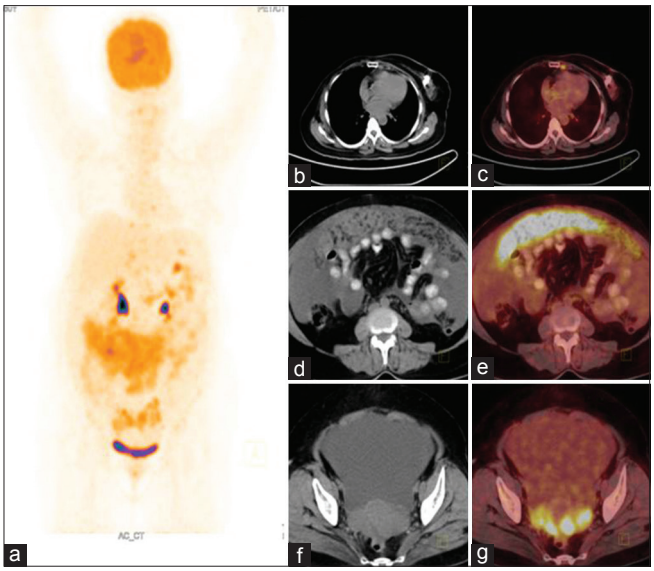

Figure 2: Representative case for true-positive 2: A 46-year-old female, a known case of carcinoma right breast, posttherapy, presented with ascites and abdominal pain. On 18F-fluoro-2-deoxyglucose positron emission tomography–computerized tomography, it was diagnosed with metabolically active ascites and metabolically active ascites with multiple peritoneal deposits and metabolically active bilateral ovaries. CA125 was done, found to be elevated. Exploratory laparotomy was done. Postoperative histopathological examination was reported as serous cystadenocarcinoma in bilateral ovaries. (a) MIP image, (b-g) computerized tomography and positron emission tomography–computerized tomography-fused images

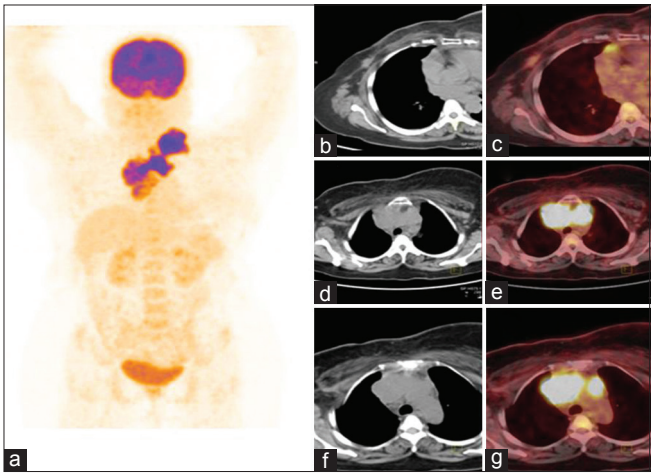

Figure 4: Representative case for false-positive 2: A 42-year-old female, a known case of carcinoma right breast, postbreast conservation surgery, on regular follow-up, was diagnosed with a large irregular metabolically active soft-tissue density mass lesion in anterior mediastinum. On 18F-fluoro-2-deoxyglucose positron emission tomography–computerized tomography, we suspected a metachronous second primary in the thymus, measuring 14.2 × 7.9 cm with maximum standardized uptake value of 14.3. computerized tomography-guided biopsy was taken from the lesion, which came out to be benign thymoma. (a) MIP image, (b-g) computerized tomography and positron emission tomography–computerized tomography-fused images

Results

A total of 223 female patients with breast cancer, with a mean age of 45.3 ± 15.4 years, were included in the study. 37/223 (16.5%) cases were suspected with

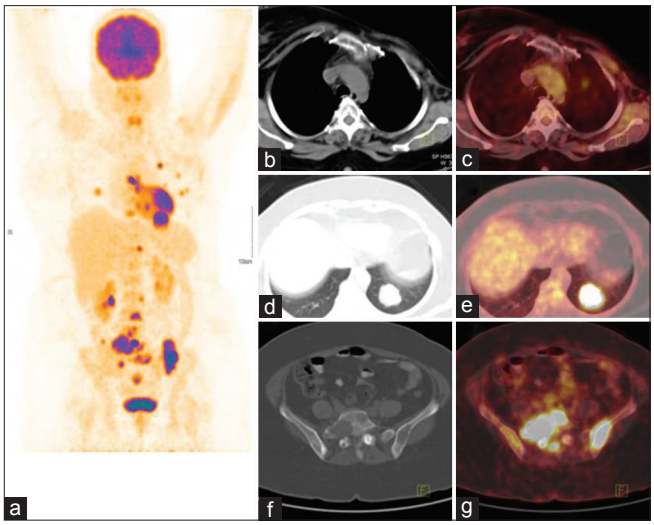

Figure 3: Representative case for false-positive 1: A 51-year-old female, who is a known case of carcinoma left breast post therapy, presented with low back ache. On 18F-fluoro-2-deoxyglucose positron emission tomography–computerized tomography, there was a well-defined metabolically active soft-tissue density lesion in left lung lower lobe, along with multiple lytic metabolically active skeletal metastases. In view of chronology and exclusively lytic lesions, suspected to be a metachronous primary. Computerized tomography-guided biopsy was reported to be Her-2 neu positive metastatic breast carcinoma. (a) MIP image, (b-g) computerized tomography and positron emission tomography–computerized tomography-fused images

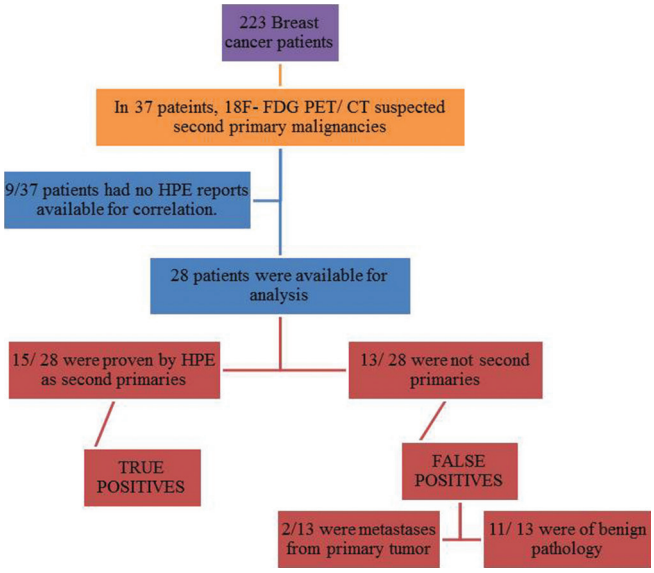

Chart 1: Study analysis

metachronous second primaries on 18F-FDG PET-CT. Of the 37 suspected cases, only 28 (75.6%) had HPE available for correlation and the remaining 9 (24.3%) had no HPE report available for correlation. Of the 28 cases with HPE reports, 15 (53.6%) were proven as metachronous second primaries and the remaining 13 (46.4%) were either a part of metastatic disease or a benign pathology [Chart 1 and Table 1].

On correlation of 18F-FDG PET-CT-suspected lesions with HPE reports (n = 28), 15/28 were positive for metachronous

Table 1: 18F-fluoro-2-deoxyglucose positron emission tomography–computerized tomography suspected second primaries are tabulated (*n*=37). HPE: Histopathological examination

Site	No. of suspected 2nd primaries	No. of lesions for which HPE available for analysis
Thyroid	11	6
Contralateral breast	9	9
Endometrium	5	3
Lung	4	3
Ovary	4	3
Stomach	1	1
Bladder	1	1
Nasopharynx	1	1
Thymus	1	1

Table 2: Histopathological examination correlation analysis of suspected second primaries on 18F-fluoro-2-deoxyglucose positron emission tomography– computerized tomography. HPE: Histopathological examination

HPE proven suspected 2nd primary lesions (*n*=28)	HPE positive for 2nd primary (*n*=15)	HPE negative for 2nd primary (*n*=13)
Contralateral breast (9)	8	1
Thyroid (6)	0	6
Ovary (3)	2	1
Endometrium (3)	2	1
Lung (3)	1	2
Stomach (1)	1	0
Bladder (1)	1	0
Nasopharynx (1)	0	1
Thymus (1)	0	1

second primary that included 8/9 in contralateral breast, 2/3 in ovaries, 2/3 in endometrium, 1/3 in lung, 1/1 in stomach, and 1/1 in urinary bladder [Table 2].

In rest of 13 patients, two patients (15.4%), both from lung, showed metastasis from the first primary, whereas remaining 11 patients were found to be of benign pathology. Of the 11 benign diseases, 6/11 were in the thyroid comprising thyroiditis (2/6) and benign adenomatous goiter (4/6), 1/11 each in contralateral breast, ovary, endometrium, nasopharynx, and thymus [Table 3].

On studying the profile of metachronous SPMs in breast cancer patients, the most common site for the second primary was obtained in contralateral breast (53%), followed by ovary (13%) and endometrium (13%) [Chart 2].

In our study, the true-positive rate was 53.6% (15/28) and false-positive rate was 46.4% (13/28). The false-positive rate was the highest for the lesions suspected in thyroid (6 of 13,

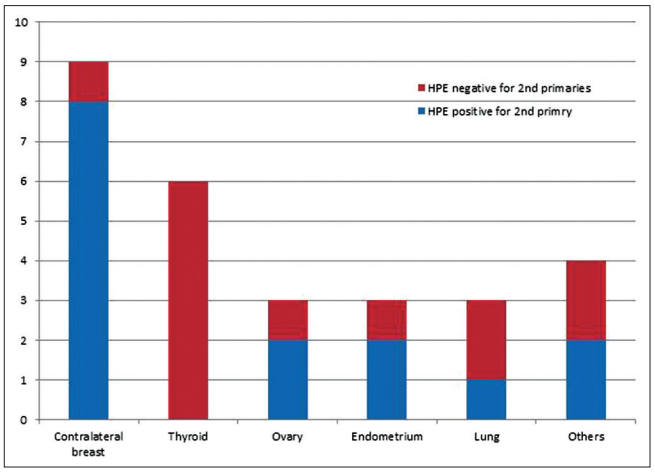

Chart 2: Histogram showing different sites of metachronous primaries suspected using 18F-fluoro-2-deoxyglucose positron emission tomography–computerized tomography

46.2%), followed by lung (2/13, 15.4%). The true-positive and false-positive results are represented as bar diagram [Chart 3]. The incidence of metachronous second primaries in breast cancer was found to be 67.3/1000 breast cancer patients. PET CT images of some representative cases for true positive, true negative, false positive, false negative cases are shown here [Figures 1-4].

Discussion

18F-FDG is a structural analog of glucose, which enters the cells through the glucose transporters. It is then converted to 18F-FDG 6-phosphate by hexokinase and is metabolically trapped within the cell. It is a nonspecific tumor tracer, the localization of which is based on metabolic activity.[18]

In a study done by Korczynska *et al*., on metachronous primaries in breast cancers, they found the most common second primary in breast cancer patients on follow-up to be contralateral breast cancer, with an incidence of 51.1%. The second and third most common metachronous primaries were found to be endometrium (7.9%) followed by the ovary (7.6%).[19] This strongly correlated with our study, where we got the most common second primary as contralateral breast cancer with an incidence of 53%, followed by endometrium and ovary, each with 13% incidence.

In a study done by Xion *et al*., they found that younger patients have a high risk of developing contralateral breast cancer, and the risk decreases after attaining 40 years of age. Furthermore, they reported that BRCA1 and BRCA2 mutations are also found more in younger patients.[20] These results correlated strongly with our study as the mean age of patients presented with contralateral breast cancer was 40.2 ± 2.8 years in our study.

In our study, the most common second primary was in the contralateral breast and the ovary. Here, it is worth noting that hereditary breast and ovarian cancer syndrome is a high-penetrance, autosomal-dominant breast and ovarian cancer predisposition caused by germline mutations in

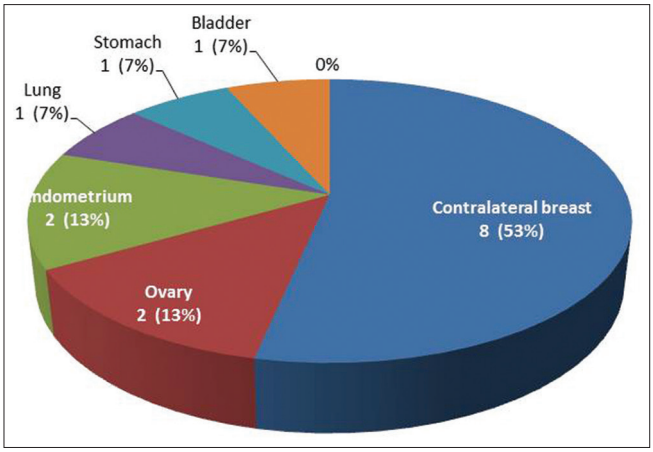

Chart 3: The profile of histopathological examination-proven metachronous second primary malignancies in breast cancer patients

Table 3: Histopathological examination-proven cases negative for metachronous second primaries

Suspected 2nd primary	Metastatic breast cancer	Benign pathology
Thyroid (6)	0	6 Thyroiditis (2)
Lung (2)	2 (Metastases from primary)	Adenomatous goitre(4)
Ovary (1)	0	0
Endometrium (1)	0	1 (Endometriosis)
Contralateral breast (1)	0	1 (Endometrial hyperplasia)
Nasopharynx (1)	0	1 (Fibrocystic Disease)
Thymus (1)	0	1 (Non specific inflammation)
Nasopharynx (1)	0	1 (Benign Thymoma)
Thymus (1)	0	1

the genes BRCA1 and BRCA2, resulting in synchronous bilateral breast cancers, metachronous contralateral breast cancers, and ovarian cancers.[21]

A second primary can be suspected if any of the following is present:

a. Atypical metastatic spread of primary tumor[22]
b. High tumor burden relative to tumor marker load
c. New metastatic spread (e.g., liver and lung) several years after a primary cancer diagnosis
d. Single new metastatic lesion after a primary cancer diagnosis (e.g., single pulmonary nodule in a patient with otherwise complete response or remission)
e. Chronological atypical metastatic spread (e.g., relapse 5 years after remission)
f. Recurrence in patients with exposure to environmental carcinogens (e.g., smoking)
g. Suspicion of hematological malignancy after prior chemotherapy (e.g., etoposide, anthracyclines)
h. Suspicion of secondary malignancy in patients with prior radiation for malignancy and especially if recurrence in prior radiation field
i. Suspicious lesion on imaging (e.g., PET-CT) detected at staging or in follow-up
j. Differential SUV of suspected lesions on PET-CT (e.g., lesions with very high SUV and lesions with low SUV).[21]

If a metachronous SPM is suspected, a histological confirmation should be pursued if the patient is considered for active treatment.[21]

The presence of new metabolically active lesion in an unusual site, or a solitary large lesion in an otherwise responded case, or a focal FDG uptake, should rise the suspicion of second primary. In our study, the false-positive rates are high in lesions suspected in thyroid nodules (6/28), which represent that benign adenomatous goiters and inflammation may cause more concentration of FDG.

Conclusion

Metachronous second primary cancers in breast cancer patients are not very rare. As 18F-FDG is a nonspecific tumor tracer, any new metabolically active lesion in an unlikely site on follow-up 18F-FDG PET-CT should be suspected for a second primary, especially in the contralateral breast. A high imaging suspicion on 18F-FDG PET-CT helps in early detection of second primary cancers, thereby facilitating early and appropriate management.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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