Chapter 9
Clinical Evaluation of Focused High-Resolution Breast PET

Kanae Kawai Miyake and Yuji Nakamoto

Abstract Breast cancer has high incidence among women worldwide. Previous studies indicate that conventional whole-body positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) can be used to detect metastasis in patients with breast cancer. However, it may not perform well in the assessment of the primary site, mainly due to limited spatial resolution. To circumvent this limitation, some groups have developed high-resolution PET systems that are specifically designed for breast evaluation. In this chapter, we review features of dedicated breast PET systems and present examples of clinical studies performed thus far. These include our clinical experiences with a comprehensive breast PET system, using a ring-shaped scanner. Future developments related to specific breast PET systems are also discussed.

Keywords Dedicated PET • High resolution • Breast cancer

9.1 Introduction

Breast cancer is one of the most common malignancies among women worldwide, with estimates of 232,340 new cases of invasive breast cancer in the United States and 1.8 million new cancer cases from 188 countries in 2013 [13, 17]. Several randomized, controlled trials in Europe and the United States showed that mammography screens contributed to a reduction of breast cancer mortality by 25–48% [9, 35, 37], underscoring the benefits of early detection using imaging techniques. Individualized minimal invasive multidisciplinary approach, in conjunction with lumpectomy, sentinel lymph node biopsy, radiation therapy, and/or systemic therapy, is one of the current treatment trends for breast cancer [18, 19]. Thus, imaging techniques that allow early detection to tailor personalized therapy may play an important role in breast cancer diagnosis and prognosis.

K.K. Miyake • Y. Nakamoto (✉)
Department of Diagnostic Imaging and Nuclear Medicine, Kyoto University Graduate School of Medicine, 54 Shogoinkawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan
e-mail: ynakamo1@kuhp.kyoto-u.ac.jp

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Positron emission tomography (PET) is a useful technique, which enables to visualize biologic functional processes and molecular features within the human body. Potential clinical roles of PET techniques for breast cancer may include the early detection, problem solving in difficult mammographic cases, staging, restaging, treatment monitoring, and prediction of treatment efficacy. However, whole-body PET imaging results with ^{18}F-fluorodeoxyglucose (FDG) have revealed the limited diagnostic performance of conventional PET imaging in the evaluation of primary breast cancers [10], mainly due to the low spatial resolution of PET scanners. For instance, sensitivity for the visualization of primary tumors smaller than 1 cm was shown to be low [2]. To overcome this problem, high-resolution PET systems for focal assessment of breast lesions have been developed by several groups.

9.2 Types of Focused Breast PET Scanners

A dedicated breast PET system provides high-resolution PET images with a limited field of view (FOV). In comparison to conventional whole-body PET, focused breast PET systems offer unique structural and computing features, such as close proximity to the breast, small detector elements, depth-of-interaction (DOI) measurement capability, and sophisticated reconstruction algorithms, which provide higher spatial resolution and higher photon sensitivity. In keeping with this notion, the design of dedicated breast PET scanners that have been developed so far can be comprised into two groups [8]: positron emission mammography (PEM) (Fig. 9.1a) and fully tomographic dedicated PET scanner (Fig. 9.1b, c). A list of manufactures is provided in Table 9.1.

PEM has two detector heads integrated with planar or curved breast compression paddles, which acquire limited-angle tomographic images from incomplete 3D data obtained with a mildly compressed breast (Fig. 9.1a). The positioning of the breast is similar to that in mammography, and two projections (craniocaudal and mediolateral oblique) are usually obtained. The Flex Solo II scanner (Naviscan, San Diego, USA)

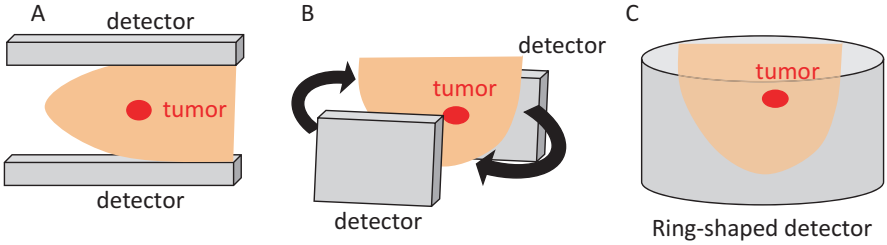

Fig. 9.1 Types of dedicated breast PET scanners. (**a**) Positron emission mammography (PEM). (**b**) Fully tomographic dedicated breast PET with dual-plate detector rotating around the breast. (**c**) Fully tomographic dedicated breast PET with ring-shaped detector

Table 9.1 Examples of dedicated breast (db) PET systems

PEM	Fully tomographic dedicated breast PET	
	Rotating planar head type	Ring-shaped detector type
PEM Flex Solo II (Naviscan) High-resolution PEM (Stanford U)	Clear-PEM (Hospital of Portuguese Institute of Oncology) PEM/PET (West Virginia U) dbPET/CT (UC Davis)	MAMMI (Oncovision) Elmammo (Shimadzu) Partial ring dbPET (Pennsylvania U)

is a PEM device that was cleared for marketing by the US Food and Drug Administration (FDA) in 2009 [24] and is currently the most common and commercially available dedicated breast PET system in the United States. Usually, a scanning time for one projection is 7–10 min [25, 34]. The in-plane spatial resolution was reported to be 2.4 ± 0.3 mm full width at half maximum (FWHM) for images reconstructed with a three-dimensional (3D) list-mode maximum likelihood expectation maximization (MLEM) algorithm. On the other hand, the cross plane spatial resolution is low, with a reported FWHM of 8.0–8.2 mm [24, 25], but attenuation and scatter corrections are available. This system is equipped with quantitative metrics to measure quantitative values, called PEM uptake values (PUV) [36]. A biopsy capability is included in this model.

The fully tomographic dedicated PET systems are newer generations of PET devices that acquire complete 3D data from an uncompressed breast, and there are several variations in the detector design. One is a dual- or multi-plate detector rotating around the breast (Fig. 9.1b), such as Clear-PEM developed by the Portuguese consortium under the framework of the Crystal Clear Collaboration at CERN [1] and PEM/PET system developed at West Virginia University [32]. Another type of the fully tomographic dedicated PET systems is a ring-shaped detector encircling the breast (Fig. 9.1c), which includes MAMMI (Oncovision, Valencia, Spain) and Elmammo (Shimadzu, Kyoto, Japan).

In Kyoto University, authors examined a scanner performance of the Elmammo prototype (Shimadzu, Kyoto, Japan) and have been performing human imaging with this system since 2009 [26]. Elmammo has a complete ring-shaped detector, consisting of 36 detector blocks arranged in three contiguous rings with 12 detector modules, which have a transaxial diameter of 185 mm and an axial FOV of 155.5 mm (Fig. 9.2). Each detector block has four layers with a 32 × 32 array of 1.4 × 1.4 × 4.5 mm^3 lutetium gadolinium oxyorthosilicate (LGSO) crystals, coupled to a 64-channel position-sensitive photomultiplier tubes (PSPMT). This system has also DOI measurement capability. Elmammo is one of those systems that can achieve the highest spatial resolution among PET systems for human applications. With the Elmammo prototype, minimal FWHMs in the radial, tangential, and axial directions are 1.6, 1.7, and 2.0 mm and 0.8, 0.8, and 0.8 mm, for filtered back projection (FBP) and 3D dynamic row-action maximum likelihood algorithm (DRAMA) reconstructions, respectively [26]. These values are much smaller than the FWHM obtained with whole-body PET or PET/CT systems of approximately 5–7 mm [7, 12]. Elmammo has capabilities of attenuation and scatter corrections and holds a

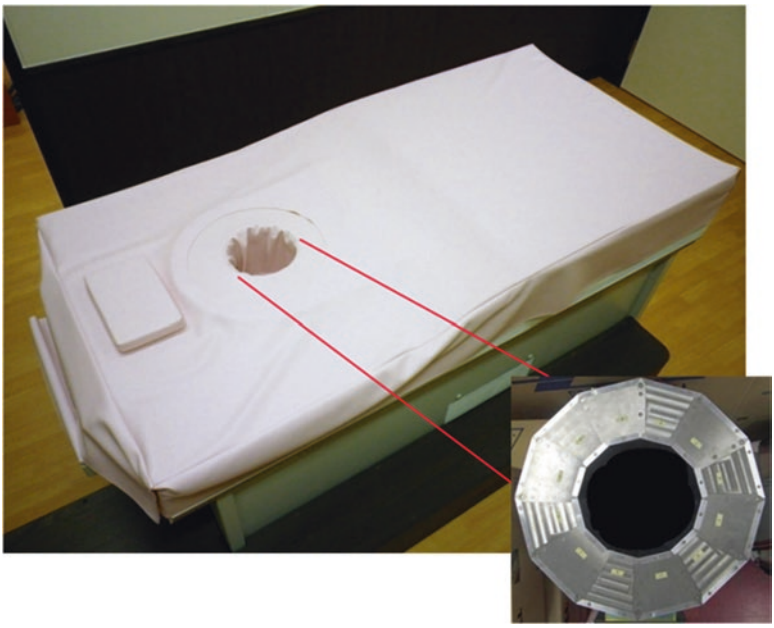

Fig. 9.2 Elmammo prototype (Shimadzu, Kyoto, Japan). This is a fully tomographic dedicated breast PET system with ring-shaped detectors. A patient lies in the prone position with her breast in the aperture of the ring-shaped detector (Cited from Miyake et al. [26])

quantitative metrics to obtain standard uptake value (SUV). A breast is usually scanned for 5 min with a patient lying in a prone position. Because the axial FOV of the ring-shaped scanner is designed to be large enough to cover the entire depth of a breast, the whole image is obtained at once without changing the position of the detector. Elmammo is commercially available since 2014 in Japan.

9.3 Clinical Values of Focused Breast PET Systems

In comparison to conventional whole-body PET, the potential advantages of the high-resolution PET systems may include (1) improvement of detection of breast cancer uptake, (2) visualization of detailed distribution of PET tracers accumulated in breast lesions, and (3) quantification of tumor uptake with less biased interpretation, resulting from the partial volume effect. Although available published data are still limited, there have been several published studies that addressed the diagnostic values of dedicated breast PET with ^{18}F-FDG in the detection of breast cancers in patients with suspicious lesions or established cancers. However, no or very few studies have addressed the diagnostic values of dedicated PET systems in the screening of asymptomatic women or assessment of treatment efficacy. In the following section, we summarize results of reported studies and describe potential advantages and disadvantages for the clinical use of dedicated breast PET.

9.3.1 Diagnostic value in Patients with Confirmed Breast Cancers

Several studies have addressed the diagnostic values of dedicated breast PET with ^{18}F-FDG in the detection of breast cancers in patients with known or suspected cancer lesions. As summarized in Table 9.2, most of these studies were performed with PEM scanners, which showed sensitivities of 80–95% and varied specificities that ranged from 33 to 100% in the detection of breast cancers [4, 14, 23, 28, 33]. There has been one study for a ring-shaped dedicated PET device (Elmammo prototype) that showed a sensitivity of 82% and a specificity of 50% [21]. Recently, a meta-analysis was performed for a total of eight PEM articles published between 2000 and 2012, which showed pooled sensitivities and specificities on lesion-basis analysis of 85% (95% CI, 83–88%) and 79% (95% CI, 74–83%), respectively, with area under the curve (AUC) of 0.88 [11]. These results are highly similar or slightly better than those of whole-body PET, with a sensitivity of 83% (95% CI, 73–89%) and a specificity of 74% (95% CI, 58–86%) [10].

However, these studies enrolled patients with confirmed breast cancers or suspicious lesions diagnosed based on conventional breast examinations, such as clinical diagnosis and mammography. Hence, overall sensitivities could have been elevated due to the high ratio of relatively large cancers. From a clinical point of view, in patients with recently diagnosed breast cancers, the main role of the dedicated breast PET may be the detection of additional lesions, because the new findings may change the treatment strategy, particularly in cases in which a conservative therapy is envisioned. Thus, some studies provided data with stratifying lesions to known index cancers and additional lesions in the ipsilateral or contralateral breasts.

For known index breast cancers, reported sensitivities of ^{18}F-FDG PEM are uniformly high, ranging from 92 to 95% (Table 9.3) [4, 5, 22, 34]. Two studies showed the sensitivities of PEM for index cancers were significantly higher than those of whole-body PET (56–68%) [22, 34]. In addition, Kalinyak et al. showed PEM (95%) had higher sensitivity than whole-body PET/CT (87%, $p = 0.03$) [22].

Table 9.2 Overall diagnostic performance of ^{18}F-FDG dbPET in detection of cancers in patients with suspected or known breast cancer

Authors	Year	dbPET type	No. of patients	Sensitivity[a]	Specificity[a]
Murthy et al.	2000	PEM	16	80%	100%
Levine et al.	2003	PEM	16	86%	91%
Rosen et al.	2005	PEM	23	86%	33%
Berg et al.	2006	PEM	94	90%	86%
Eo et al.	2012	PEM	101	95%	NA
Iima et al.	2012	Ring shaped	69	82%	50%

dbPET dedicated breast PET, *NA* not available
[a]Lesion-basis analysis

Table 9.3 Sensitivities of ^{18}F-FDG PET systems for index breast cancer

Authors	Year	No. of patients	Analysis	PEM	wbPET	wbPET/CT
Berg et al.	2006	77	Lesion basis	93%		
Kalinyak et al.	2014	69	Breast basis	92%[a]	56%	
		109	Breast basis	95%[b]		87%
Schilling et al.	2011	208	Lesion basis	93%[a]	68%	
Berg et al.	2011	388	Lesion basis	93%		

wbPET whole-body PET, *NA* not available
[a]Significantly superior compared to whole-body PET ($p < 0.05$)
[b]Significantly superior compared to whole-body PET/CT ($p < 0.05$)

Table 9.4 Diagnostic performance of ^{18}F-FDG PET systems in detection of additional ipsilateral breast cancer

Authors	Year	No. of patientss	Analysis	Sensitivity			Specificity		
				PEM	wbPET	wbPET/CT	PEM	wbPET	wbPET/CT
Kalinyak et al.	2014	69	Breast basis	47%[a]	6.7%		91%	96%	
		109	Breast basis	57%[a]		13%	91%		95%
Schilling et al.	2011	208	Lesion basis	85%	NA		74%	NA	
Berg et al.	2011	388	Breast basis	51%			91%		
			Lesion basis	41%			80%		

wbPET whole-body PET, *NA* not available (although scan was performed)
[a]Significantly superior compared to the other modality ($p < 0.05$)

For additional ipsilateral breast cancer, PEM had sensitivity of 41–85% and high specificity ranging from 74 to 91% (Table 9.4) [5, 22, 34]. Although the sensitivity of PEM was still limited, Kalinyak and colleagues demonstrated that PEM (47–57%) was more sensitive than either whole-body PET (6.7%, $p < 0.05$) or whole-body PET/CT (13%, $p < 0.01$) [22] (Table 9.4).

In the detection of additional breast cancers in the contralateral breasts, Berg et al. showed sensitivities of ^{18}F-FDG PEM were only 20% (3 out of 15) in the prospective reading session and 73% (11 out of 15) in the retrospective reading sessions [6].

Detection and visualization of sub-centimeter breast cancers (≤10 mm) have been challenging issues for conventional PET imaging. Whole-body PET has a limited sensitivity for sub-centimeter cancers, with reported sensitivities of 0% for T1a (>1 mm and ≤5 mm) invasive cancers and 13–39% for T1b (>5 mm and ≤ 10 mm) invasive cancers [3, 22]. However integrated whole-body PET/CT could provide improved sensitivities of 0–40% for T1a and 71–83% for T1b [21, 22]. In dedicated breast PET systems, according to data from small subpopulations, sensitivities of dedicated breast PET range 25–100% (average 46% for 28 reported lesions) for T1a

Table 9.5 Sensitivities of ^{18}F-FDG dbPET for sub-centimeter invasive cancer

Authors	Year	dbPET type	T1a (>1 and ≤5 mm)		T1b (>5 and ≤10 mm)	
			No. of lesions	Sensitivity[a] (%)	No. of lesions	Sensitivity[a] (%)
Berg et al.	2006	PEM	2	50	6	67
Schilling et al.	2011	PEM	4	100	21	86
Berg et al.	2011	PEM	16	25	13	46
Kalinyak et al.	2014	PEM	4	75	40	95
Iima et al.	2012	Ring-shaped	2	50	86	81
Total			28	46	86	81

dbPET dedicated breast PET
[a]Lesion-basis analysis

and 46–86% (average 81% for 86 reported lesions) for T1b (Table 9.5) [4, 5, 21, 22, 34]. Collectively, these data suggest that dedicated breast PET scanners are more sensitive than conventional PET scanners in the detection of sub-centimeter tumors. Kalinyak and colleagues demonstrated that in T1b cancers of index tumors, PEM has a significantly higher sensitivity than whole-body PET in the same population (95% versus 37%, $n = 19$, $p = 0.002$) [22].

In summary, current data may indicate that dedicated PET systems could yield better ability to visualize small cancers and additional ipsilateral breast cancers in patients with known breast cancer, compared to conventional whole-body PET systems. In our experience, we encountered several cases in whom PET with ring-shaped scanner (Elmammo prototype) performed better than conventional whole-body PET, in visualizing a sub-centimeter breast cancer (Fig. 9.3) and multiple additional cancers in the affected breast (Fig. 9.4).

It remains to be determined if dedicated breast PET practically contributes to the breast cancer detection in the current clinical setting, in which breast MRI is usually the second-line imaging after the application of conventional mammography and ultrasonography to diagnose breast cancers. Breast MRI is known to have high sensitivity for primary breast cancers. Notably, several studies that compared the diagnostic performance between PEM and breast MRI in patients with known or suspected breast cancer showed no difference in sensitivity [5, 6, 34]. Thus, it might be too optimistic to think dedicated PET with ^{18}F-FDG can replace breast MRI. Some practitioners suggest the clinical role of dedicated breast PET with ^{18}F-FDG may be an alternative examination to breast MRI in patients who are not able to tolerate breast MRI [6, 11, 15, 16].

Emerging technologies, such as multimodality imaging and application of new PET tracers, potentially allow further improvement of the breast cancer detection with dedicated PET systems. Berg et al. demonstrated that integration of PEM and

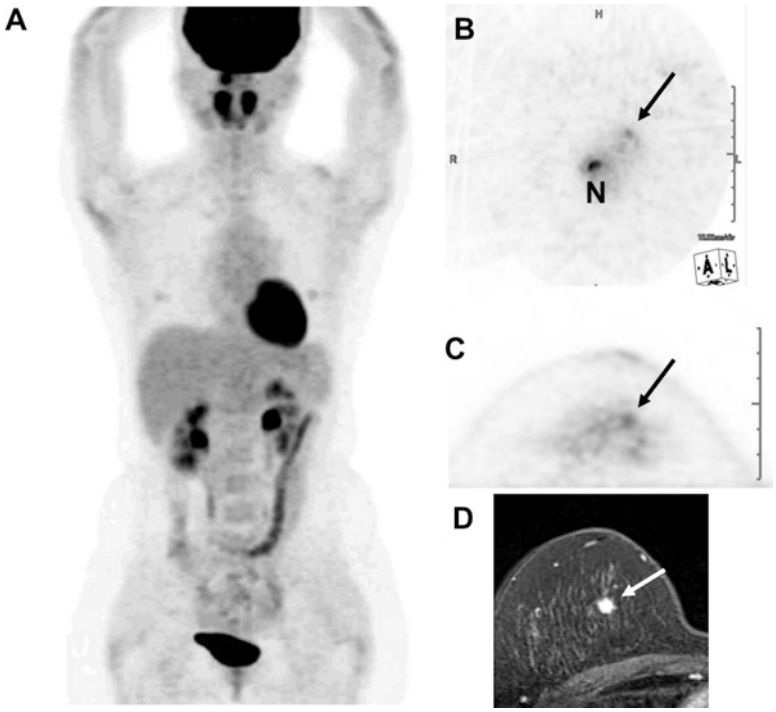

Fig. 9.3 A 55-year-old female with a 6-mm breast cancer in the right breast: Histology, invasive ductal carcinoma. While no apparent abnormal uptake is observed on whole-body PET/CT (**a**; maximal intensity projection PET image) after the administration of ^{18}F-FDG, dedicated breast PET (Elmammo prototype.; standard reconstruction mode) shows focal uptake (*arrows* in **b** [coronal image] and **c** [axial image]) corresponding to the cancer which enhances on MRI (*arrow* in **d**).

MR imaging increased cancer detection, compared to MR imaging alone (74% vs. 60%, $p < 0.001$) [5]. With the development of PET agents, dedicated breast PET could be used for the evaluation of expression status of molecules for targeted therapy, such as hormone receptors and human epidermal growth factor receptor 2 (HER2), and the functional status, such as tumor hypoxia. Making the most of the unique features of PET as functional imaging may provide clues to identify and establish a role of dedicated breast PET, which may be distinctive from that of breast MRI.

9.3.2 Screening of Breast Cancer in Asymptomatic Females

To the best of our knowledge, there have been no published studies investigating the diagnostic performance of dedicated PET systems in screening of asymptomatic females for the diagnosis of breast cancer. Given that dedicated breast PET can

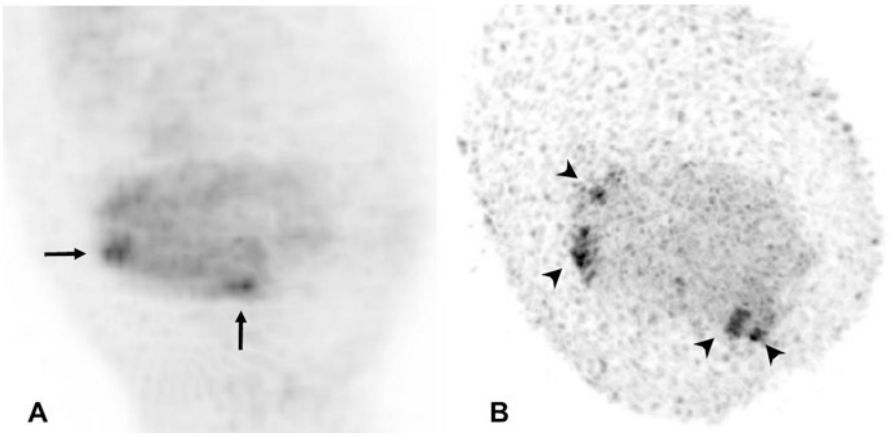

Fig. 9.4 A 58-year-old female with multifocal breast cancer: Histology, invasive ductal carcinoma. Compared to ^{18}F-FDG whole-body PET (**a**, coronal image), more cancer foci are visualized on ^{18}F-FDG dedicated breast PET (**b**, Elmammo prototype; enhanced-resolution reconstruction mode; coronal image)

visualize small cancers better than whole-body PET, the former may improve the detection rate of breast cancers in broad screening populations. However, radiation exposure and high operating cost could hinder the widespread use of dedicated breast PET systems as a screening modality. It has been estimated that common dose of ^{18}F-FDG, used in either dedicated breast PET or whole-body PET, is associated with higher radiation exposure than screening mammography, which creates a higher risk of radiation-induced cancer [20, 29]. Further discussions are needed to assess the benefits and the risks that are inherent to the application of dedicated PET systems for the breast cancer screening program. Recently, private cancer screening projects with whole-body PET/CT or PET/MRI are getting common in Japan. Exceptionally in this setting, dedicated breast PET can be easily used as an addtional study without further radiation exposure.

9.3.3 Distribution Assessment

Intratumoral heterogeneity is one of the hot topics in the PET oncology field. Like in other tumors, breast cancer may exhibit intra-tumor structural and functional heterogeneity, which may also be influenced by distinct gene expression patterns. Such heterogeneity could conceivably lead to altered distribution of PET tracers within the tumor. Dedicated breast PET may allow the visualization of more detailed distribution of PET tracers accumulated in the breast, compared to conventional whole-body PET. Figure 9.5 is an example in which dedicated breast PET visualized

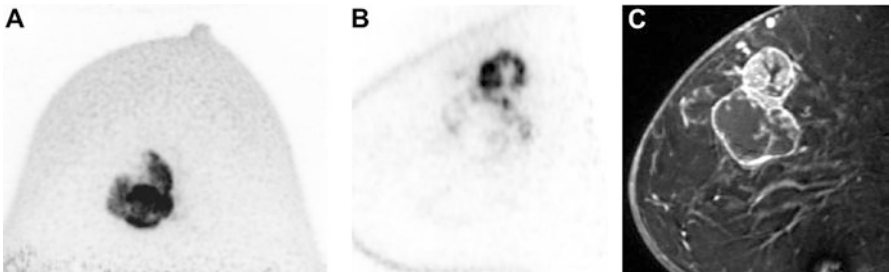

Fig. 9.5 A 73-year-old female with a solid and cystic breast cancer: Histology, invasive ductal carcinoma. Maximal intensity projection (**a**) of dedicated breast PET (Elmammo prototype; standard reconstruction mode) shows heterogeneous accumulation of ^{18}F-FDG to the tumor. On sagittal image of dedicated breast PET (**b**), intense uptake is observed corresponding to the enhancing solid parts of the tumor on MRI (**c**), indicating that detailed geographic distribution of FDG accumulation can be visualized on dedicated breast PET

detailed distribution of ^{18}F-FDG within a tumor. A high-resolution distribution map of PET tracers may be useful to determine appropriate biopsy sites. In manner, morphological PET findings that are specific for breast cancer could be identified and thus generate precise and detailed PET-MRI fusion images, which may provide a better understanding to personalized physiopathology of breast cancers.

9.3.4 Quantitative Analysis

Quantitative values such as PUV and SUV can be obtained with some dedicated breast PET systems. Increase of spatial resolutions potentially contributes to the reduction of the bias caused by the partial volume effect, which commonly underestimates quantitative values in smaller lesions on whole-body PET images. Reliability of quantitative values is under investigation in some systems.

9.3.5 Dedicated Breast PET-Guided Biopsy

Some of dedicated PET devices have been equipped with a biopsy capability. Biopsy capability has a merit in enabling histologic evaluation of each suspicious or equivocal findings on dedicated breast PET. Because the half-life of ^{18}F-FDG is 110 min, ^{18}F-FDG accumulated in a target lesion, which is visualized on dedicated breast PET, serves as a marker during the biopsy procedure.

9.4 Future Visions

One of the future trends in dedicated breast PET imaging may be multimodality imaging. Integration of this device to the other imaging modalities may hold advantages to make it easier to correlate dedicated PET images to other findings and provide anatomical maps that may be helpful for the accurate interpretation of functional information on dedicated PET. These maps could also be instrumental to compensate for the technical and diagnostic limitations of dedicated PET, such as FOV at the deep breast near the chest wall or the occurrence of false negatives. There have been several ongoing projects to generate integrated systems. In the University of California, Davis, a hybrid system of dedicated PET and CT scanning (dedicated breast PET/CT) has been developed [1]. In Washington University, a high-resolution PET insert that works in conjunction with a whole-body PET/CT system based on the "virtual pinhole PET" concept is under development [38]. With this system, whole-body PET images with higher-resolution images of the area close to the insert can be obtained. Under the framework of the Crystal Clear Collaboration at CERN, the integrated system of Clear-PEM with ultrasound is under development [27]. A ring-shaped PET scanner for simultaneous breast PET/MR imaging has been developed in the Brookhaven National Laboratory [31]. This MRI-compatible PET scanner is designed to be placed within the breast radiofrequency coil of a 1.5 T MRI scanner.

Development and broad access to additional PET tracers are one of the biggest issues that may be associated to the future evolution of dedicated breast PET imaging. There are various PET tracers that have been developed and can be used to characterize breast cancers (Table 9.6). However, clinical application of PET tracers other than ^{18}F-FDG is still limited. Breast cancer is one of the tumors in which

Table 9.6 Potential PET tracers for breast cancers

PET tracer	Target
^{18}F-fluoroestradiol (FES)	Estrogen receptor
^{18}F-fluorofuranyl norprogesterone (FFNP)	Progesterone receptor
^{89}Zr-trastuzumab	HER2
^{64}Cu-DOTA-trastuzumab	HER2
^{18}F-$Z_{HER2:342}$-Affibody	HER2
^{64}Cu-TP3805	VPAC1
^{18}F-2-fluoropropionyl-labeled PEGylated dimeric RGD peptide (FPPRGD2)	$\alpha_v\beta_3$ Integrin
^{89}Zr-bevacizumab	VEGF-A
^{18}F-fluorothymidine (FLT)	Proliferation
^{11}C-choline	Membrane synthesis
^{11}C-methionine	Protein synthesis
^{18}F-fluoromisonidazole	Hypoxia
^{18}F-annexin V	Apoptosis

HER2 human epidermal growth factor receptor 2, *VEGF* vascular endothelial growth factor

several key molecules linked to the effectiveness of systemic hormone therapy and chemotherapy in individual tumors have been already identified [18, 19, 30]. Noninvasive methods that can visualize the expression status of these molecules may be useful to evaluate the spatial heterogeneity of the molecules within tumors and to monitor the dynamics of temporal expression changes. There is an urgent need for development and broad access to additional PET tracers.

9.5 Conclusions

Technological innovation has led to the development of dedicated breast PET systems with high spatial resolutions. Although available clinical data are still limited, the ones available suggest that dedicated PET scanners could improve the detection of small breast cancers, as compared with the conventional PET scanners. Increased spatial resolution may also help to visualize detailed distribution of PET tracers within a tumor and could provide quantitative values with less bias caused by the partial volume effect. With the development of the multimodality techniques and new PET tracers for breast cancers, dedicated breast PET imaging may potentially allow further evolution in future breast cancer diagnosis and prognosis.

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