Detection of Breast Cancer by PET

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Introduction

Positron emission tomography (PET) is one of the nuclear medicine imaging modalities using positron-emitting radioisotopes as tracers. PET and PET/ computer tomography (CT) have gained widespread acceptance as a promising imaging modality in the oncologic field in the clinical practice since its introduction in the 1990s. The fundamental strength of PET over conventional imaging is the ability to convey various functional and metabolic information that anatomic image cannot provide. The primary PET tracer used in PET imaging is ^{18}F-fluorodeoxyglucose (^{18}F-FDG), a glucose analog. The increased glycolytic rate and glucose avidity of malignant cells in comparison to benign tissue allow ^{18}F-FDG PET and PET/CT imaging to depict cancers and distinguish them from benign tissue.

On the breast cancers, many studies of whole-body ^{18}F-FDG PET and PET/CT have been done to seek its clinical utility. In the staging and the restating, whole-body PET or PET/CT has higher diagnostic performance than conventional imaging modalities in the detection of extra-nodal metastasis [1, 2], distant metastasis [3], and recurrence [4–6]. However, no definite advantage of whole-body PET and PET/CT over conventional diagnostic modalities has been found in the evaluation of primary tumors and axillary nodal metastasis. The primary limitation of ^{18}F-FDG PET and PET/CT is low spatial resolution. Thus, the sensitivity of whole-body PET systems is limited in sub-centimeter tumors [7]. The sensitivity for the axillary nodal metastasis is lower than sentinel lymph node biopsy [8]. Until September 2021, National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines said the use of ^{18}F-FDG PET/CT was not indicated in the staging of clinical stage I, II, or operable stage III breast cancer [9].

To improve the diagnostic performance of PET imaging for the primary sites, high-resolution PET systems dedicated for the breast have been developed. These PET systems have detectors with small field of view (FOV), which are positioned close to the breast. With the close proximity of the detector to the breast, the small detector elements, and other technical developments, the breast PET systems are intended to maximize the spatial resolution with sufficient photon sensitivity and to improve the detection of small breast cancers.

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Types of High-Resolution Breast PET Systems and Examination Protocols

There have been several designs of high-resolution breast PET systems, which are generalized into two types (Fig. 1): (1) "positron emission mammography (PEM)" and (2) a fully tomographic type, representatively ring-type dedicated breast PET (dbPET).

PEM has a dual-head system compressing the breast mildly like mammography or tomography and provides limited-angle tomographic images [10]. Patients are positioned similar to mammography or tomography to obtain craniocaudal (CC) and mediolateral oblique (MLO) views with gentle compression applied to stabilize the breast. Scan time is typically 10 min per breast per view, resulting in total of 40 min or more. The PEM Flex Solo II scanner (CMR Naviscan, Carlsbad, CA) is the most clinically validated, commercially available breast PET system. The in-plane resolution is high, whereas cross-plane resolution is limited [11, 12]. A PEM-guided biopsy system is equipped to sample FDG-avid breast lesions [13].

A fully tomographic type, representatively ring-type dbPET, a newer generation of breast PET systems acquiring complete three-dimensional data and providing fully tomographic images in any direction [14, 15]. Unilateral breast is scanned without compression in the patient in prone position. Commercially available ring-type dbPET includes MAMMI (OncoVision, Valencia, Spain) and Elmammo (Shimadzu co., Kyoto, Japan). MAMMI has a transaxial FOV of 170 mm in diameter, and a 40-mm-long axial FOV that moves axially to cover up to 170 mm [15]. Elmammo has a transaxial FOV of 185 mm in diameter and a 155.5-mm-long axial FOV [14]. Both have achieved high spatial resolution in all three spatial directions (full width at half maximum (FWHM) of <2.0 mm for radial, tangential, and axial directions). With the capabilities of attenuation and scatter corrections, standard uptake values (SUV) are measurable.

The breast PET imaging with ^{18}F-FDG requirements before examinations should follow the general recommendations of ^{18}F-FDG PET studies, e.g., at least 4 h fasting [16, 17]. Waiting time is usually 60–90 min post injection. In

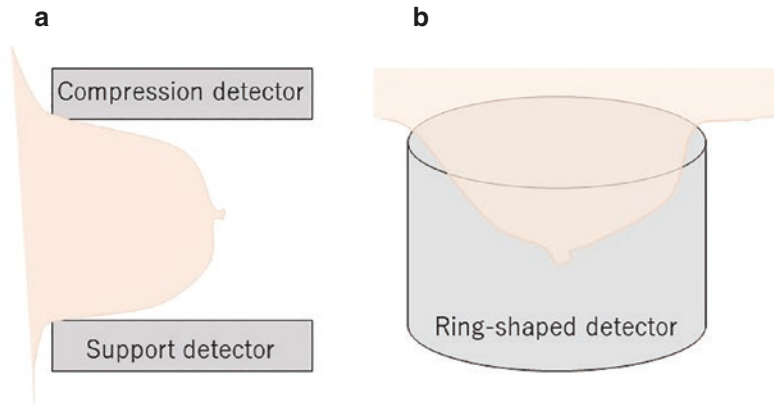

Fig. 1 Types of breast PET: Positron emission tomography (PEM) (**a**) vs. ring-type dedicated breast PET (**b**)

Japan, breast PET exams have been covered by public health insurance since 2013, which mandates their use in combination with conventional whole-body PET, PET/CT, or PET/ magnetic resonance imaging (MRI).

Interpretive Criteria: Lexicon

Increased glycolytic metabolism can be induced not only in malignant tumors but also in inflammation or benign entities. The accumulation of ^{18}F-FDG in such benign process results in false positives. Several studies have suggested that adding morphological assessment, which was made possible by the advent of high-resolution breast PET, may help differentiating malignant uptake and benign uptake, as well as characterizing breast cancers [18–22]. In order to establish and facilitate a comprehensive diagnostic approach of breast PET based on uptake features, "lexicon," a standardized terminology, has been proposed for describing and reporting of the uptake features on breast PET. Some terms were aligned to the Breast Imaging-Reporting and Data System (BI-RADS) for MRI provided by the American College of Radiology (ACR) [23].

The first reported lexicon was that for PEM published in 2011 by Narayanan et al. [19]. This PEM lexicon consists of terms for background uptake, lesion (focus/foci, mass, and non-mass), and associated findings. Assessment categories, which are analogous to BI-RADS categories, are also provided. It has been demonstrated that experienced breast imagers achieved high inter-observer agreement after approximately 2-h training on PEM [24], suggesting that reproducible assessment is possible with the lexicon.

More recently, in 2021, lexicon for dbPET has been proposed by investigators in Kyoto University [25]. The dbPET lexicon consists of terms for image quality, background fibroglandular uptake, and breast lesion uptake (focus/foci, mass uptake, non-mass uptake). The capability of dbPET to obtain complete 3D information and provide SUV is beneficial in evaluating detailed 3D morphology of breast uptake and comparing intensities between studies. The outline of dbPET lexicon, version 1.0, is described below.

Assessment of *image quality* is unique in dbPET and is the first step to describe dbPET findings. *Noise* and *field of views (FOV)* are included in this assessment. Noise tends to be relatively higher and the photon sensitivity be lower at the edge of the detector where the gamma-ray coincidences from the annihilation of positrons decrease [14]. Attention must be paid for noise, because noise can be false positives as well as cause false negatives by masking true lesion uptake. Noise level is categorized as *minimal*, *mild or limited to the edge of FOV*, *moderate*, and *marked* (Fig. 2). *FOV* is determined by how much of the breast is included in the FOV of

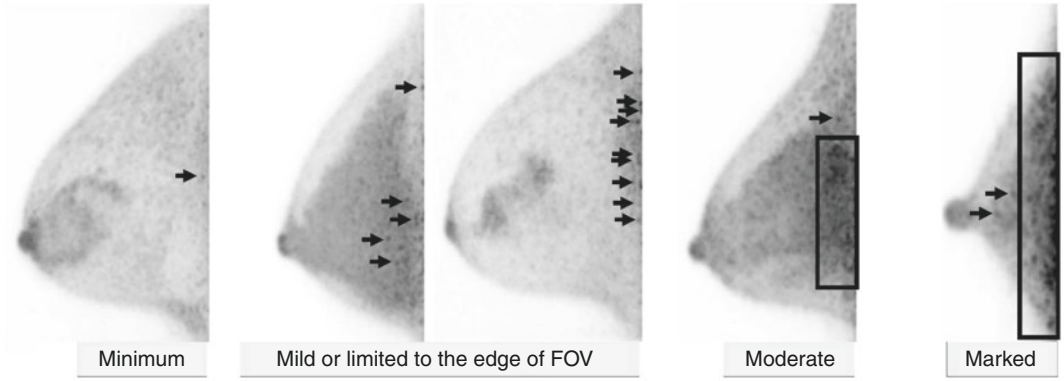

Fig. 2 Noise. Noise level is categorized using the 4-point scale; *minimal*, *mild or limited to the edge of FOV*, *moderate*, and *marked*. (From Miyake et al., Diagnostics (Basel) 2021;11(7):1267)

dbPET and is categorized as *full, almost full*, *partial*, and *limited* (Fig. 3). Because of the structural limitation, breast PET has a relatively large blind area at the chest side [26], which potentially causes false negatives especially for women with small breasts, those with very large breasts, those with chest wall pain due to rib fracture, etc., and those with a chest wall deformity. Further improvement of the bed and the training of technologists for positioning may be clues for reducing the blind area and allowing the visualization of posterior lesions. The routine assessment of the image quality using lexicon may aid in knowing whether dbPET has sufficient quality for the evaluation in each individual case, and also helps give feedback to the technologists for further improvement.

Fibroglandular tissue usually has higher ^{18}F-FDG accumulation compared with fat, thus is seen as ^{18}F-FDG-avid structure on dbPET. In the dbPET lexicon, background breast fibroglandular uptake (bFGU) is assessed in terms of fibroglandular extent, intensity, distribution, and symmetry. Among four bFGU intensity categories (*faint*, *mild*, *moderate*, and *intense*), the most common one may be *mild*, followed by *moderate* or *faint*. *Intense* bFGU may be much less common, but can be seen in lactating breasts or pathological breasts. It should be noted that intense bFGU may hide breast cancers.

A lesion is defined as an area of abnormal uptake that is unique and different from the bFGU.

Lesions are classified as a *focus* (Fig. 4), *mass uptake* (Fig. 5), and *non-mass uptake* (NMU) (Fig. 6) based on the three-dimensional morphologic features. A *focus* is a dot-like small uptake (usually ≤5 mm) that is difficult to characterize further. *Mass uptake* is uptake larger than 5 mm composed of a three-dimensional uptake finding, which usually has relatively abrupt margins. *NMU* is uptake that has a pattern different from that of the bFGU and has a shape that cannot be called a focus or a mass.

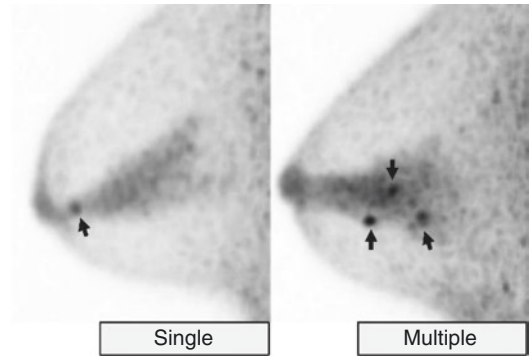

Fig. 4 Focus. A focus is a dot-like small uptake that is difficult to characterize further, and categorized as *single* or *multiple.* (From Miyake et al., Diagnostics (Basel) 2021;11(7):1267)

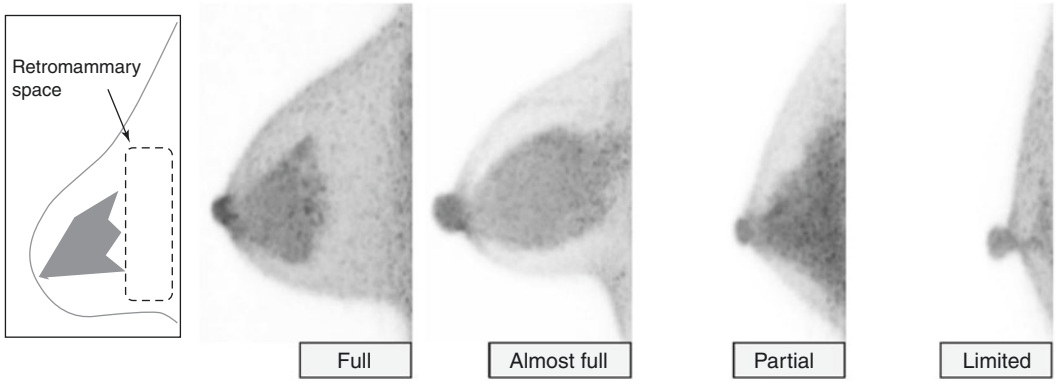

Fig. 3 Field of view (FOV). FOV is categorized as *full*, *almost full*, *partial*, and *limited*. (From Miyake et al., Diagnostics (Basel) 2021;11(7):1267)

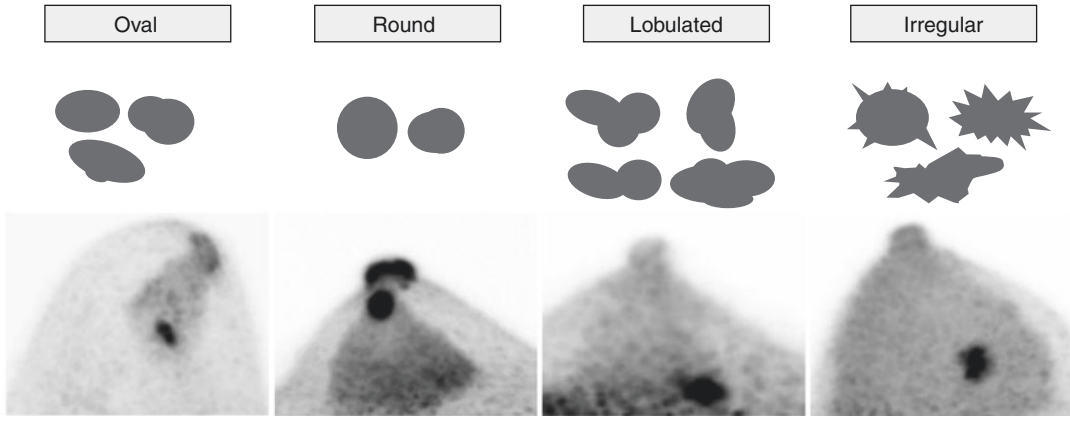

Fig. 5 Mass uptake. Mass uptake is uptake larger than 5 mm composed of a three-dimensional uptake finding, which usually has relatively abrupt margins. (From Miyake et al., Diagnostics (Basel) 2021;11(7):1267)

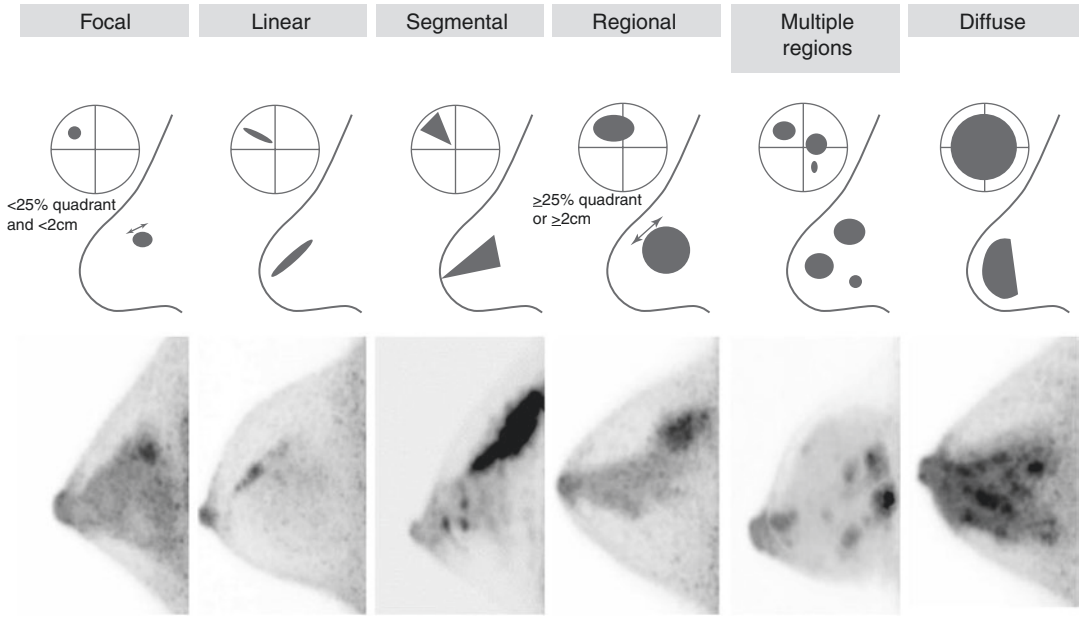

Fig. 6 non-mass uptake (NMU). NMU is uptake that has a pattern different from that of the bFGU and has a shape that cannot be called a focus or a mass. (From Miyake et al., Diagnostics (Basel) 2021;11(7):1267)

Detection of Cancers with Breast PET

In 2014, Caldarella et al. published a meta-analysis of eight published studies in which PEM was performed in a total of 873 women with breast lesions to detect malignant lesions early [27]. They showed that pooled sensitivity and specificity of PEM were 85% (95% confidential interval [CI], 83%–88%; I^2 73.8%) and 79% (95% CI, 74%–83%; I^2 62.8%), respectively.

Table 1 summarizes the sensitivities of breast PET for breast cancers in comparison with whole-body PET/CT according to tumor size [28–33]. Overall, the most of breast cancers larger than 2 cm were detectable even with

Table 1 Sensitivity for breast cancers according to tumor size: Breast PET versus whole-body (WB) PET/CT

References	Types of breast PET	≤1 cm		1–2 cm		>2 cm	
		Breast PET (%)	WB PET/CT (%)	Breast PET (%)	WB PET/CT (%)	Breast PET (%)	WB PET/CT (%)
Eo [28]	PEM	73	60	95	84	100	96
Kalinyak [29]	PEM	92	72	100	92	95	100
Yamamoto [30]	PEM	67*	13	64	36	100	88
Nishimatsu [31]	dbPET	57	43	95	91	100	100
Yano [32]	PEM	52*	32	91	91	–	–
Sueoka [33]	dbPET	79*	52	93	88	96	99

* Significantly superior compared to WB PET/CT ($p < 0.05$)

both whole-body PET/CT and breast PET, resulting in almost equivalent sensitivities between the two modalities. However, whole-body PET/CT demonstrated limited performance in smaller tumors, with a sensitivity ranging from 13% to 72% for tumors ≤1 cm. On the other hand, breast PET had the sensitivities of 52–92% (52–92% for PEM, 57–79% for dbPET) in the detection of tumors ≤1 cm. Yamamoto et al. reported that PEM was significantly more sensitive than PET/CT in tumors of equal or less than 1 cm (66.7% vs. 13.3%; $p = 0.008$), while not in tumors of 1–2 cm nor in tumors of larger than 2 cm [30]. Yano et al. showed that the sensitivity of PEM was significantly higher than that of PET/CT in sub-centimetric invasive cancers (52% vs. 32%, $p = 0.03$; 50% [3/6] vs. 0% [0/6] for T1a, and 52% [13/25] vs. 40% [10/25] for T1b), while no difference was found in the tumors larger than 10 mm (91% [12/23] for both modalities) [32]. Sueoka et al. investigated diagnostic performance of dbPET in a total of 639 invasive breast cancers subjected to both dbPET and whole-body PET (using PET/CT) before surgery [33]. They found that the overall sensitivity of dbPET was higher than that of whole-body PET (91.4% vs. 80.3%, $p < 0.001$), and the difference was significant in sub-centimetric tumors (80.9% vs. 54.3%, $p < 0.001$; 89.2% [33/37] vs. 62.2% [23/37] for T1mi, 76.9% [40/52] vs. 38.5% [20/52] for T1a, and 80.0% [88/110] vs. 59.1% [65/110] for T1b).

Ductal carcinoma in situ (DCIS) can be either positive or negative on breast PET with ^{18}F-FDG. More DCIS can be detected with breast PET compared with whole-body PET systems. Yamamoto et al. showed PEM identified five of six DCIS (71.4%), but whole-body PET did none of seven DCIS (0%)[30]. According to a multicenter series reported by Berg et al., the sensitivity of PEM for identifying DCIS in ipsilateral breast in presurgical planning examinations for patients with newly diagnosed breast cancer was 41% (23/56) [34]. Graña-López et al. performed dbPET for 139 surgery-confirmed pure DCIS cases and showed that dbPET was positive only in 8% (7/89) of low-risk DCIS but in 90% (45/50) of high-risk DCIS [35]. They suggested the possibility of dbPET in distinguishing indolent DCIS from potentially hazardous DCIS and supporting active surveillance for the management of those women with low-grade DCIS.

Diagnostic performance of breast PET among modalities has been investigated in a few studies (Table 2) [34, 36]. According to Berg et al., conventional imaging including mammography with or without targeted ultrasonography (US) had poor sensitivity (27% in the per-breast analysis and 21% in the per-lesion analysis) in the diagnosis of ipsilateral additional lesions [34]. When compared with MRI, PEM had comparable or lower sensitivities, but had greater specificity, therefore less likely to prompt unnecessary biopsies. They concluded that PEM is complementary to MRI in defining the preoperative disease extent and is an alternative in women who cannot tolerate MRI due to claustrophobia and contrast media allergy.

Table 2 Diagnosis of ipsilateral additional cancers in patients with known breast cancer

References	No. of patients	Analysis	Sensitivity			Specificity		
			PEM	MRI	CI	PEM	MRI	CI
Schilling [36]	208	Per lesion	85% (34/40)	98% (39/40)	–	74% (20/27)	48% (13/27)	–
Berg [34]	388	Per breast	51% (42/82)	60% (49/82)	27% (22/82)	91% (279/306)*	86% (264/306)	97% (298/306)
		Per lesion	41% (47/116)*	53% (61/116)	21% (24/116)	80% (151/189)*	66% (124/189)	94% (178/189)

Conventional imaging (CI) includes mammography with or without targeted ultrasonography
* Significant difference between PEM and MRI ($p < 0.05$)

Breast Cancer Screening Using PET and Breast PET

Mammography remains a mainstay of breast cancer screening. US may also be used as an adjuvant breast cancer screening modality. Recently, breast MRI is recommended for screening women who are at high risk for breast cancer. However, PET is not a standard modality for breast cancer screening, and its use for asymptomatic women is debatable. On the other hand, in Japan, PET cancer screening using whole-body PET systems, mostly, PET/CT, with or without the combination of breast PET is widely performed as opportunistic screening project aimed at the detection of cancer at an early stage. "The Guidelines of FDG-PET Cancer Screening" has been provided by The Japanese Society of Nuclear Medicine and the Japanese Council of PET Imaging (first version in 2004 [37], latest version 2019 [38] as of August 2021). Here, we review current evidence on the performance of breast cancer screening using PET or breast PET, discuss its merits, concerns, and perspectives.

Early reports of the whole-body PET cancer screening program showed the limited values in the breast cancer detection, with the detection rates ranging 0.18–0.23% [39–41]. Whole-body PET or PET/CT seemed to hold insufficient performance compared with breast cancer screening by mammography and physical examination, in which the cancer detection rate has been reported as 0.31% [42]. According to the Ministry of Health, Labour and Welfare in Japan, the benchmark of cancer detection rate at population-based mammography screening is 0.23% or more [43].

In 2015, Minamimoto et al. reported the results of breast cancer detection in the whole-body PET cancer screening program from a nationwide Japanese survey [44]. Among 62,054 asymptomatic females who underwent the whole-body PET or PET/CT with ^{18}F-FDG between 2006 and 2009, 473 cases who had findings of possible breast cancer in any screening test were analyzed. Finally, 161 cases were verified as breast cancer, and 83.0% of breast cancer cases were stage 0 or I. They showed that a relative sensitivity of whole-body PET (83.9%, n = 473) was higher than that of mammography (77.5%, n = 145) and similar to that of US (84.0%, n = 160). However, in a direct comparison on the same set of subjects, the relative sensitivity of whole-body PET for invasive cancers tended lower than that of mammography without statistical significance (PET vs. mammography, 61.5% vs. 73.1%, n = 26) and was significantly lower than that of US (PET vs. US, 67.6% vs. 91.2%, n = 34), suggesting limited performance of conventional whole-body PET and PET/CT.

In 2016, Yamamoto et al. published a preliminary report of breast cancer screening by PEM [45]. They reviewed 265 women who underwent PEM after whole-body PET scanning with ^{18}F-FDG between 2011 and 2014, consisting of 165 asymptomatic women and 100 women who had breast symptoms (including symptoms highly

suggestive for breast cancer). Of 265 participants, six breast cancers in six participants were detected, including five invasive breast cancers and one DCIS. The screening-detected cancers were positive on PEM in all six cases, but only in two cases on whole-body PET. The overall recall rate, cancer detection rate, and positive predictive value (PPV) of PEM were 8.3%, 2.3%, and 27.3%, respectively. They concluded that their results indicate that PEM may be an acceptable modality for breast cancer screening.

Torii et al. reported the initial results of breast cancer screening using ring-type dbPET performed in 519 asymptomatic women who received opportunistic PET cancer screening during June 2016 and June 2017, the first year of this project [46]. The overall recall rate and PPV of dbPET were 27.6% and 2.8%, respectively. The initial recall rate was high due to frequent false positives. However, later, Yuge et al. reviewed the follow-up results from 2016 to 2020, and showed that the recall rate successfully decreased year-by-year to around 11% in later years and became lower than that of digital mammography plus digital breast tomosynthesis [47].

^{18}F-FDG is not a specific tracer for breast cancers and can accumulate in various benign entities, such as inflammation, complicated cyst, fat necrosis, intraductal papilloma, fibroadenoma, fibrocystic change, etc., resulting in potential false positives. Breast PET is expected to detect more early breast cancers than whole-body PET system with its improved sensitivity for smaller lesions. However, at the same time, breast PET holds the risk of increasing the number of false-positive findings. This is problematic in the breast cancer screening for asymptomatic women, because lower prevalence of cancers (or low pre-test probability) will generate more false positives than true positives. Currently, efforts are made to reduce false positives. One of such measures is the stratification of breast uptake based on its morphological features, which may be able to be established if the widespread of use of the lexicon is achieved. So far, several studies have suggested that morphological uptake features aid in the prediction of malignancy. Narayanan et al. demonstrated that lobulated or irregular uptake morphology was the strongest predictor of malignancy, followed by ipsilaterality and PUVmax, in the diagnosis of additional cancers using PEM in patients with newly diagnosed breast cancers [19]. Satoh et al. found that mass uptake was significantly associated with malignancy compared to focus in unexpected uptake on dbPET [22]. Sasada et al. showed that mass and focal or segmental non-mass lesions were significantly associated with malignancy in 709 patients with breast cancer [21]. Noise reduction or distinction of noise from true uptake is another on-going approach to reduce false positives. Yuge et al. demonstrated that the reproducibility assessment using a pair of dbPET images generated from half list-mode data was useful to discriminate noise from true uptake [48]. Nevertheless, false positive is a common issue among various modalities. On contrast-enhanced MRI, breast parenchymal enhancement (BPE) is commonly seen especially in the first and fourth weeks of the menstrual cycle [49] and generates false positives as well as false negatives by hiding true lesions. Breast PET has been shown to have a higher specificity compared to contrast-enhanced MRI [34].

The potential advantage of breast PET may be that it can maintain diagnostic ability in dense breast, which is often difficult to be assessed on mammography. Background ^{18}F-FDG uptake on either PEM or whole-body PET has been reported to increase significantly with mammographic breast density [50, 51]. However, Vranjesevic et al. demonstrated, despite increase of ^{18}F-FDG uptake with breast density, peak SUV in dense breasts never exceeded 1.5, which is below a cut-off level commonly used to distinguish malignancy from benign [51]. Their findings suggest that breast density is unlikely to impair the performance of ^{18}F-FDG PET in detecting breast cancer.

The major concerns related to breast PET screening may be radiation exposure and high costs. The radiation exposure must be carefully considered in cancer screening for healthy subjects. A typical ^{18}F-FDG dose of 185–370 MBq

(5–10 mCi) results in an estimated whole-body dose of approximately 3.5–7.0 mSv, which is more than 5–10 times greater than that from two-view mammography (0.3–0.6 mSv) [52]. According to the International Commission on Radiation Protection, the cancer incidence induced by radiation exposure is estimated as 0.0048% per mSv. When breast PET is performed in adjunct with whole-body PET/CT scan like in the PET cancer screening in Japan, more radiation exposure is added by the CT scan (estimated radiation dose of 5.7–11.5 mSv) [40]. Nevertheless, the screening using whole-body PET systems has an advantage of being able to assess all tumors throughout the body at once, not just breast cancers. From the viewpoint of radiation exposure, a risk–benefit analysis of ^{18}F-FDG PET cancer screening based on a Japanese nationwide survey showed that it is beneficial for women above 30s for PET and above 50s (variable injection dose) or 60s (constant injection dose) for PET/CT [53]. In the situation where the whole-body cancer screening using whole-body PET systems is performed, the addition of breast PET may be beneficial because breast PET potentially improves the detection rate of early breast cancers without additional radiation exposure. However, it is still unknown if breast PET would be an appropriate modality used for population-based breast cancer screening. Some think it is unlikely that breast PET becomes a modality for breast cancer screening like mammography [54]. The requirement for fasting and long study time (around 100 min) is not conducive to patient throughput in a screening setting. In addition, shielding requirements for a breast PET scanner due to the high-energy photons from ^{18}F-FDG may make it challenging to install breast PET in most breast centers. All efforts must be made to reduce radiation dose while maintaining diagnostic image quality, and to seek the appropriate position of breast PET in the breast cancer screening.

In 2018, Japanese Breast Cancer Society published a revised Breast Cancer Practice Guideline and provided a new statement on breast cancer screening using PET or breast PET for women with dense breasts. They say that although not yet established, evidence suggests the use of PET or breast PET as an auxiliary modality for mammography possibly contributes to increase the detection of breast cancer in dense breast, thus it is not denied that the PET is used as an opportunistic breast cancer screening modality, if she understands the disadvantages including cost and radiation exposure. It is considered to be a huge step forward, since there had been no positive consensus about the use of PET in the local breast cancer assessment. With the on-going efforts to the establishment of more sophisticated diagnostic approach, the methodological improvement to reduce radiation exposure, as well as the advent of PET tracers, breast PET has a potential to evolve the breast cancer diagnosis. Continuing accumulation of experience and further verification will reveal the true values of breast PET in the breast cancer screening.

Summary

In summary, breast PET, either PEM or dbPET, is a modern functional imaging modality used in the detection of breast cancer and the assessment of tumor biology. Several studies demonstrated that breast PET with ^{18}F-FDG has improved detectability for small cancers than conventional whole-body PET systems. There has been limited evidence on the performance of breast PET in the breast cancer screening, but preliminary studies suggest breast PET likely has a reasonable diagnostic performance. However, there are several concerns to be addressed, including frequent false positives, radiation exposure, and high cost. Further studies are warranted to sophisticate the breast cancer diagnosis using breast PET and figure out the true values of breast PET in the breast cancer screening.

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