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Diagnostic and prognostic value of ^{18}F-FDG PET/CT imaging in suspected recurrence of male breast cancer

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Purpose **Male breast cancer (MBC) is a rare malignancy, with recurrence being one of the main adverse predictors for prognosis. The aim of the study was to evaluate the diagnostic and predictive value of fluorine-18-fluorodeoxyglucose (^{18}F-FDG) PET/CT in the setting of suspected recurrence of MBC.**

Patients and methods **Retrospective analysis of PET/CT findings was performed in 23 previously treated, histologically proven patients with MBC (mean age: 59.3 ± 10.9 years; range: 36–79 years) with suspected recurrence. Kaplan–Meier disease-specific survival analysis was made with respect to histological, hormonal profile as well as PET/CT findings.**

Results **Of the 23 patients, 19 (82.6%) showed recurrence. Recurrence at primary site with/without regional/distant site recurrence was seen in 12 (52.2%) patients. Only metastatic recurrence without primary site was seen in seven (30.4%) patients. Bone was the most common site of distant metastasis (14/23) followed by lungs (9/23), liver (4/23), brain (2/23), and adrenal (1/23). No recurrence (regional/distant) was noted in 4/23 (17.3%) patients; however, three of them had ^{18}F-FDG-avid soft tissue lesions in esophagus, rectum and tongue, correspondingly, confirmed as second primaries with histopathology. Disease-specific survival analysis yielded nodal ($P = 0.01$) as well as distant metastases ($P = 0.02$) as the main survival predictors on PET/CT. Lung ($P = 0.001$), followed by liver ($P = 0.009$), and skeletal ($P = 0.01$) metastases were the most adverse survival predictive factors.**

Conclusion **^{18}F-FDG PET/CT showed good diagnostic and prognostic utility in recurrent MBC. It was better than bone scan in evaluation of skeletal metastases. Most importantly, ^{18}F-FDG PET/CT helped in early detection of second malignancy and their clinical management in studied patients.** ***Nucl Med Commun*** **40:63–72**

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Introduction

Male breast cancer (MBC) is a rare malignancy, with an estimated incidence rate of 0.5–1% of all breast cancer cases and less than 0.1% of all male cancers [1–3]. Nevertheless, recent data indicate that the incidence of MBC is slowly rising [4,5]. Given the rarity of the disease, major information about MBC has been obtained from extrapolation from breast cancer trials in their female counterpart [6], but certain discerning differences in phenotype and clinical behavior of MBC distinguish it from its female counterpart. The late and often asymptomatic clinical presentation and rarity of the incidence of MBC preclude the use of early screening/detection, and the disease usually presents at advanced stages compared with breast cancer in female patients [7]. Patients with MBC are also more frequently hormone receptor (HR) positive compared with female patients [8]. More advanced local tumor stage, high incidence of lymph node invasion at the time of diagnosis, close proximity to the skin and nipple facilitating early invasion of lymphatic vessels and development of regional/distant metastasis make MBC relatively unfavorable with respect to prognosis. However, recent studies have contradicted this and showed similar survival rates between the two sex groups [9–13].

Although there is emergence of new diagnostic and therapeutic approaches in breast cancer, disease recurrence continues as one of the main adverse predictors for prognosis in MBC [14,15]. Recent population-based studies have shown a steady rate of mortality in patients with proven metastatic disease, further asserting the need for special focus in advanced and recurrent diseases [16]. Simultaneous anatomical and functional information derived with PET/CT makes it an attractive diagnostic alternative over conventional modalities like computed tomography (CT) and MRI, especially in evaluation of disease recurrence. Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) PET/CT is a well-recognized modality

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in recurrence evaluation and has shown high performance in clinical management of breast cancer in females [17–20]. However, the role of PET/CT in management of MBC has been sparsely reported, may be owing to the rarity of MBC. Some of these studies have evaluated the role of ^{18}F-FDG PET/CT in a pooled study population for staging, restaging and response evaluation comprising a limited number of patients, but none of them have evaluated its precise role in disease recurrence [21–23]. In this study, we aimed to evaluate the utility of ^{18}F-FDG PET/CT in the evaluation of recurrence in patients with MBC. The feasibility of predicting the prognosis with the functional parameters/recurrence profile derived from PET/CT along with the histopathological/immunohistochemical (IHC) profile of the patients was also done.

Patients and methods

The data of ~26 000 patients with cancer who underwent ^{18}F-FDG PET/CT from period of May 2010 to June 2017 were screened from the picture archiving and communication system of the PET/CT facility in our institute (a tertiary care and academic center) with keywords 'breast cancer,' and all female patients were excluded. The medical records of the 44 male patients with breast cancer were further reviewed to exclude the patients with any of the following exclusion criteria: patients with cancer other than breast cancer and patients who underwent PET/CT for indication other than recurrence evaluation. Finally the data of 23 histologically proven patients with MBC, with clinical or previous imaging studies (ultrasonogram, CT, or MRI) suspicion for recurrence were retrospectively evaluated. This single institutional study was duly approved by the Institutional Ethics Committee. Written informed patient consent was obtained from all the patients at the time of their ^{18}F-FDG PET/CT study.

The initial histopathology after surgery identified infiltrating ductal carcinoma in 22 patients and infiltrating lobular carcinoma in one patient. The initial grades of the primary tumor along with the HR status were available in all except four patients. There was no patient with grade I tumor in our study group. The histopathological and hormonal profiles of the patients are detailed in Table 1.

All the patients were treated previously with surgery/chemotherapy/hormonal therapy/radiotherapy (RT) alone or in combinations of multiple treatment modalities before the ^{18}F-FDG PET/CT study. Of 23 patients, 16 underwent initial surgery [modified radical mastectomy (MRM) alone in 12, MRM + axillary clearance in three, and lumpectomy in one] for the primary lesions. Of these 16 patients, 14 received the combination of additional treatments in the form of RT, chemotherapy and hormonal therapy, and the remaining two did not receive any additional treatment apart from surgery. The remaining seven of the 23 patients received systemic chemotherapy without undergoing initial surgery for the primary lesions. Two patients received hormonal therapy and another two patients received RT in addition to chemotherapy in these seven patients. All the patients underwent ^{18}F-FDG PET/CT for the evaluation of suspected recurrence either owing to pertinent clinical symptoms/signs or based on radiological imaging results. Overall, 20 of 23 patients were suspected for recurrence on the basis of clinical symptoms/signs with or without radiological imaging (5/23 patients were evaluated for a visible/palpable nodularity in the chest wall at the postoperative site, 5/23 had significant bony pain with elevated serum alkaline phosphatase levels, 10/23 patients had nonspecific symptoms like loss of weight or appetite/generalized body pain/dysphagia with CT evidence of suspicious lesions in the chest/abdomen, and the rest three of 23 patients were asymptomatic but had nodules in the chest radiography/CT suspicious for metastases in the routine follow-up). The interval between the last treatment given and ^{18}F-FDG PET/CT done for suspected recurrence ranged from 3 to 96 months (mean: 21.8 ± 24.7 months).

Table 1 Summary of patients' characteristics

Characteristics	Value
Total patients (*N*)	23
Age [mean (range)] (years)	59.3 ± 10.9 (36–79)
Histopathological diagnosis	
Infiltrating ductal carcinoma	22
Infiltrating lobular carcinoma	1
Pathologic grading at initial diagnosis [*n* (%)]	
Grade 1	0
Grade 2	13 (56.5)
Grade 3	6 (26.2)
Not available	4 (17.3)
Hormonal profile (immunohistochemistry)	
ER +	14/23
Both ER and PR +	9/23
HER2/neu +	2/23
Triple negative: (ER −, PR −, HER2/neu −)	1/23
Ki-67 index (>14%) and (<14%)	7/23 and 16/23
Not available	4/23

ER, estrogen receptor; PR, progesterone receptor.

^{18}F-FDG PET/CT study

Imaging was performed using a dedicated hybrid PET/CT scanner (Discovery STE 16 or Discovery 710; GE Healthcare, Milwaukee, USA). All patients fasted for at least 6 h before the study. Scanning was initiated ~60 min after intravenous administration of 300–370 MBq of ^{18}F-FDG. Diagnostic contrast-enhanced CT [contrast was infused at a rate 3 ml/s, total volume being 1.2 × weight (kg) of patient] was acquired first followed by PET acquisition in 6–7 bed positions (2 min/bed position) from the vertex to the mid-thigh. The CT parameters were 120 kV tube voltage, 250 mA tube current, with a slice thickness of 3.75 mm. Data obtained from the studies were reconstructed using iterative reconstruction (ordered subset expectation maximization) algorithm with attenuation correction. Transaxial, sagittal, and coronal images were generated after reconstruction.

Data analysis

PET data were analyzed by a volume-of-interest (VOI) approach. Circular or elliptic VOIs were placed manually over the tumor site on transaxial images. Sagittal and coronal image reconstruction was performed to ensure correct VOI placement. The maximum tumor standardized uptake value (SUV_{max}) for each VOI was automatically calculated. Pooled data from the histopathological/clinical or imaging follow-up were taken as gold standard. Follow-up period ranged from 4 to 85 months (mean: 22.2 ± 22.8 months) from the date of ^{18}F-FDG PET/CT examination.

Statistical analysis

All the statistical analysis was performed using Statistical Package for the Social Sciences software (version 22; IBM, Armonk, New York, USA). SUV results were reported as mean ± SD and as median with interquartile range (interquartile range: 25–75th percentiles), as appropriate. Normality of quantitative data was checked by measures of Kolmogorov–Smirnov tests of normality. For estimating disease-specific survival (DSS) time, survival curves were constructed by Kaplan–Meier curves, and their significance was compared by log-rank (Mantel–Cox) method. Given the smaller sample size, categorical variables were compared using the two-tailed Fisher's exact test for association with survival status. Multivariate analysis for survival time was conducted with Cox regression to evaluate the significance of the selected prognostic factors on survival and to estimate the hazard ratios. All statistical tests were two-sided and performed at a significance level of P less than 0.05.

Results

A total of 23 male patients (mean age: 59.3 ± 10.9 years, range: 36–79 years) with histologically proven breast cancer (two patients had bilateral MBC) and having suspicion of disease recurrence fulfilled the inclusion criteria. ^{18}F-FDG PET/CT showed recurrence in 19/23 (82.6%) patients. Recurrence at the primary sites with or without regional/distant recurrence was noted in 12/23 (52.2%) patients. The mean SUV_{max} at the primary site recurrent lesions was 6.5 ± 4.5 (range: 2.1–16.3). In seven patients, only metastatic lesions were noted without any evidence of recurrence at the primary sites.

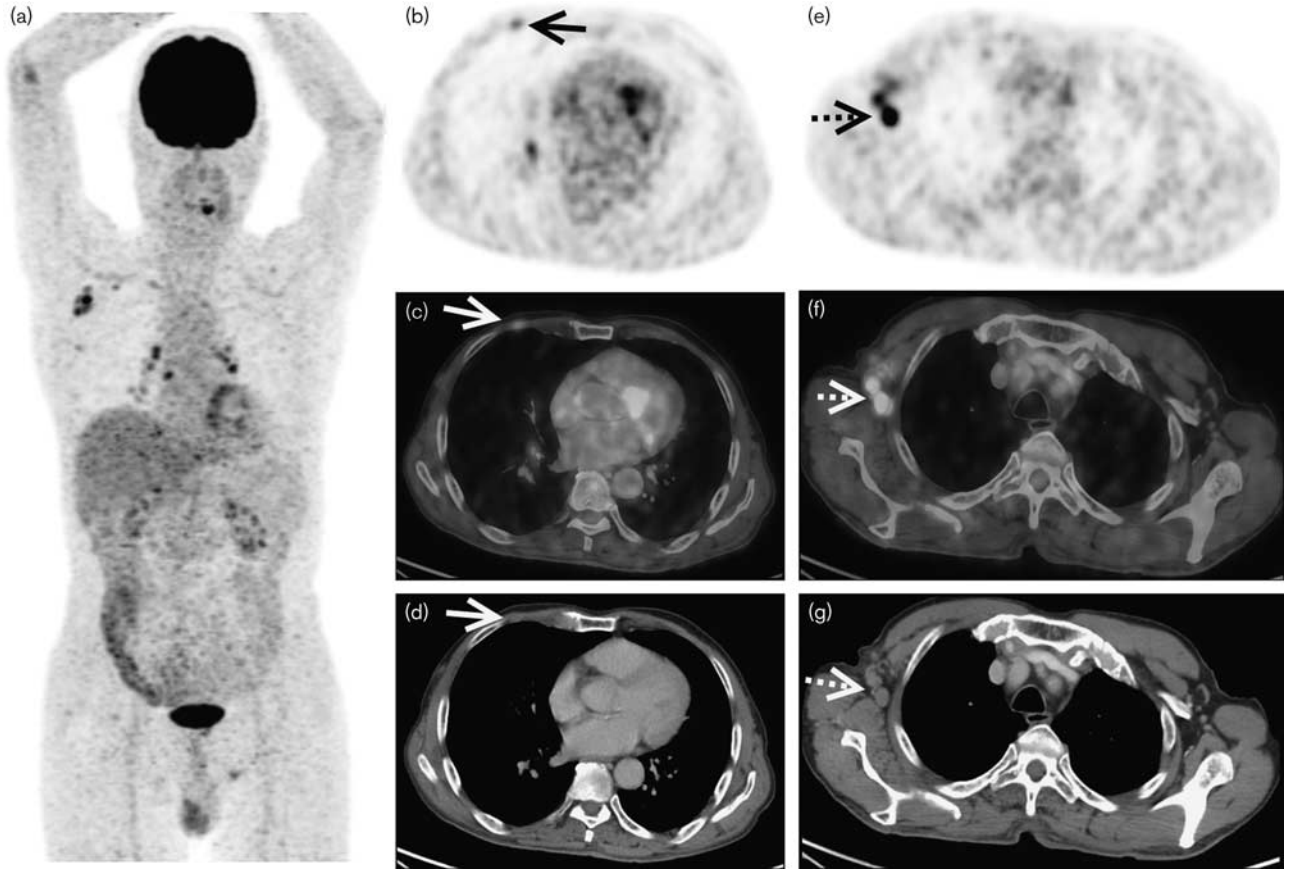
Tracer-avid lymph nodes were noticed in 13/23 (56.5%) patients, ipsilateral axillary lymph nodes in eight patients with mean SUV_{max} of 5.8 ± 2.5 (range: 2.9–9.8) and contralateral axillary lymph nodes in two patients with the SUV_{max} of 3.6 and 6.2, correspondingly. Ipsilateral supraclavicular lymph node involvement with SUV_{max} of 9.2 was noted in one patient. Mediastinal lymph nodes were positive for abnormal ^{18}F-FDG uptake in 10 patients with mean SUV_{max} of 7.1 ± 2.7 (range: 3.6–11.1). No patient in the study group had internal mammary lymph node involvement. Figure 1 represents ^{18}F-FDG PET/CT findings showing tracer-avid recurrence in the right chest wall and axillary lymph nodes confirmed on subsequent histopathology.

Distant metastatic lesions with or without primary/nodal recurrence were noticed in 15/23 (65.2%) patients. Bone was the most common site for distant metastasis (14/23 with mean SUV_{max} of 9.2 ± 5.7; range: 1.7–19.4) followed by lung (9/23 with mean SUV_{max} of 5.3 ± 4.1; range: 2.4–13.5) and liver (4/23 with mean SUV_{max} of 7.2 ± 4.2; range: 1.7–10.6). Metastases were also noted in the brain (two patients) and in adrenal (one patient). Ten patients also underwent technetium-99m-methylene diphosphonate whole-body skeletal scintigraphy before (within 3 months) the ^{18}F-FDG PET/CT. Bone scintigraphy identified skeletal metastases in 5/10 (50%) patients, whereas one more patient in addition to these five was found to be positive for skeletal metastases on ^{18}F-FDG PET/CT. Figure 2 shows local metastasis in the right chest wall along with extensive hepatic, skeletal, and brain metastases in a patient presenting with right chest wall pain after 19 months of MRM.

Four of the 23 (17.3%) patients did not show any disease-specific recurrence (either local/regional/distant) on PET/CT. However, three of these four patients showed increased ^{18}F-FDG uptake with soft tissue lesions in the contrast-enhanced CT of ^{18}F-FDG PET/CT, one each in esophagus, rectosigmoid and tongue correspondingly, suggestive of development of second primaries, which were later confirmed on histopathological examination. All these patients received additional appropriate treatment for the second primary. The patient with rectosigmoid lesion underwent lower anterior resection with left hemicolectomy followed by RT. His postoperative histopathology showed mucin-secreting adenocarcinoma. The patient with tongue primary was not willing for surgery. He was managed with brachytherapy with interstitial implant in left lateral border of tongue and external beam RT. These patients (with second primary in rectum and tongue respectively) did not have any other lesions to label as recurrence from MBC in the ^{18}F-FDG PET/CT study. The patients with rectosigmoid and tongue malignancies remained asymptomatic and had no recurrence in follow-up radiological imaging (CT head and neck and CT abdomino-pelvic region). The patient with esophageal carcinoma as second primary succumbed to the disease despite receiving additional treatment. This patient was excluded from the overall survival analysis. The remaining one patient in whom no recurrence was detected is on follow-up with oral hormonal therapy and doing well without any symptoms. Figure 3 shows incidental detection of ^{18}F-FDG-avid wall thickening in the rectosigmoid in a patient who had previously undergone MRM and RT to chest wall.

Nineteen patients with PET/CT-detected recurrence related to MBC (either local/regional/distant) were provided additional treatment in the form RT/chemotherapy/hormonal therapy alone or in combination, except in two patients in whom significant co-morbidity precluded

Fig. 1



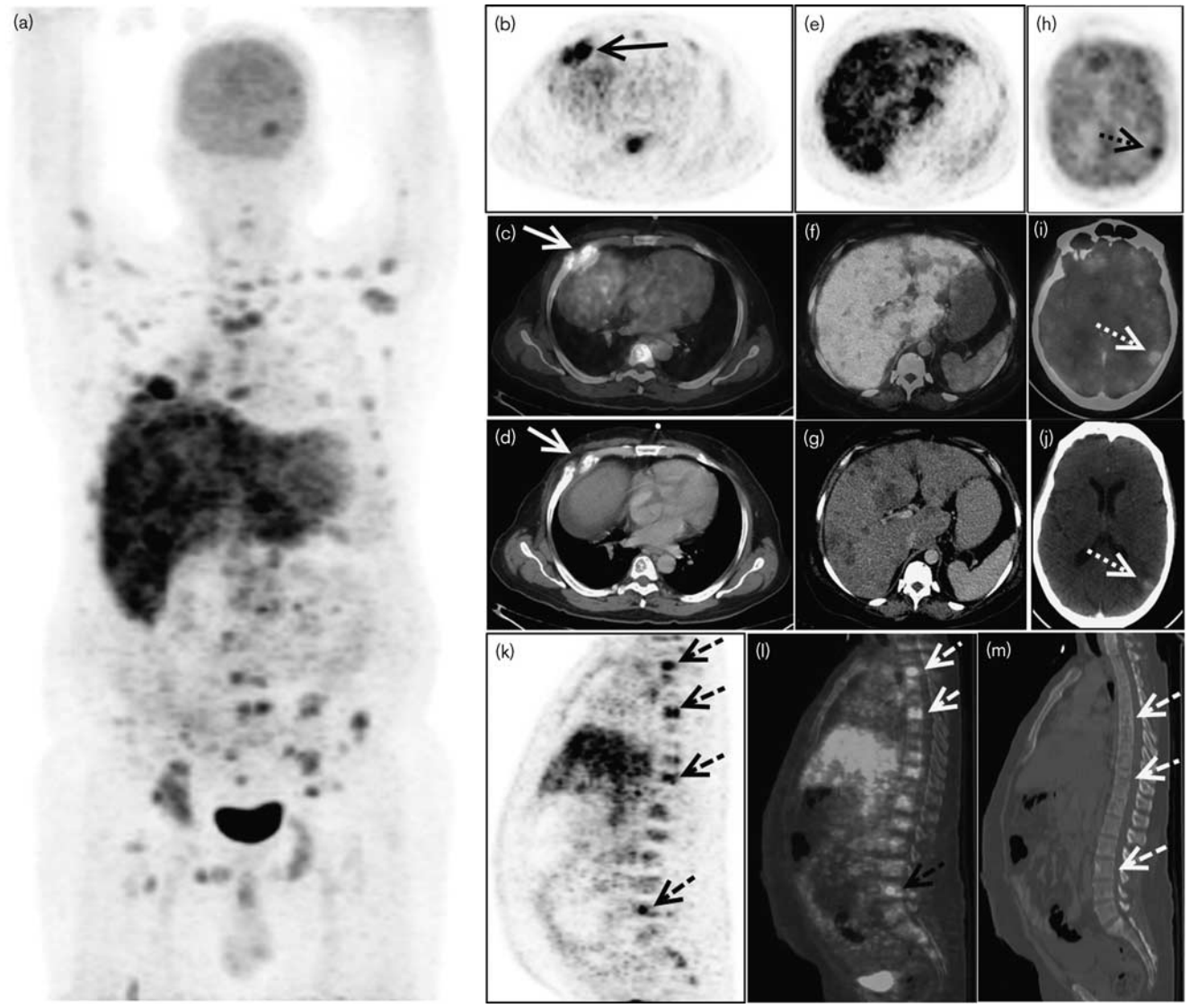
^{18}F-FDG PET/CT images of a 68-year-old male after 9 months of lumpectomy for right-sided male breast cancer, showing tracer uptake in the right axillary and chest wall region on maximum intensity projection image (a), ^{18}F-FDG-avid ($SUV_{max} = 2.6$) nodular lesion in the right chest wall (arrows: b–d) and ^{18}F-FDG-avid ($SUV_{max} = 9.8$) enlarged right axillary lymph nodes (dotted arrows: e–g) in axial PET, axial fused PET/CT and corresponding axial CT. The patient underwent excision of the lesions with confirmed MBC recurrence on histopathology. The patient is doing well on follow-up. CT, computed tomography; ^{18}F-FDG, fluorine-18-fluorodeoxyglucose; SUV_{max}, maximum standardized uptake value.

the use of additional therapy. Follow-up was available in all the 23 patients, with mean follow-up period of 22.2 ± 22.8 months (range: 4–85 months) from the date of ^{18}F-FDG PET/CT. Eleven patients succumbed to disease including one diagnosed to have second primary in the esophagus. So disease-specific mortality from MBC was noted in 10 of 23 patients, and further survival analysis was done excluding the patient with esophageal malignancy.

Kaplan–Meier overall survival analysis was done with all patients (except the one with esophageal primary who succumbed to the disease) with respect to parameters like initial tumor grade, hormonal profile, recurrence at the primary site, and regional/distant metastatic disease detected on ^{18}F-FDG PET/CT. The mean survival time was more (52.9 ± 11.1 months) in patients with initial IHC finding of estrogen receptor (ER) positivity compared with ER-negative group (17.0 ± 6.2 months). However, the results were not statistically significant ($P = 0.12$). Furthermore, patients having grade II disease at the time of diagnosis had more mean DSS time than of grade III patients (47.6 ± 10.7 vs. 12.4 ± 2 months), though this was not statistically significant ($P = 0.50$). Similarly, no statistically significant difference was noticed in the mean survival time with respect to progesterone receptor (PR) status ($P = 0.09$), HER2/neu receptor positivity ($P = 0.13$) and Ki-67 index ($P = 0.68$; with Ki-67 > 14% vs. Ki-67 < 14%).

The presence of nodal as well as distant metastases on ^{18}F-FDG PET/CT was the main factor determining the patient survival. Mean survival time in the 13 patients with nodal lesions detected on PET/CT (axillary/supraclavicular/mediastinal) was 16.5 ± 4.4 months compared with 65.2 ± 11.8 months in the node-negative group, which was significantly different in the log-rank test ($P = 0.01$). Fifteen patients with distant metastasis detected on ^{18}F-FDG PET/CT had a significantly shorter mean survival time of 30.3 ± 9.0 months compared with those with no distant metastasis (59.7 ± 14.9 months) ($P = 0.02$).

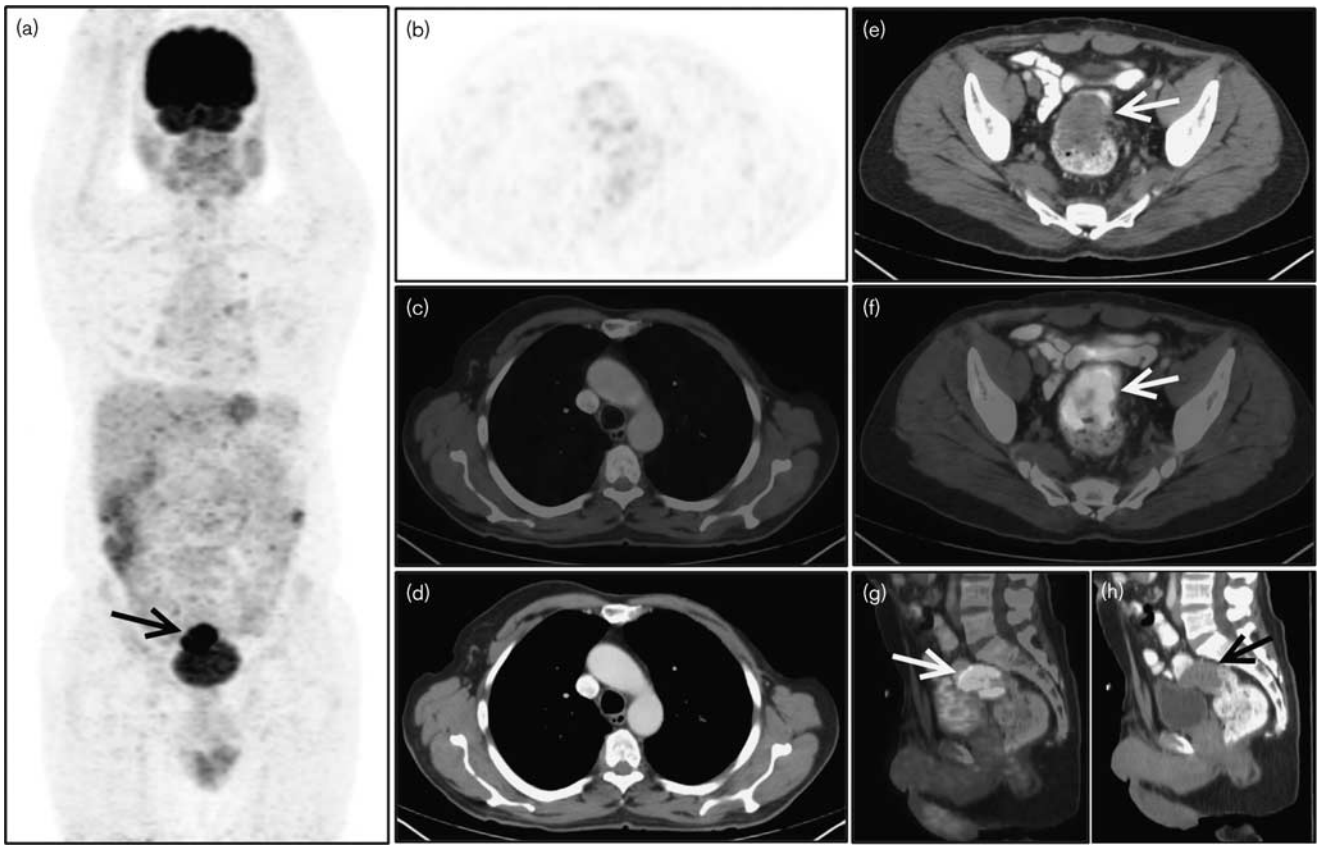
Fig. 2



^{18}F-FDG PET/CT images of a 42-year-old male with history of multiple bony pain 19 months after modified radical mastectomy for right-sided breast cancer, showing multiple foci of tracer uptake in maximum intensity projection (a), ^{18}F-FDG-avid lesion in the right chest wall with rib involvement (arrows: b–d), multiple hypodense lesions in the liver (e–g), lesion in the left parieto-occipital junction of the brain (dotted arrow: h–j) and multiple lytic-sclerotic lesions in the skeletal sites (broken arrows: k–m) in cross-sectional PET, fused PET/CT, and CT images, suggesting widespread metastases. The patient ultimately succumbed to the disease despite receiving additional palliative chemotherapy. CT, computed tomography; ^{18}F-FDG, fluorine-18-fluorodeoxyglucose.

For the distant metastatic sites, the presence of lung metastasis was the most adverse predictive factor for survival. The patients with lung metastases had statistically significant difference ($P=0.001$) in mean survival time (18.0 ± 8.1 months) than those without lung metastasis (60.8 ± 10.5 months). Almost similar difference in survival time was observed in patients having liver ($P=0.01$) and skeletal metastases ($P=0.006$) against those without having these metastases. Multivariate analysis done among the significant adverse prognostic parameters in ^{18}F-FDG PET/CT (lung and regional metastasis) by Cox proportional hazard regression method also resulted in significant difference ($P<0.001$) with hazard ratio of 24.2 [95% confidence interval (CI): 2.6–222.5] for presence of lung metastasis ($P=0.005$) and 20.6 (95% CI: 1.8–230.8) for presence of regional nodal metastasis ($P=0.01$), showing that lung metastasis was the significant independent adverse predictor. The presence/absence of recurrence at the primary site ($P=0.56$) and the ^{18}F-FDG uptake value at the recurrent primary site ($SUV_{max;}$ $P=0.4$) did not correlate with survival in the study. Fischer's exact test also yielded similar results showing

Fig. 3



^{18}F-FDG PET/CT images of a 67-year-old man who presented with loss of weight and appetite 64 months after undergoing modified radical mastectomy and radiotherapy for left-sided male breast cancer. No abnormal tracer uptake is noticed in the postoperative sites in maximum intensity projection (MIP) (a) and axial PET (b), fused PET/CT (c) and corresponding CT images (d). An abnormal tracer uptake (arrow) is seen in the suprapubic region (MIP:a), which localized to asymmetrical mural thickening in the rectosigmoid junction (arrows) in the axial (e, f) and corresponding sagittal (g, h) CT and fused PET/CT images with no abnormal tracer uptake elsewhere (b–d). Endoscopic biopsy histopathology showed adenocarcinoma. The patient underwent left hemicolectomy and additional radiotherapy with postoperative histopathology of mucinous adenocarcinoma, proved to be second malignancy. He is well on follow-up. CT, computed tomography; ^{18}F-FDG, fluorine-18-fluorodeoxyglucose.

significant association/relationship between the survival status with presence of lung ($P=0.003$), liver ($P=0.03$), skeletal ($P=0.009$) as well as any of the distant site metastasis ($P=0.02$). Different survival predictors with their mean survival times and P value are detailed in Table 2, and the corresponding Kaplan–Meier DSS plots with different predictor parameters are shown in Fig. 4. Additional treatment (surgery/chemotherapy/RT/hormonal) was provided to all the patients in whom PET/CT showed recurrence. However, two patients had significant morbidity, which precluded any additional treatment in them. The detailed patient, histopathological, imaging, and follow-up parameters are given in Table 3.

Discussion

Despite having several phenotypic differences as well as worse prognostic profile as compared with female breast cancer, less attention had been given to MBC because of the rarity of its incidence, leading to treatment algorithms derived from studies in the female counterpart. ^{18}F-FDG PET/CT is already well established as an imaging modality in the management of female patients with breast cancer [24–26]. Recurrence plays a crucial role in the prognosis of breast carcinoma, and irrespective of the recent advances offering new therapeutic approaches, metastatic disease still constitutes the most significant adverse predictor of survival with a stable hazard of dying over a long time [27].

In the present study, ^{18}F-FDG PET/CT showed recurrence (both local and distant) in 82.6% of patients and significant number of patients had distant metastases (65.2%) indicating its good diagnostic utility in MBC. The reported literature on recurrence rate in MBC varies widely from 7.8 to 60.9%, largely owing to the vast variation in sample sizes [28,29]. In the present study, ^{18}F-FDG PET/CT showed higher recurrence rate likely owing to the fact that most of the patients were symptomatic and the study was specifically done for the

Table 2 Survival analysis with respect to histopathological, imaging and treatment parameters

Parameters	*n*	Alive at follow-up	Deceased at follow-up	Survival time [mean ± SE (95% CI)]	*P* value (< 0.05 significant)
Grade					
II	12	6	6	47.6 ± 10.7 (26.6–68.6)	0.5
III	6	3	3	12.4 ± 2.1 (8.4–16.4)	
ER					
+	13	8	5	52.9 ± 11.1 (31.2–74.6)	0.12
−	5	1	4	17.0 ± 6.2 (4.8–29.2)	
PR					
+	10	8	2	56.1 ± 11.7 (32.9–79.1)	0.09
−	8	1	7	23.1 ± 10.4 (2.7–43.6)	
HER2/neu					
+	2	1	1	9.5 ± 2.4 (4.6–14.3)	0.13
−	16	8	8	51.5 ± 9.8 (32.2–70.9)	
Ki-67 (%)					
< 14	11	5	6	41.5 ± 11.8 (18.4–64.7)	0.68
> 14	7	4	3	45.4 ± 13.6 (18.7–72.1)	
Primary site recurrence					
+	12	7	5	46.7 ± 12.1 (23.1–70.4)	0.56
−	10	5	5	32.6 ± 12.6 (7.8–57.3)	
Nodal metastases					
+	13	5	8	16.6 ± 4.4(8.0–25.1)	**0.01**
−	9	7	2	65.2 ± 11.8 (41.9–88.4)	
Any of distant metastases					
+	15	5	10	30.3 ± 9.1 (12.5–48.1)	**0.02**
−	7	7	0	59.7 ± 14.9 (30.3–89.0)	
Lung metastasis					
+	9	1	8	18.0 ± 8.1 (1.9–34.0)	**0.001**
−	13	11	2	60.8 ± 10.5 (40.1–81.4)	
Liver metastases					
+	4	0	4	11.2 ± 3.6 (4.0–18.5)	**0.01**
−	18	12	6	49.3 ± 9.9 (29.9–68.7)	
Skeletal metastases					
+	14	4	10	18.9 ± 4.7 (9.7–28.2)	**0.006**
−	8	8	0	69.5 ± 13.4 (43.1–95.8)	

Significant *P* values are given in bold.
ER, estrogen receptor; PR, progesterone receptor.

indication of suspected recurrence. In female patients with breast cancer, ^{18}F-FDG PET/CT has been reported to have very good utility in finding the recurrent primary and locoregional lymph nodal metastasis in supraclavicular and internal mammary region [30,31]. The current study also corroborates these results, with 52.5% of the total patients showing local recurrence in PET/CT.

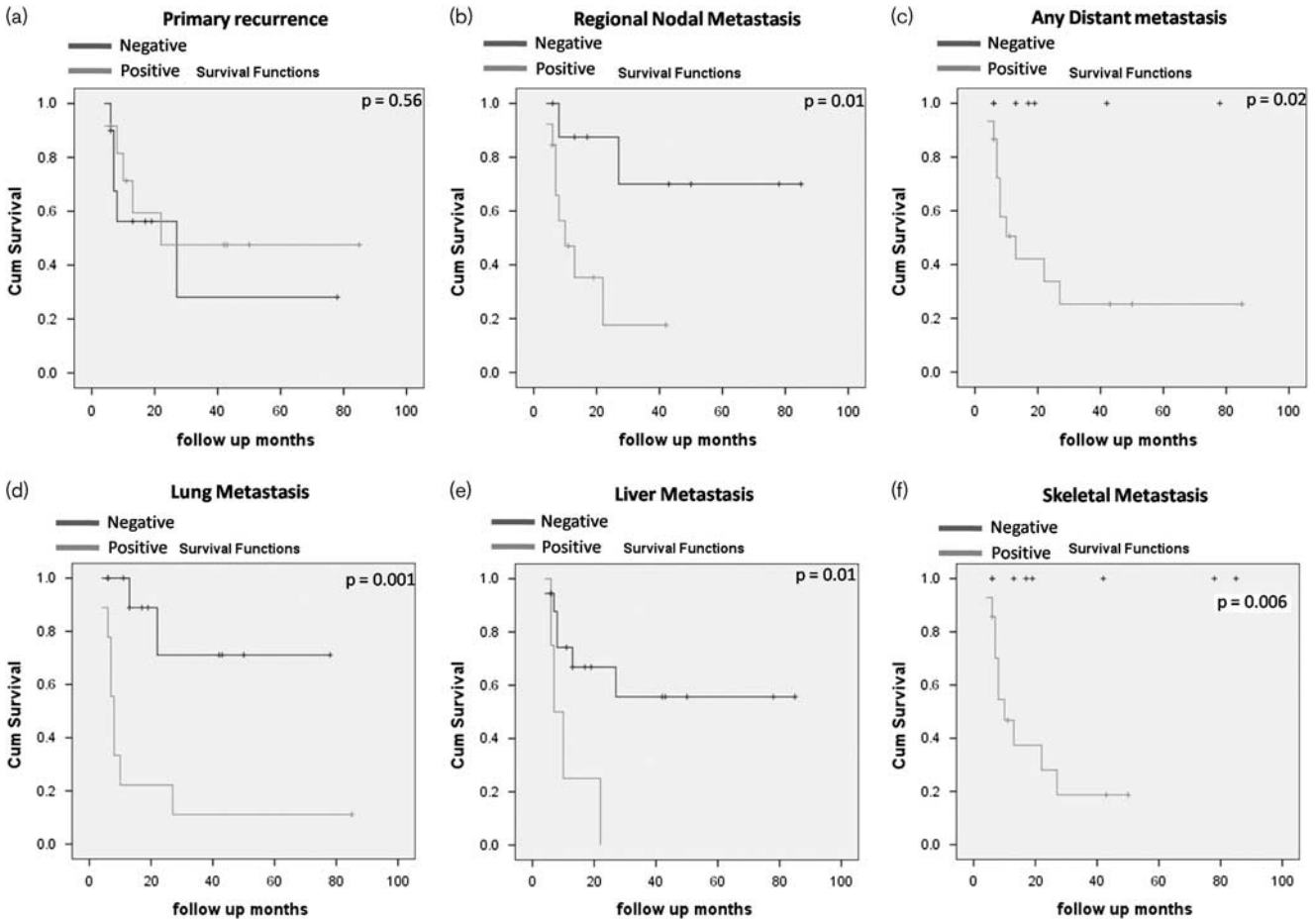
This study also highlights the major utility of ^{18}F-FDG PET/CT in detecting distant metastases in 65.2% of the patients. Bones were the most frequent site of distant metastasis in our study similar to those reported earlier [32,33]. ^{18}F-FDG PET/CT was better than skeletal scintigraphy in the assessment of skeletal metastasis, as reported previously also [21]. This may be attributed to the limited sensitivity of the bone scan to lytic metastasis as seen in breast cancer [34]. ^{18}F-FDG PET/CT performed well in diagnosing lung and hepatic metastases, and even in brain metastases, which are usually missed because of physiological tracer uptake.

Although four patients did not have any recurrent local/distant metastatic lesions related to MBC on ^{18}F-FDG PET/CT, ^{18}F-FDG-avid lesions in three out of four patients in the esophagus, rectosigmoid and tongue correspondingly prompted histopathological analysis, which identified a second malignancy at the corresponding sites (adenocarcinoma of esophagus, mucinous adenocarcinoma in the rectosigmoid and well-differentiated squamous cell carcinoma in the tongue). The mean time of diagnosis of these second malignancies in the three patients after the last treatment for MBC was 43.0 ± 29.7 months (range: 9–64 months). The incidence of second malignancy (13.1%) in our patients correlates well with the report of an international multicenter study comprising 3409 patients with primary MBC, found to have second malignancy in 426 (12.5%) [35]. Second primary neoplasias involving the small intestine (standardized incidence ratio: 4.95, 95% CI: 1.35–12.7), rectum (1.78, 1.20–2.54), pancreas (1.93, 1.14–3.05), skin (non-melanoma: 1.65, 1.16–2.29), prostate (1.61, 1.34–1.93), and lymphohaematopoietic system (1.63, 1.12–2.29) were the most commonly seen malignancies in the afore-cited study. In another study comprising 1926 patients with MBC, the incidence of second malignancy was 11.5% [36]. The timely detection of second malignancy in our study resulted in appropriate and judicious management of these patients. PET/CT being a whole-body procedure with the added advantage of providing hybrid functional/structural imaging in a single study has an extra edge over other conventional modalities, especially when looking for second malignancies which can occur at any site in these patients.

In the follow-up, death as an outcome was observed in 11 (47.8%) of the 23 patients, although disease-specific mortality to MBC was noted in 10 (43.5%) patients. Among the initial histopathological and IHC predictors used for analyzing the survival outcome (initial grade, ER, PR, HER2/neu, and Ki-67 status), ER positivity showed a positive trend on prognosis in the Kaplan–Meier survival analysis, although the results were not statistically significant. Although patients with Ki-67 index greater than 14% had a lesser mean survival time compared with those with Ki-67 of less than 14%, it was not statistically significant ($P = 0.68$; Table 2). In a previously reported study evaluating the correlation of hormonal receptor as well as IHC parameters on MBC survival showed similar results that ER positivity ($P = 0.03$) had a positive effect on survival whereas Ki-67 and PR status did not correlate with survival [37]. In another study involving 3341 patients with MBC, ER/PR positivity was associated with decreased hazard for death in the 5-year survival analysis [38]. The proportion of ER/PR-positive patients in the afore-cited study was 82.9%, whereas in the index study, it was 94.7%, which may be because of the smaller patient number in our study. MBC is also reported to be different from female patients with breast cancer for being more HR positive.

Among ^{18}F-FDG PET/CT parameters assessed for predictors of survival, the metabolic uptake at the recurrent primary site was not predictive of survival. One of the

Fig. 4



The Kaplan–Meier disease-specific survival plots with the survival predictors on ^{18}F-FDG PET/CT. No significant difference in mean survival time with the presence or absence of recurrence at the primary site on ^{18}F-FDG PET/CT was observed in the survival plot (a). However, the presence of nodal metastases (b) and the presence of any distant site metastasis (c) on ^{18}F-FDG PET/CT were significant adverse predictors of survival. Among the sites for distant metastases, the presence of lung (d), liver (e), and skeletal (f) metastasis was independent significant adverse predictors of survival with significant *P* values (< 0.05).

three already published studies on the role of ^{18}F-FDG PET/CT in MBC also reported that metabolic parameters like SUV_{max}, tumor lesion glycolysis, and metabolic tumor volume did not correlate with survival [23]. However, in this study, nodal as well as distant metastases (visceral and skeletal) were found to be strong adverse predictors of survival. There was significant mortality in the distant metastatic group (10/15; 66.7% of patients with any of the distant metastases succumbed to the disease) even after additional treatment, whereas no disease-specific mortality was noted in the nonmetastatic group. This further reinforces the fact that more vigilant and aggressive follow-up measures are needed in advanced MBC. Previous studies have also shown evidence relating nodal and visceral metastasis (especially lung and liver) as well as PET positivity as an adverse survival predictor in MBC [22,39].

Although retrospective nature and low patient number are the inherent limitations of the present study, every effort has been made to minimize the errors and ensure statistical validity. Although the study was from single institution (tertiary care academic institute), our patient group was phenotypically representative of large study population groups of MBC. The previous limited studies on the role of ^{18}F-FDG PET/CT in MBC were done with pooled study population for miscellaneous indications. They reported good clinical utility of ^{18}F-FDG PET/CT in initial staging, restaging and treatment response assessment in MBC, especially in the recurrence scenario [21–23]. Our study evaluated role of ^{18}F-FDG PET/CT in the specific setting of disease recurrence, and also validated the same. In addition, the findings of PET/CT proved to be significant predictors of survival as well. However, these results need to be

Table 3 **Disease, histopathological, imaging, and follow-up characteristics of the patient studied for recurrence evaluation**

			Immunohistochemistry												
Patient no.	Age (years)	Initial grade	ER	PR	HER2 neu	Ki-67 (%)	Primary site recurrence (SUV_{max})	Regional nodal metastasis	Lung (SUV_{max})	Liver (SUV_{max})	Bone (SUV_{max})	Second primary	Additional therapy	Time of follow-up in months (from PET/CT)	Status at last follow-up
1	67	II	1	1	0	<14	0	0	0	0	0	Esophagus	1 (RT)	23	Deceased
2	52	II	0	0	0	<14	0	0	1 (9.8)	1 (10.6)	1 (13.2)	–	1 (CT + RT)	7	Deceased
3	66	II	1	1	0	<14	1 (3.7)	0	1 (2.9)	0	0	–	1 (S + HR)	85	Alive
4	54	II	1	0	0	20	0	1	0	0	0	–	1 (HT)	78	Alive
5	68	II	1	0	1	70	0	0	1 (8.1)	1 (1.7)	1 (10.8)	–	0	6	Deceased
6	67	II	1	0	0	30	0	1	1 (2.7)	0	1 (1.7)	–	1 (CT)	27	Deceased
7	62	II	1	1	0	25	0	1	1 (3.2)	0	1 (10.8)	–	0	7	Deceased
8	42	II	0	1	0	<14	1 (16.3)	1	0	1 (10.2)	1 (12.3)	–	1 (CT)	22	Deceased
9	47	II	0	1	0	<14	1 (7.6)	0	1 (2.4)	1 (6.22)	1 (5.6)	–	1 (CT + RT)	10	Deceased
10	60	II	1	1	0	<14	1 (5.5)	1	0	0	1 (3.1)	–	1 (CT + RT + HT)	50	Alive
11	72	II	1	1	0	<14	0	0	0	0	0	–	1 (HT)	19	Alive
12	48	II	1	1	0	25	1 (3.9)	1	0	0	1 (3.5)	–	1 (S + HT)	43	Alive
13	60	II	0	1	0	<14	1 (14.0)	1	0	0	0	–	1 (S + CT)	42	Alive
14	55	III	1	0	0	<14	0	1	1 (13.5)	0	1 (19.4)	–	1 (CT)	8	Deceased
15	79	III	1	0	0	<14	1 (5.0)	1	0	0	1 (3.5)	–	1 (CT)	13	Deceased
16	50	III	1	1	1	45	1 (8.6)	1	0	0	1 (6.6)	–	1 (CT + HT)	11	Alive
17	57	III	0	1	0	<14	1 (2.1)	0	1 (2.7)	0	1 (19.1)	–	1 (RT)	4	Deceased
18	67	III	1	1	0	20	0	0	0	0	0	Rectum	1 (S + RT)	17	Alive
19	76	III	1	1	0	<14	0	0	0	0	0	Tongue	1 (RT + BT)	13	Alive
20	62	NA	–	–	–	–	1 (2.6)	0	1 (2.5)	0	1 (11.6)	–	1 (CT)	8	Deceased
21	36	NA	–	–	–	–	0	1	0	0	1 (7.8)	–	1 (CT)	6	Alive
22	50	NA	–	–	–	–	1 (5.9)	1	0	0	0	–	1 (S + HT)	6	Alive
23	68	NA	–	–	–	–	1 (2.6)	1	0	0	0	–	1 (S)	6	Alive

0, negative; 1, positive; BT, brachytherapy; CT, chemotherapy; ER, estrogen receptor; HT, hormonal therapy; NA, not available; PR, progesterone receptor; RT, radiotherapy; S, surgery; SUV_{max}, maximum standardized uptake value.

validated with larger prospective and multi-institutional studies.

Conclusion

^{18}F-FDG PET/CT showed good diagnostic as well as prognostic utility in the scenario of recurrent MBC. PET/CT is better than bone scan in the evaluation of skeletal metastases. Most importantly, the timely detection of a second malignancy in three patients benefited in their clinical management. Simultaneous functional/structural information with whole-body assessment potentiates ^{18}F-FDG PET/CT as a powerful diagnostic and prognostic imaging tool in the recurrence evaluation and can help in bringing out the much needed individualized and risk adapted therapy for this rare malignancy, especially in the current scenario of rising incidence of MBC.

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Conflicts of interest

There are no conflicts of interest.

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