Review Article

Novel frontiers of dedicated molecular imaging in breast cancer diagnosis

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Abstract: Breast cancer (BC) is the most common cancer in women worldwide. In the last years, the contribution of nuclear medicine has grown based on the use of dedicated molecular breast devices for diagnosis and biopsy. Recent technical improvements have been achieved in order to increase the detection of smaller breast lesions using lower doses of radiotracers as well as to facilitate accurate biopsy sampling. Furthermore, new prototypes have been developed combining anatomic and functional imaging. Although the gamma-emitting ^{99m}Tc-sestamibi (^{99m}Tc-MIBI) and the positron-emitting ^{18}F-fluorodeoxyglucose (^{18}F-FDG) are the most widely used radiotracers, several new tracers have been investigated to target more specific biologic features of BC like proliferation, angiogenesis and tumour receptor status. Dedicated molecular breast devices have been introduced as an adjunct imaging tool to mammography (MG) and ultrasound (US) in the clinical work-up for BC. Additionally, due to the increased interest in molecular tumour subtype analysis and ribonucleic acid (RNA)-based gene expression profiling tests in the routine clinical practice, a possible new clinical application of dedicated breast imaging concerns locally advanced BC, principally in order to visualise intra-tumour metabolic heterogeneity enabling selection of areas with highest tracer uptake (vital tissue) for core needle biopsy. Hence, it will be possible to more adequately tailor the individual treatment, also enabling therapy response monitoring. This review evaluates the current and future perspectives as well as the shortcomings of breast imaging using dedicated nuclear medicine devices.

Keywords: Breast cancer (BC); breast dedicated systems; radiotracer-guided biopsy

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General introduction

Breast cancer (BC) is the most common tumour in women worldwide, with an estimated 252,710 cases and 40,610 deaths in the United States of America (USA), in 2017 (1). Currently, mammography (MG) is the primary screening test for BC (2). However, MG has a limited ability to detect breast lesions in dense breasts (3). Since the detection of BC in an early stage is associated with better prognosis (4), other imaging modalities have been introduced as complementary tools to MG (2). Indeed, magnetic resonance imaging (MRI) is recommended for BC screening in high-risk women (5-7). However, this procedure is limited in patients with obesity, claustrophobia, presence of implanted devices and renal insufficiency (8). In the last years, there has been an increasing interest towards nuclear medicine imaging techniques that enable the visualization of malignant functional changes in breast tissue. Several dedicated molecular imaging devices, including both single-photon and positron emission-based systems, are nowadays used as adjunct modalities to improve the detection of breast malignancies (9). Until now the main approach using dedicated molecular breast imaging (MBI) has been oriented to the complementary aspects provided by this modality for assessing extent of primary disease in patients with newly diagnosed BC and for problem solving, especially in patients with very dense breasts (10). However, a new area of interest has recently been delineated on the basis of the potential visualization of heterogeneity in locally advanced breast cancer (LABC). In this respect, and thanks to a better resolution, dedicated molecular breast devices appear to be more suitable than conventional tomographic imaging (PET/CT, SPECT/CT) opening a new diagnostic window for tumour characterization and biopsy (11). In this review we discuss these advances in dedicated breast imaging with an emphasis on recently introduced dedicated devices and radiotracers.

Dedicated nuclear medicine breast imaging

In *Table 1*, the characteristics of some commercially available dedicated breast imaging devices are summarized.

MBI

The terminology MBI is habitually used to refer to dedicated breast devices based on the use of single-photon emitting radiotracers like ^{99m}Tc-sestamibi (^{99m}Tc-MIBI) (12). One of the first devices using MBI technology was a single detector system known as breast-specific gamma imaging (BSGI) developed by Dilon Diagnostics (Newport News, Virginia, USA) (13). More recently, dual-head detector MBI systems like Discovery NM750b and LumaGem 3200s were introduced by GE Healthcare (Milwaukee, Wisconsin, USA) and by Gamma Medica, Inc. (Northridge, California, USA), respectively (14). All these devices are generically included in the MBI modality using a positioning similar to that of MG. In particular, the breast is placed between a compression paddle and the detector for BSGI or between two detectors when using the MBI device. The advantages of single-head configuration are lower costs and the possibility to perform a biopsy using an available complementary tool (15,16). The advantages of dual-head configuration are higher spatial resolution and therefore a potentially higher detection rate of small breast tumours and the possibility to use lower injected doses of ^{99m}Tc-MIBI (17,18). The clinical protocol consists of an intravenous administration of the radiotracer (740–1,100 MBq ^{99m}Tc-MIBI for single-head or 150–300 MBq for dual-head systems) into the arm contralateral to the breast lesion. Image acquisition starts 5–10 minutes after injection of the radiotracer and includes acquisitions of 8–10 minutes in both craniocaudal (CC) and mediolateral oblique (MLO) projections of each breast (*Figure 1*), with a duration of approximately 40 minutes in total per study (19). Since for MBI positioning is analogous to that of MG, nuclear medicine technologists need to receive an additional training in mammographic positioning. MBI images are interpreted according to a functional BI-RADS classification lexicon (19,20). Sun *et al.* reported a meta-analysis including a total of 19 studies on clinical usefulness of MBI for diagnosis of BC. The authors showed pooled sensitivity of 95% (95% CI: 93–96%) and pooled specificity of 80% (95% CI: 78–82%) for detecting BC, including eight studies and 2,183 lesions (21). MBI examinations are well tolerated by patients, no preparation (e.g., fasting) is required and the acquisition is performed in a comfortable upright position of the patient. Nevertheless, MBI examinations require the use of ionizing radiation. Newest MBI devices allow a reduced administered dose of 150–300 MBq ^{99m}Tc-MIBI (18) resulting in an effective whole body dose of 1.2–2.4 mSv (22).

Positron emission mammography (PEM)

PEM is a dedicated breast imaging device, commercially introduced by CMR-Naviscan Corporation (Carlsbad,

Table 1 Summary of characteristics of some commercially available dedicated breast imaging devices

Device	Design	Detector type	FOV (cm)	3D	Modality used for image correlation	Patient positioning	Breast compression	Biopsy possibility
Dilon 6800 (Dilon Diagnostics)	Single flat panel	NaI	20×15	No	MG	Seated	Yes	FDA-approved
Dilon 6800 Acella (Dilon Diagnostics)	Single flat panel	CsI	25×20	No	MG	Seated	Yes	FDA-approved
Discovery NM750b (GE Healthcare)	Dual flat panels	CZT	24×16	No	MG	Seated	Yes	FDA-approved
LumaGEM 3200s (Gamma Medica)	Dual flat panels	CZT	20×16	No	MG	Seated	Yes	Not FDA cleared
PEM Flex Solo II (CMR Naviscan Corporation)	Dual flat panels	LYSO	24×16.4	Yes	MG	Seated	Yes	FDA-approved
Clear-PEM (Crystal Clear Collaboration)	Dual flat panels rotating	LYSO	16.2×14.1	Yes	MRI	Prone	Yes	Not known
O-scanner (Shimadzu Medical Systems)	Three full rings	LGSO	18[d], 15.5[a]	Yes	MRI	Prone	No	Not known
	Two partial rings	LGSO	17.9[d], 10.5[a]	Yes	MRI	Semi-prone	No	Not known
MAMMI-PET (Oncovision)	Single full ring	LYSO	17[d], 4[a]	Yes	MRI	Prone	No	Prototype
	Double full rings	LYSO	17[d], 9.4[a]	Yes	MRI	Prone	No	Prototype

[d], diameter; [a], axial FOV length. FOV, field of view; 3D, three dimensional; BI-RADS, Breast Imaging Reporting and Data System; NaI, sodium iodide; MG, mammography; FDA, Food and Drug Administration; CsI, cesium iodide; CZT, cadmium zinc telluride; LYSO, lutetium-yttrium oxyorthosilicate; MRI, magnetic resonance imaging; LGSO, lutetium gadolinium oxyorthosilicate.

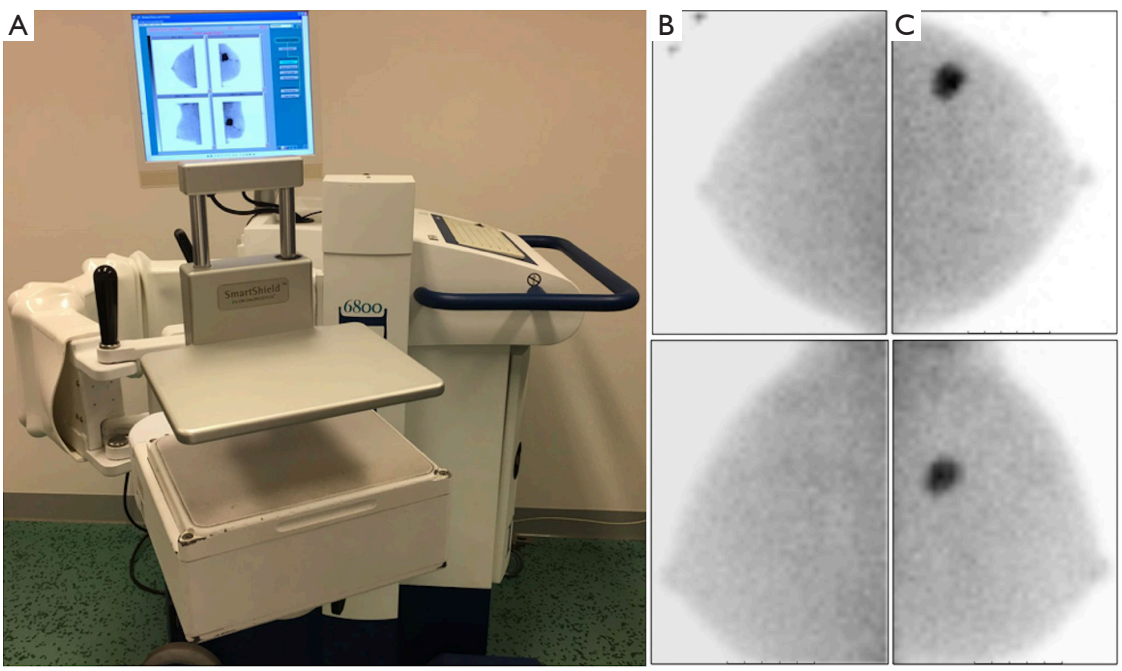

Figure 1 (A) Breast-specific gamma imaging (BSGI) device with in foreground the gamma camera detector and a compression paddle to immobilize the breast during image acquisition. BSGI craniocaudal (B) and latero-oblique (C) images of both breasts in a 49-year-old woman showing an 18-mm invasive ductal carcinoma in the left breast.

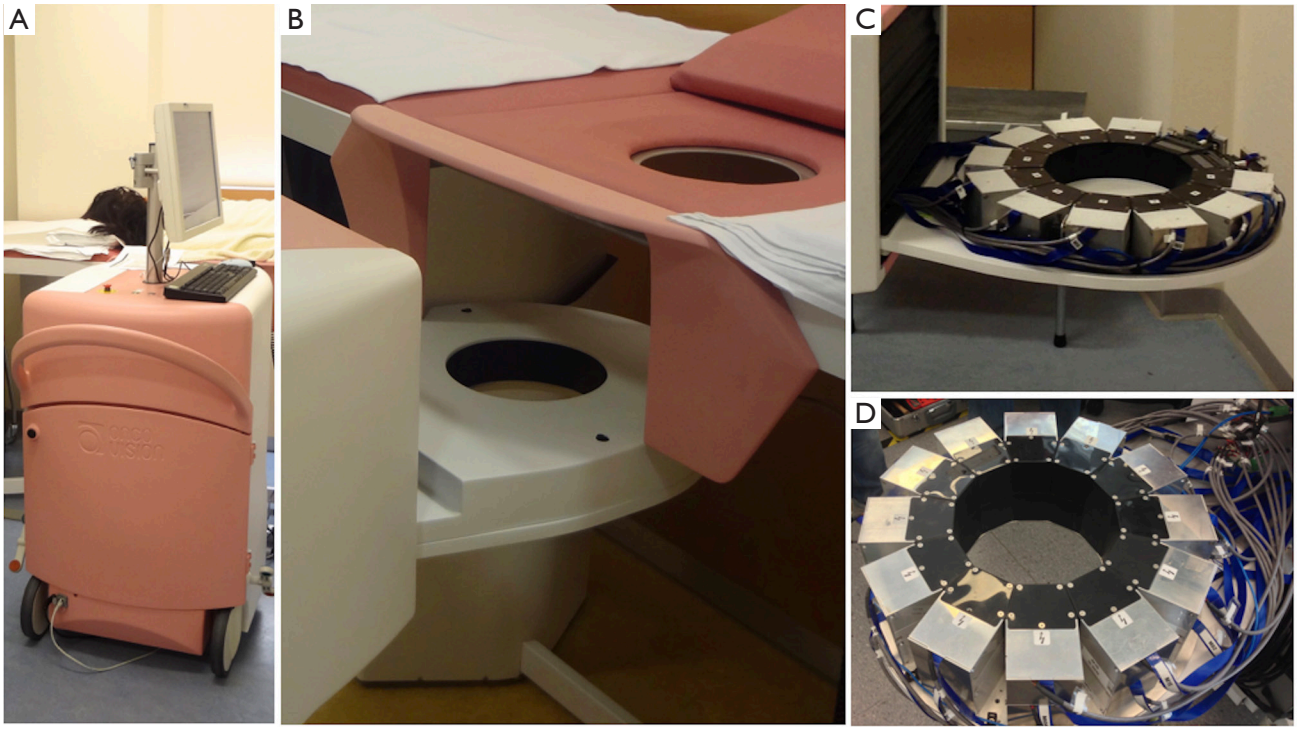

Figure 2 MAMMI-PET device for breast imaging with patient in prone position (A) with hanging breast configuration thanks to the special bed and ring camera (B). On the right, internal view of the scanner showing a version with a single (C) and a double (D) full ring of detectors. MAMMI, MAMmography with Molecular Imaging; PET, positron emission tomography.

California, USA), based on the use of positron-emitting radiopharmaceuticals like ^{18}F-fluorodeoxyglucose (^{18}F-FDG). PEM uses two flat detectors with mild compression of the breast and the patient in seated position. The PEM images are comparable to CC and MLO projections of MG (23). Unlike whole body positron emission tomography combined with computed tomography (PET/CT), PEM allows the detection of small breast lesions using lower ^{18}F-FDG doses with shorter acquisition times (24). The clinical PEM imaging protocol includes an intravenous injected dose of ^{18}F-FDG (approximately 370 MBq) into an antecubital vein contralateral to the breast lesion. Prior to ^{18}F-FDG injection, all patients have to fast for at least 4–6 hours and the blood glucose level has to be below 200 mg/dL. Images are acquired 60–120 minutes after radiotracer injection and require approximately 20 minutes per breast (10 minutes per CC and 10 minutes per MLO views) (25). PEM images are interpreted according to a functional BI-RADS classification (26). The sensitivity of PEM has been found to be 93% for known index lesions as small as 3 mm. Although this sensitivity is comparable to MRI, specificity of PEM is higher than MRI (74% *vs.* 48%) for the identification of unsuspected lesions (27). A meta-analysis evaluating 8 studies and 873 patients showed pooled sensitivity and specificity for PEM of 85% (95% CI: 83–88%) and 79% (95% CI: 74–83%) respectively (28). Advantages of PEM in comparison to PET/CT are in depicting small lesions as well as the possibility to perform breast biopsies using a special module (29). Despite the radiation exposure, PEM is considered an alternative tool in case of contraindications for MRI like overweight, claustrophobia, presence of implanted devices and renal insufficiency.

Dedicated breast PET devices

MAMmography with Molecular Imaging (MAMMI)-PET is a new breast dedicated PET system. MAMMI-PET is manufactured by Oncovison (Valencia, Spain) with a single or double full ring of detectors for tomographic image reconstruction with high resolution (1.6 mm). MAMMI-PET does not require compression of the breast; actually, the patient is positioned in prone position with hanging breast (30,31) as illustrated in *Figure 2*. Although there

are few studies on MAMMI-PET, this device enables the visualization of small tumours as well as tumours with heterogeneous ^{18}F-FDG uptake (11,32). In an extensive evaluation including 234 index lesions of at least 5 mm size in BC patients, MAMMI-PET was found to be more sensitive than standard PET/CT for lesions within the field of view (FOV) (33). Similar to other dedicated breast imaging devices (23), proper positioning of the breast is essential for MAMMI-PET examinations and some difficulties of the device to visualize breast lesions located close to the pectoralis muscle have been reported causing the need of a technical optimization of the bed for prone patient positioning (33). The MAMMI-PET protocol provides an intravenous administration of the radiotracer (180–240 MBq of ^{18}F-FDG) according to the body mass index. Images are obtained 60–120 minutes after the radiotracer injection with an acquisition time of approximately 5–15 minutes per breast depending on the breast size and type of device used (single or double ring) (11). The use of standardized terminology to report MAMMI-PET images has not been defined yet. One of the advantages of MAMMI-PET is the ability to perform semiquantitative analysis by measuring the standardized uptake value (SUV). Compared to the whole body PET/CT, MAMMI-PET offers lower doses as well as shorter acquisition times.

Recently, another dedicated breast PET (dbPET) device, known as O-scanner (Shimadzu, Kyoto, Japan) has been developed (34). This device consists of 36 detector modules arranged in three contiguous full rings with an estimated spatial resolution of 1.5 mm at the centre of FOV. Working protocols using O-scanner are comparable to the MAMMI-PET but acquisition times are shorter due to a transaxial effective FOV of 180 mm. Nishimatsu *et al.* have evaluated the diagnostic performance of O-scanner compared to whole body PET/CT including 179 index BC lesions in 150 patients. Based on pathological findings, the authors did not find a significant difference between both devices in term of sensitivity per patient and per lesions (95% and 92% for O-scanner *vs.* 95% and 88% for PET/CT, respectively). However, tumour-to-background ratios were significantly higher for O-scanner increasing levels of confidence in the diagnosis by observers thanks to higher tumour conspicuousness.

The same group of investigators also evaluated a dbPET with an open end through which the patient's arms can be placed. This device known as C-scanner, consists of 24 detector blocks arranged in two contiguous rings. Its evaluation in 159 women showed a lesion-based sensitivity of 81.1% increasing to 93% when lesions outside the FOV of the system were excluded (35).

Current indications

Currently, dedicated nuclear breast imaging is considered as a complementary imaging tool to MG and ultrasound (US) in patients with the following conditions: (I) with newly diagnosed BC to exclude multicentric, multifocal or contralateral disease and to assess response to neoadjuvant chemotherapy; (II) with suspected recurrence, especially when previous malignancy is occult on MG and US; (III) with indeterminate breast lesions and remaining diagnostic concerns; (IV) with technically difficult breast imaging like dense breast tissue, prosthesis; (V) with contraindication to MRI like claustrophobia, presence of implanted devices, renal insufficiency (19).

Dedicated breast devices for radioguided biopsy

In addition to dedicated breast imaging various complementary tools using radioguidance for lesion localization and vacuum-assisted biopsy have recently been developed.

MBI-guided biopsy

MBI-guided biopsy is a tool based on the use of ^{99m}Tc-MIBI as guiding radiotracer. One of the first developed devices (GammaLōc®, Dilon Technologies, Newport News, USA) has been validated and approved by the Food and Drug Administration (FDA) in 2009 for complementary use with the BSGI camera. The tool is equipped with a small, single-head detector with a slant-hole collimator for dedicated stereotactic localization (*Figure 3*). The patient is in seated position and the breast is mildly compressed between the grid paddle and the detector. The biopsy protocol is based on a 5-step procedure: (I) scout image and two stereotactic images (±20 degree angle) are obtained to determine the positioning of the lesion; (II) the software measures the index lesion coordinates; (III) the trocar needle is placed into the breast; (IV) subsequently, the verification of the correct needle placement is performed using Cerium-139 (^{139}Ce) as source; (V) this is followed by the biopsy using a vacuum-assisted device (VAD), a clip marker is placed at the biopsy site, a postbiopsy specimen scan is performed to confirm adequate biopsy specimens and postbiopsy MG is acquired to

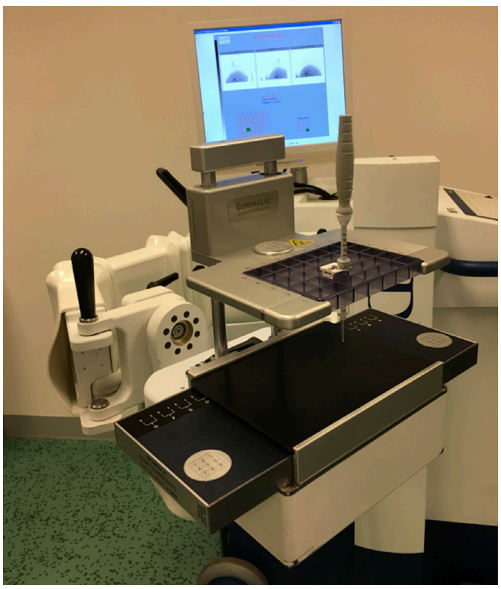

Figure 3 Biopsy device for complementary use with the BSGI device now equipped with a grid paddle for both breast immobilization and vacuum-assisted biopsy. For calculation of the depth of the primary breast lesion two stereotactic images are acquired using a slant-hole collimator placed oppositely to the biopsy device. BSGI, breast-specific gamma imaging.

evaluate the placing of the clip (16). Recently, the first clinical study has been performed including 38 patients (38 lesions). This biopsy tool was technically successful in all ^{99m}Tc-MIBI avid lesions. Indeed, all biopsy samples were radioactive and proved adequate for histopathology analysis. The mean procedure time was 71 minutes (range, 44–112 minutes). All biopsy procedures were well-tolerated by the patients (two hematomas and three vasovagal reactions). Based on these results, this new biopsy tool appears to be technically feasible to obtain accurate radioactive samples (36). However, further studies are needed to investigate the role of this device in the clinical work-up.

PEM-guided biopsy

PEM-guided biopsy is a biopsy device using principally ^{18}F-FDG as radiotracer. This device has been validated in 2001 (37) and has been approved by FDA in 2008. PEM-guided biopsy is a portable and compact device comprising two plate PET detectors and stereotactic technology (Stereo Navigator™ Naviscan, Carlsbad, California, USA) to calculate the coordinates of the breast lesion. The patient is in seated position and the breast is placed between both PET detectors with mild compression. The biopsy procedure involves five steps as follows: (I) initial biopsy scan to identify and target the lesion; (II) alignment scan to verify the correct position of the needle using Germanium-68 (^{68}Ge) as line source; (III) prebiopsy scan to confirm the correct positioning with biopsy needle in the breast; (IV) postbiopsy scan to ensure appropriate lesion is removed and (V) specimen scan to confirm adequate biopsy specimens. Postbiopsy MG is performed to ensure that clip placement corresponds with the biopsy site (29). To date, one multicentre study has been performed including 19 patients (24 lesions) showing that this biopsy device proved technically successful in all cases and was well-tolerated by patients. The authors reported a median procedure time of 32 minutes (range, 19–119 minutes), and 58% (14/24) of biopsied lesions were smaller than 10 mm (29). Based on these results, PEM-guided biopsy appears to be a promising biopsy tool for ^{18}F-FDG-avid breast lesions. In particular, this device allows re-imaging of the biopsied breast and biopsy sampling to ensure adequate biopsy without injection of an additional radiotracer. Recently, Argus *et al.* evaluated the feasibility of performing diagnostic PEM and PEM-guided biopsy on the same day, including 20 patients (27 lesions). The authors showed that it is possible for most patients (24/27 lesions) reducing radiation dose for both patient and medical staff (38).

MAMMI-guided biopsy

Recently, a semi-robotized system for MAMMI-guided biopsy tool was developed in the context of the European Union FP7-SME-2013-606017 MAMMOcare project and has technically been validated in 2017 (39). This biopsy tool comprises a dedicated dual-ring PET-detector with automated lesion localization software together with a vacuum-assisted biopsy needle attached to a robot-controlled arm (*Figure 4*). The patient is in prone position and the breast is placed in the opening of the device without compression (hanging freely). The biopsy procedure requires five steps. (I) First, acquisition of the whole hanging breast with closed PET-ring is acquired to determine the index lesion coordinates, afterward the system automatically calculates the shortest needle trajectory and subsequently positions the biopsy needle in that trajectory. (II) Second, scanning with the closed PET-ring and mild compression is obtained including only the part of breast with the index lesion. This step aims to adjust the new index lesion coordinates due to breast compression.

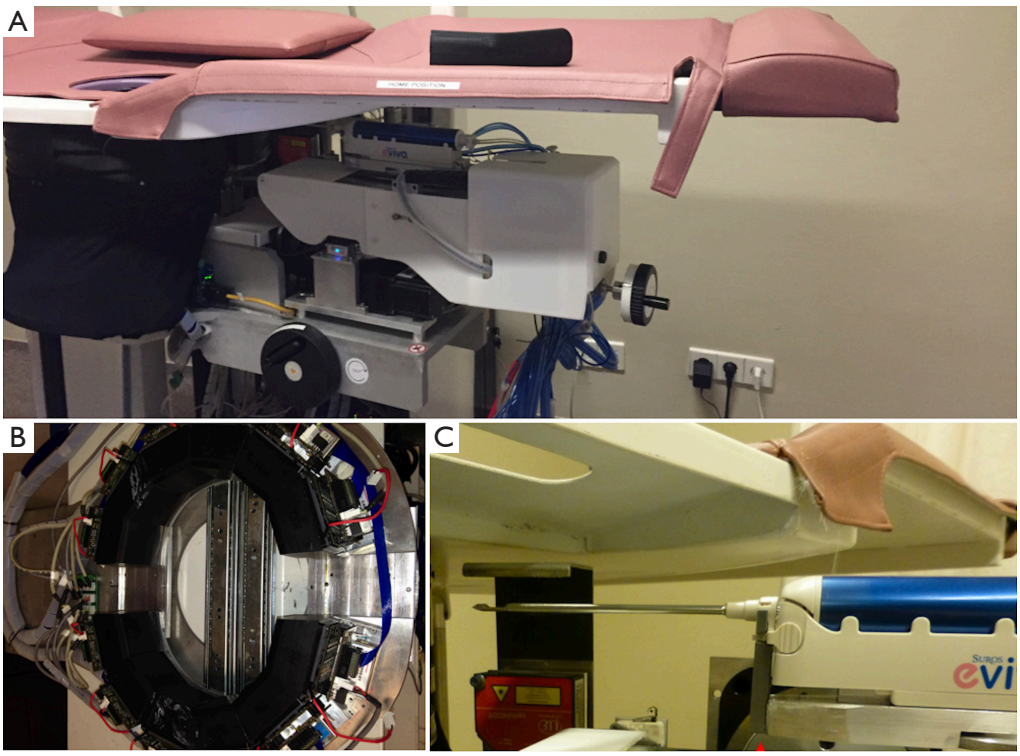

Figure 4 Prototype of the MAMMOcare device composed of a special bed for prone position of the patient, a PET-ring detector for image acquisition and a semi-robotized arm for vacuum-assisted biopsy (A). For biopsy, the PET-ring moves from a closing stand to an opening one (B) facilitating introduction of the needle (C). PET, positron emission tomography.

(III) Third step involves placing a biopsy needle into the index lesion, with the affected breast in compression and opened PET-ring. (IV) A new acquisition is performed with needle in place to verify the correct needle position in the index lesion. (V) Finally, biopsy is performed manually using VAD. Based on phantom experiment, the estimated time per lesion is approximately 30 minutes (39). Until now, only a technical evaluation has been performed showing an accuracy of 0.5, 0.6 and 0.4 mm for the x/y/z-axes. The system has been developed to optimize both conventional histopathology and ribonucleic acid (RNA)-based molecular diagnostics but no clinical study has yet been reported in the current literature.

Future applications

Targeted biopsy and precision breast cancer medicine

In the last years, the interest toward molecular analysis in routine practice has been increasing. This analysis is based on the tumour's gene expression profiles measuring RNA levels for selected genes. Several genomic tests have been developed for breast tumours (40,41). Among them, the MAMMAPrint (Agendia, Amsterdam, The Netherlands) test measures the expression of 70 genes through microarray analysis (42) for predicting the risk for tumour recurrence and for better selecting patients for adjuvant chemotherapy (43). Therefore, the goal of breast biopsy is to obtain an adequate sampling not only for increasing the likelihood of finding tumour tissue, but also for assessing the tumour subtype and genetic expression profile. This will facilitate stratifying patients and planning target-specific therapies in the context of a recently introduced concept of precision medicine in BC (44). Buyse *et al.* reported that only 81% of the tumour samples obtained with US-guided biopsy contained sufficient RNA for genetic analysis (45). Radioguided biopsy offers the possibility to obtain radioactive tumour samples that correspond with vital tumour areas clear of both necrotic and stromal tissue. Therefore, radioguided biopsy may be able to obtain sufficient RNA in the sampling useful for genetic expression profiles based on the principle of radiotracer uptake that associates areas with higher ^{18}F-FDG

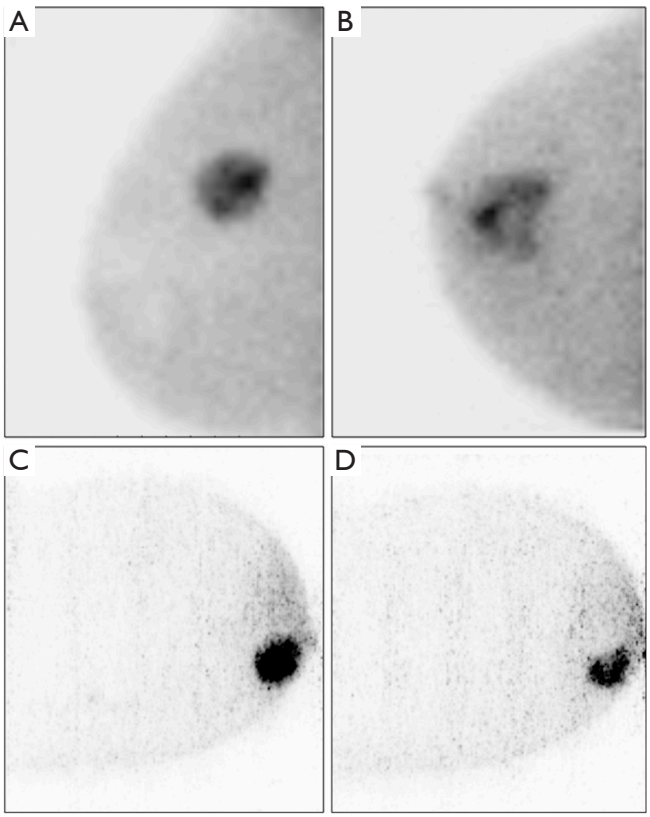

Figure 5 Heterogeneous uptake of ^{99m}Tc-MIBI in invasive ductal breast carcinoma with a 3-cm lesion (A) and a 5-cm lesion (B) as shown using breast-specific gamma imaging. In another patient, heterogeneous uptake of ^{18}F-FDG is seen after the first cycle of neoadjuvant chemotherapy in the superior part of the lesion (D), which was homogenous at baseline acquisition (C) with a dedicated hanging breast PET scanner. ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; PET, positron emission tomography.

uptake with those parts of the tumour with increased glycolysis, representing the most proliferative parts of the tumour. As reported in the literature, high ^{18}F-FDG uptake in the primary tumour is associated with poor prognostic features such as grade 3 and triple negative BC (46,47). A similar working model is assumable using ^{99m}Tc-MIBI which also shows a positive association between the level of tracer uptake in breast tumours and the amount of viable tumour tissue. Hence, the possibility for biopsy of the most proliferative part of the tumour may increase the accuracy of tumour sampling for genetic analysis, and consequently lead to better individual treatment planning with possible improvement of patient outcome.

This new clinical possibility for targeted biopsy using radioguidance was the rationale for design of the precision biopsy device described in the above mentioned MAMMOcare project. This may be of interest in LABC, principally in tumours with heterogeneous uptake (*Figure 5*) enabling selection of those areas with highest tracer uptake, avoiding sampling of necrotic or fat tissues. Indeed, Koolen *et al.* reported non-correspondence of ≥2 cm between the core biopsy location indicated with a marker and the tumour area with highest ^{18}F-FDG uptake in 28 (14%) of 203 tumours in stage II and III BC (48). Further studies are needed to evaluate the feasibility of this potential application.

Use of new radiotracers for MBI, PEM, MAMMI

^{99m}Tc-MIBI and ^{99m}Tc-tetrofosmin are currently used as gamma-emitting radiotracers to detect BC. ^{99m}Tc-MIBI is the preferred radiotracer for MBI due to its uptake inside mitochondria (49), thus reflecting mitochondrial activity and electric transmembrane potential of BC cells (50,51). ^{99m}Tc-tetrofosmin is similar to ^{99m}Tc-MIBI with localization mostly within cytosol (49,52,53). Another potential gamma-emitting radiotracer is ^{99m}Tc-maraciclatide, also known as ^{99m}Tc-NC100692, which is an angiogenesis marker. Indeed, ^{99m}Tc-maraciclatide binds to receptors of integrins, such as αvβ3, which are significantly upregulated in endothelial cells during angiogenesis (54). In a series evaluating 39 patients ^{99m}Tc-maraciclatide showed comparable lesion uptake to ^{99m}Tc-MIBI in both malignant and benign breast lesions (55). Furthermore, as shown in *Table 2*, there are new radiotracers like ^{99m}Tc-annexin V for apoptosis (56), ^{99m}Tc-bombesine for gastrin-releasing peptide receptor (57) and ^{123}I-labeled estrogen receptor (ER) ligand (58).

Regarding the positron-emission radiotracers, ^{18}F-FDG is the most used tracer in BC. ^{18}F-FDG is a glucose analogue, and so it is used for assessing the metabolism of breast tumour cells. In the last years, several new radiotracers (as shown in *Table 2*) have been developed: (I) ^{18}F-fluoromisonidazole (^{18}F-FMISO) as a marker of tumour hypoxia; (II) ^{18}F-fluorothymidine (^{18}F-FLT) reflecting cell proliferation; (III) ^{18}F-galacto-recognizing arginine-glycine-aspartic acid (^{18}F-Galacto-RGS) as an angiogenesis tracer; (IV) ^{18}F-annexin as an apoptosis radiotracer; (V) radiopharmaceuticals with receptor affinity like ^{18}F-fluoroestradiol (^{18}F-FES) for estrogen receptor (ER); ^{18}F-fluoro furanyl norprogesterone (^{18}F-FFNP) for progesterone receptor (PR), and ^{89}Zr-trastuzumab for human epidermal growth factor receptor 2 (HER2) (59).

Table 2 Some existing and potential radiotracers for dedicated molecular breast imaging

Radiotracer	Type of emission	Functional information (uptake mechanism)
^{99m}Tc-MIBI	Single-photon	Mitochondrial uptake
^{99m}Tc-maraciclatide	Single-photon	Angiogenesis
^{99m}Tc-annexin V	Single-photon	Apoptosis
^{99m}Tc-bombesine	Single-photon	Binding to BN receptor
^{123}I-labeled Z-MIVE	Single-photon	Binding to ER
^{18}F-FDG	Positron	Glucose metabolism
^{18}F-FMISO	Positron	Hypoxia
^{18}F-FLT	Positron	Proliferation
^{18}F-Galasco-RGS	Positron	Angiogenesis
^{18}F-annexin	Positron	Apoptosis
^{18}F-FES	Positron	Binding to ER
^{18}F-FFNP	Positron	Binding to PR
^{89}Zr-trastuzumab	Positron	Binding to HER2

^{99m}Tc-MIBI, technetium 99m-methoxyisobutylisonitrile; BN, growth factor bombesin; ^{123}I-labeled Z-MIVE, iodine 123 labeled cis-11β-methoxy-17α-iodovinyl estradiol; ER, estrogen receptor; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; ^{18}F-FMISO, ^{18}F-fluoromisonidazole; ^{18}F-FLT, ^{18}F-fluorothymidine; ^{18}F-Galacto-RGS, ^{18}F-galacto-recognizing arginine-glycine-aspartic acid; ^{18}F-FES, ^{18}F-fluoroestradiol; ^{18}F-FFNP, ^{18}F-fluoro furanyl norprogesterone; HER2, human epidermal growth factor receptor 2.

Dedicated hybrid systems

Another important advance in BC imaging is the development of dedicated hybrid devices combining anatomic and functional imaging. Various prototypes concerning these hybrid systems have been introduced in recent years.

Dual-modality breast tomosynthesis (DMT)

DMT is a new hybrid scanner, which includes the digital X-ray detector and an MBI detector. Both detectors rotate around a common axis with mild breast compression (60). DMT provides co-registered anatomic and functional breast images in three dimensions (3D). Although the results of the clinical pilot studies are encouraging, further studies will be necessary in order to optimize patient positioning and the acquisition protocol as well as to assess the additional value of this device relative to the separate modalities (60).

Dedicated breast SPECT/CT

Recently, a new dedicated hybrid system has been developed using single photon emission computed tomography combined with low-dose CT technology (breast SPECT/CT) (61). Compared to planar devices, dedicated breast SPECT/CT enables 3D imaging, and functional and anatomic fused images, without the necessity for breast compression, making it more comfortable for the patients and with possibility to perform *in vivo* quantification of ^{99m}Tc-MIBI uptake.

MBI/US system

An integrated MBI/US prototype composed of an upper US mesh panel and a lower MBI detector has recently been developed (62). An optical tracking system provides the real-time position of the US probe relative to the breast lesion. A software application enables projection of the US FOV onto the MBI images. Therefore, this prototype system allows to integrate the anatomical US images with the functional MBI images. Hence, MBI/US may resolve positive findings on MBI that are occult on MG, as well as obtain a better lesion correlation between US and MBI (62).

Concluding remarks

The increasing use of dedicated devices for molecular

imaging in BC goes hand in hand with an evolution concerning their clinical applications. Based on the initial experience with these devices in detection of small breast lesions, there is a growing interest in studying the metabolic heterogeneity in LABC, opening a future window for tumour characterization and selection of areas for biopsy. In the context of precision medicine, the contribution of dedicated BC imaging using different radiotracers may become important not only to personalize therapeutic approaches on an individual basis, but also to monitor primary tumour response. Finally, the incorporation of allied technologies tends to gradually transform the current generation of dedicated nuclear medicine devices into hybrid systems with the ability to simultaneously evaluate the functional and morphological characteristics of BC.

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Footnote

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