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REVIEW ARTICLE

The current role of nuclear medicine in breast cancer

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ABSTRACT

Breast cancer is the most common cancer in females worldwide. Nuclear medicine plays an important role in patient management, not only in initial staging, but also during follow-up. Radiopharmaceuticals to study breast cancer have been used for over 50 years, and several of these are still used in clinical practice, according to the most recent guideline recommendations.

In this critical review, an overview of nuclear medicine procedures used during the last decades is presented. Current clinical indications of each of the conventional nuclear medicine and PET/CT examinations are the focus of this review, and are objectively provided. Radionuclide therapies are also referred, mainly summarising the methods to palliate metastatic bone pain. Finally, recent developments and future perspectives in the field of nuclear medicine are discussed. In this context, the promising potential of new radiopharmaceuticals not only for diagnosis, but also for therapy, and the use of quantitative imaging features as potential biomarkers, are addressed.

Despite the long way nuclear medicine has gone through, it looks like it will continue to benefit clinical practice, paving the way to improve healthcare provided to patients with breast cancer.

INTRODUCTION

Breast cancer (BC) continues to be the leading cause of cancer incidence in females worldwide (2.3 million new cases in 2020, corresponding to 11.7% of all cancers) and the fifth leading cause of cancer mortality (685,000 deaths in 2020).[1]

Nuclear medicine has played an important role in oncology since the first radiopharmaceuticals started to be used in clinical practice.[2] Significant developments have occurred in this transversal medical discipline during the 21st century, both in the diagnostic and therapeutic fields, leading to patients' healthcare and quality of life improvement.[3] Nuclear medicine is useful in BC by contributing to its primary diagnosis, locoregional and systemic staging, monitoring and predicting response to therapy, and identifying progression or recurrence.

Based on our clinical experience, we identified radionuclide-based diagnostic and therapeutic procedures commonly used in daily practice. Then, we revised each topic, by conducting a comprehensive, critical and objective analysis of current literature, selecting the most important published guidelines and/or other significant papers and documents that support each indication.

This critical review provides a comprehensive overview of nuclear medicine procedures used over the past 50 years and summarises the current clinical indications of conventional nuclear medicine and positron emission tomography/CT

(PET/CT) examinations. Finally, recent developments and future perspectives in nuclear medicine are discussed.

HISTORICAL SUMMARY

The use of radiopharmaceuticals in BC started in the 40's with Phosphorus-32. Since then, several other gamma-camera and PET radiopharmaceuticals were investigated during the 70s and 90s.[4,5]

Cardiotoxicity of chemotherapeutic agents such as doxorubicin is a common side-effect of treatment. In this context, multigated radionuclide angiography (MUGA) has been helpful for more than 50 years.

The advent of the phosphate labelled radiopharmaceuticals in the 70s, introduced bone scanning for the evaluation of metastatic disease, which has become a routine procedure for the detection of metastatic bone lesions and monitoring the response to treatment.

Since the early 90s, lymphoscintigraphy and the identification of the sentinel lymph node (SLN) have had a significant impact on the management of patients with early BC, avoiding unnecessary axillary dissection, and greatly impacting on patient's quality of life.

Although PET has been available since the mid-80s, it has only become clinically accessible since the turn of the century, significantly changing the impact of nuclear medicine on BC staging and management.

Besides the evolution of radiopharmaceuticals, it is important to note the equipment progression in the last two decades, in particular, the change from planar scintigraphy to single-photon emission computed tomography (SPECT) and hybrid SPECT/CT, the development of breast-dedicated systems, the improvement in PET resolution and sensitivity, as well as, the dissemination of hybrid imaging, enabling faster examinations with lower doses and higher accuracy for lesion detection, compared to older generation scanners.

DIAGNOSTIC EXAMINATIONS CURRENTLY USED IN CLINICAL PRACTICE

Gamma-camera examinations

Gamma-camera imaging helps in BC detection, local and systemic staging, guiding treatment using sentinel node imaging, monitoring cardiotoxicity, and detecting recurrent disease in the skeleton (Table 1).

Multigated radionuclide angiocardiography (MUGA)

Anthracyclines and the monoclonal antibody trastuzumab, used in BC treatment, have well documented cardiotoxicity, inducing a cumulative dose-dependent effect with direct and irreversible cellular damage to myocytes, which can lead to congestive heart failure and even cardiac death.[17]

In 1969, Mason et al described a technique in which γ radiation emitted from circulating isotopes could be detected in the vascular system with the use of a gamma camera.[18] Since then, several methods of assessing cardiac function with the use of radiotracers have been developed and nowadays MUGA or equilibrium radionuclide angiocardiography (ERNA) is regarded as the gold-standard to measure cardiac function (including systolic and diastolic performance and left ventricle ejection fraction), having high reproducibility and low inter- and intraobserver variability (<5%).[7,8,19] It has proven its usefulness

Table 1. Chronological evolution of the gamma-camera examinations used in breast cancer with the respective clinical indication and type of recommendation / document

Year	Gamma-camera examination	Clinical indications	Type of recommendation (date of last update)
1969	**MUGA**	Early assessment of cardiac function after chemotherapy	• ESMO guidelines (2019)[6] • SNMMI/EANM guidelines (2020)[7] • EANM guidelines (2022)[8]
1971	**Bone scan**	Initial staging of patients with clinically positive axillary nodes, large tumours *(e.g. ≥5 cm)*, aggressive biology or clinical signs, symptoms or laboratory values suggesting metastases. Restaging in case of suspected bone metastases, (pathologic) fractures or before radionuclide therapy.	• AUC (2017)[9] • ESMO guidelines (2019)[6] • NCCN guidelines (2023)[10]
1992	**Scintimmamography / MBI**	Situations when mammography and ultrasound have limited accuracy (*e.g.* in dense breasts)	• EANM / SNMMI guidelines (2022)[11]
1993	**SLN lympho scintigraphy**	Early breast cancer and clinically negative axilla, DCIS proposed for mastectomy, patients with N1 disease that was downstaged to N0 after neoadjuvant treatment	• Consensus recommendations from an International Expert Panel[12] • EANM/SNMMI guidelines (2013)[13] • Meta-analysis[14]
1996	**ROLL/SNOLL**	Localisation of non-palpable breast lesions and identification of the SLN	• Randomised controlled multicenter trial (2012)[15] • Systematic review[16]

AUC, appropriate use criteria; DCIS, ductal carcinoma in situ;SLN, sentinel lymph node.

in cardio-oncology, enabling the early assessment of functional heart changes after chemotherapy, when compared to baseline, which emphasises the need for serial imaging during treatment, in order to improve patient management decisions.[8,19] Regarding clinical guidelines, the ESMO guidelines about early BC recommend cardiac function evaluation with echocardiogram or MUGA in patients proposed for (neo)adjuvant systemic treatment with anthracyclines and/or trastuzumab.[6] However, the NCCN guidelines on cancer survivorship v. 1.2022 consider two-dimensional echocardiogram, coupled with doppler flow studies, as the cardiac imaging modality of choice. Although MUGA provides accurate measurements of left ventricular size and function because it is less operator-dependent, it cannot assess valvular abnormalities or cardiac hypertrophy, and implies ionising radiation exposure.

Bone scan

Bone scintigraphy results from the development of ^{99m}Tc-labelled polyphosphate by Subramanian in 1971.[20] It is a relatively inexpensive and non-invasive examination, that differs from conventional radiographic studies by its ability to access the entire body and to detect altered bone metabolic activity much earlier than structural changes become apparent on other imaging procedures, such as radiography, CT and MRI.[21]

Bone scintigraphy, by means of planar, SPECT and SPECT/CT imaging can be, therefore, a powerful first-line staging and treatment response evaluation tool.[22,23] It is indicated for initial staging of patients with clinically positive axillary nodes, large tumours *(e.g. ≥5 cm)*, aggressive biology, clinical signs, symptoms or laboratory values suggesting metastatic bone disease.[6,9,24] Additionally, bone scan can be used to restage patients with bone pain "*de novo*", and when there is, clinical or on imaging, suspicion of bone metastases. It may also be appropriate to monitoring metastatic disease and to evaluate patients with pathologic fractures or patients proposed for bone pain palliation with radionuclide therapies.[9] Nevertheless, when 2-[^{18}F]FDG and/or [^{18}F]NaF PE/CT is available, it seems to overtake the majority of these clinical situations, as explained in the section about PET/CT.

Bone flare phenomenon, characterised by increased radiotracer uptake as a result of increased osteoblastic activity in the healing bone, typically seen between 2 weeks and 3 months after therapy, should be taken into consideration when evaluating these studies.[22]

Breast-dedicated imaging using single photon emitting agents: scintimammography/molecular breast imaging (MBI)

The first report of radiopharmaceutical concentration in BC occurred in 1946, when Phosphorus-32 was demonstrated to concentrate in an ulcerating BC. Since then, several single photon-emitting agents have been investigated for scintimammography, including [^{99m}Tc]MDP (1973), Thallium-201 (1978), ^{99m}Tc-radiolabelled monoclonal antibodies (carcinoembrionic antigen (CEA) in 1978), [^{99m}Tc]MIBI (1992) and [^{99m}Tc]Tetrosfosmin (1995)).[4,5]

Currently, [^{99m}Tc]Sestamibi (MIBI) is the radiopharmaceutical of choice. Breast-dedicated small field of view (FOV) γ devices (Molecular Breast Imaging—MBI, earlier referred to as Breast-Specific Gamma Imaging -BSGI) have emerged worldwide and improved spatial resolution significantly.[25] This procedure provides non-invasive *in vivo* characterisation of breast lesions and has proven to be a valuable adjunct imaging modality for BC detection, with similar sensitivity as MRI.[26] It is useful when mammography and ultrasound have limited accuracy, such as dense breasts, free silicone or paraffin injections and in patients in whom MRI is contraindicated.[11] In addition to dedicated molecular breast imaging, complementary biopsy tools using [^{99m}Tc]MIBI -guidance have been developed and clinically implemented.[27]

Despite recent evidence and its acceptance within imaging societies, its use is not recommended yet in clinical guidelines. Moreover, the NCCN guidelines on BC screening v. 1.2022 mention that there is no role for MIBI in BC screening or evaluation of breast complaints during pregnancy or lactation, accordingly to the American College of Radiology.[28]

Sentinel lymph node lymphoscintigraphy

SLN mapping and biopsy have been used in BC since 1992.[29] In 1993, Alex et al introduced and demonstrated the accuracy of gamma-probe guided localisation of lymph nodes labelled with [^{99m}Tc]Sulphur colloid.[30]

SLN biopsy (SLNB) is a highly reliable method for identifying metastatic disease in regional lymphatic nodes. Nowadays, SLN procedure is the established standard care in early BC and clinically negative axilla, in DCIS proposed for mastectomy, and in patients with N1 disease that was downstaged to N0 after neoadjuvant treatment.[12–14]

SLN procedure is less invasive and has significantly lower morbidity than axillary lymph node dissection, with similar nodal relapse rates at 5 years.[31,32]

Radioguided SLNB may use several ^{99m}Tc-based radiotracers, nanocolloidal albumin being the most frequently used in Europe. The ideal radiotracer should show a rapid transit to the SLN(s), accompanied by a prolonged retention in the node(s).[13]

Injection techniques are based either on the superficial injection approach (including periareolar, subdermal and intradermal injections) or the deep (tumour-related) injection approach (including intra- and peritumoral injections), or a combination of both. Superficial injections generate quick visualisation of the drainage channels to the axilla, while deep (tumour-related) injections can trace accessory drainage patterns.[13,33]

Radioguided occult lesion localisation (ROLL) and sentinel node and occult lesion localisation (SNOLL)

Non-palpable breast lesions, which repreent about 30% of BC diagnoses, due to the widespread use of screening, require a

precise localisation, that allows for a correct excision, with an adequate margin of healthy tissues, but at the same time limiting the extension of the surgical procedure. There are several methods used for this purpose, such as skin marking with ultrasonography, intraoperative ultrasonography, carbon localisation, Iodine-125 seeds or, wire-guided localisation, under mammographic or ultrasonographic guidance. Some of these methods, however, are characterised by limited accuracy.[34]

In 1996, ROLL, a method for localising non-palpable breast lesions pre-operatively, was developed at the European Institute of Oncology, in Milan.[35] It is a low-invasive and fast method that consist of injecting ^{99m}Tc-radiolabelled human albumin colloid into the breast lesion or peritumorally, under stereotactic mammographic or ultrasonic guidance.[15,36] Scintigraphic images are acquired and skin projection of the lesion is marked afterwards. During surgery, a hand-held gamma-detecting probe is used for intraoperative localisation, providing more control over the procedure as it may be used to confirm that the radioactivity is contained in the centre of the specimen and that none is left at the excision site.[34,35] Additionally, good results from 3D radioguided occult lesion localisation (iROLL) have been presented.[37]

SNOLL is another technique that aims to optimise the localisation of non-palpable breast lesions and the identification of SNL simultaneously in a single localisation session. The protocol is similar to ROLL, but it enables the resection of both breast lesion and SNL during the gamma-probe guided surgery.[16,36]

PET/CT

PET/CT has emerged as a powerful tool in oncology and several radiopharmaceuticals have a significant impact in the clinical management of patients with BC (Table 2).

[^{18}F]Sodium fluoride ([^{18}F]NaF)

[^{18}F]NaF is a PET radiopharmaceutical that is chemoadsorbed to the hydroxyapatite crystals, showing high affinity for the high turnover sites of the skeleton. It was initially used in 1970s for bone scanning and more recently has been used for PET/CT imaging. In oncology, it is indicated for evaluation of metastatic bone disease and treatment response of bone lesions.[38] It has higher sensitivity and specificity than bone scan, due to a higher target-to-background ratio and to the technological advantages of PET imaging (sectional imaging, better resolution, and shorter protocol) over scintigraphy.[41]

One of the most challenging questions in metastatic BC continues to be the evaluation of bone treatment response. Overall, 2-[^{18}F]FDG PET/CT has shown higher sensitivity and specificity than bone scan for the detection of bone metastases in BC patients, mainly related to bone marrow metastases and osteolytic lesions, due to their high number of viable tumour cells. However, osteoblastic lesions are relatively acellular and have abundant bone matrix, so they are better detected by radiopharmaceuticals that are chemoadsorbed to the hydroxyapatite crystals, such as [^{18}F]NaF.

When compared with 2-[^{18}F]FDG in BC patients, [^{18}F]NaF shows higher sensitivity but lower specificity in evaluating bone metastatic disease.[42] In this context, a cocktail injection of 2-[^{18}F]FDG and [^{18}F]NaF has been considered by some authors, as it would allow the detection of osteolytic, osteoblastic and bone marrow metastases, as well as, soft tissue metastases.[42]

Regarding clinical guidelines, the NCCN guidelines on BC v. 2.2023[10] state that a bone scan or [^{18}F]NaF PET/CT is indicated before pre-operative systemic therapy (of patient with[1] $c \geq$ T2, or[2] cN+, or[3] cT1c, cN0 HER2-positive disease or TNBC), and

Table 2. Dates of FDA and EMA approval of PET radiopharmaceuticals used in breast cancer with the respective clinical indication and type of recommendation/document

PET radio pharmaceutical	FDA approval	EMA approval	Clinical indications	Type of recommendation (date of last update)
[^{18}F]NaF	1972	2015 EMA/212874/2015	Bone metastases identification and treatment response assessment	• EANM/SNMMI guideline (2015)[38] • NCCN guidelines (2023)[10]
2-[^{18}F]FDG	2000 (for oncology)	2018 EMA/496103/2018	Whole-body • Systemic staging of patients with clinical Stage IIB – IV • Lesion detection when there is suspicion of recurrence • Assessing response to treatment Breast-dedicated imaging MRI contraindication	Whole-body ESMO guidelines (2019)[6] ESTRO guidelines (2020)[39] ESMO guidelines (2021)[40] NCCN guidelines (2023)[10] EANM/SNMMI guideline being revised* Breast-dedicated imaging EANM/SNMMI guideline being planned*
[^{18}F]FES (Cerianna™)	2020	Not approved	• Detection of ER-positive lesions in patients with recurrent or metastatic BC • Patients selection for hormonal therapies	• NCCN guidelines (2023)[10] • EANM/SNMMI guideline being revised*

BC, breast cancer; PET, positron emission tomography.
*Some authors are participating in these guidelines.

in patients with recurrent/Stage IV presenting with bone pain or high alkaline phosphatase values. In patients with 2-[^{18}F]FDG PET/CT clearly indicating bone metastasis, [^{18}F]NaF PET/CT is not be necessary.

2-[^{18}F]FDG

Whole body PET/CT using 2-[^{18}F]FDG

Scientific papers focusing on 2-[^{18}F]FDG as radiotracer for oncology imaging have been published since the 1980s and FDA-approval was established in 1997.

2-[^{18}F]FDG uptake correlates with cellular metabolism and it is currently the most widely used radiopharmaceutical for PET imaging in patients with BC. It is indicated for staging, restaging and evaluating the response to treatment, and significantly impacts clinical management of BC patients.

Any non-understood incidental 2-[^{18}F]FDG-avid breast focus should be further investigated, because it may correspond to a malignant lesion in more than half of the cases.[43,44]

In the regional setting, 2-[^{18}F]FDG PET/CT presents high sensitivity and specificity for detecting extra-axillary lymph node metastases, especially in the internal mammary chain (80–94% and 86–90% respectively).[45,46] When involvement of other regional lymph nodes is suspected by 2-[^{18}F]FDG PET/CT (*i.e.* axillary level III/infraclavicular, supraclavicular or internal mammary lymph nodes), treatment decisions may change, in terms of surgical management[47] and/or definition of radiation therapy fields.[48–50]

As to the systemic staging, 2-[^{18}F]FDG PET/CT is useful to detect occult distant lesions (except for brain).[51] Overall, it is superior to conventional imaging in identifying distant disease, mainly bone metastases[51,52–54] Currently, there is robust evidence that 2-[^{18}F]FDG PET/CT impacts systemic staging and clinical management of patient from clinical Stage IIB to Stage IV.[43,55,56]

Whenever there are clinical symptoms, doubtful radiologic findings or rising tumor markers suspicious for recurrence, 2-[^{18}F]FDG PET/CT outperforms conventional imaging in detection of either locoregional or distant recurrent disease[43,57,58] ›. When recurrence is already documented by conventional imaging, the addition of 2-[^{18}F]FDG PET/CT impacts patient management in more than half of the cases.[43,58]

Considering clinical guidelines, both ESMO and NCCN refer that 2-[^{18}F]FDG PET/CT is more accurate for staging non-special type high-risk patients and advanced disease (Stage III), may replace traditional imaging, and may be useful in early BC when conventional modalities are equivocal.[6,10] In patients with diagnosed or recurrent metastatic disease, 2-[^{18}F]FDG PET/CT may substitute the combination of CT and bone scan for lesions detection and therapy monitoring, particularly in the suspicion of oligometastatic disease.[10,40] In this context, ESTRO also recommends 2-[^{18}F]FDG PET/CT to better define oligometastatic disease.[39]

When assessing response to therapy, 2-[^{18}F]FDG PET/CT has been proposed for the early prediction of pathologic complete response in locoregional disease.[59] In metastatic disease, it offers good performance in evaluating the response to systemic treatment, in particular in bone metastatic disease.[43] Two semi-quantitative approaches for response evaluation were proposed in 1999 (EORTC criteria) and 2009 (PERCIST 1.0), the latter being considered more straightforward and reproducible between readers than the EORTC criteria.[60,61] Moreover, when compared with conventional imaging, metabolic-based evaluation has shown to be a superior predictor of progression-free survival and disease-free survival.[62]

Breast-dedicated imaging using 2-[^{18}F]FDG: breast-dedicated PET (MAMMI PET and positron emission mammography PEM)

MAMMI PET enables the imaging of uncompressed hanging breasts in prone position using a ring-shaped scanner with a small FOV. PEM consists of imaging acquisition with breast positioned between compression paddles.

Both equipments present higher spatial resolution, shorter imaging time, reduced attenuation and higher count sensitivity, allowing for higher sensitivity to detect primary breast malignancies than whole-body 2-[^{18}F]FDG PET/CT (identification rate of 95% *vs* 87%).[63] They also have better diagnostic performance compared with X-ray mammography or ultrasonography, but comparable to that of MRI in the identification of invasive BC. Breast-dedicated imaging PET is useful when MRI is contraindicated, mainly due to gadolinium-based contrast agents contraindication, claustrophobia, obesity, and metal implants/devices.[63]

These techniques have the advantage that its diagnostic accuracy is not affected by dense breast tissue and/or menstrual cycle. However, due to the limited FOV, both PEM and MAMMI PET can miss small deeply located lesions closer than 2 cm to the chest wall, next to the pectoral muscle, or in the axillary region.[63–65]

PEM-guided biopsy has been validated, with the advantage that specimens can be imaged to confirm adequate sampling and guide the pathologist's analysis.[66]

These breast-dedicated imaging modalities have not been included in clinical guidelines yet.

16α-18F-fluoro-17β-fluoroestradiol ([^{18}F]FES)

[^{18}F]FES is a radiolabelled ligand of oestrogen receptors (ER) that was developed in the 1980s.[67] As the expression of ER may vary in the primary and metastatic lesions of BC patients at the same time and during the course of the disease, a single biopsy may not represent the expression of these receptors in every single lesion in the body. [^{18}F]FES enables *in vivo* quantification of ER expression, obviating the need of multiple tissue sampling. It was FDA-approved in 2020 (Cerianna^{TM}) as a diagnostic agent for the detection of ER-positive lesions, as an adjunct to biopsy in patients with recurrent or metastatic BC.[68] It can also be useful to select patients for hormonal therapies, determine the ER-status in lesions that are difficult to biopsy and stage ER-positive BC

patients with low metabolic activity, such as lobular BC. Its sensitivity is high in bone, lymph nodes and brain. However, liver evaluation is limited due to its physiologic biliary excretion.[68]

Currently, only the NCCN guidelines v. 2.2023 refer to the potential use of [^{18}F]FES PET/CT in patients with recurrent/stage IV ER-positive disease and to monitor metastatic disease.

THERAPY WITH RADIONUCLIDES

The therapeutic potential of Strontium-89 was documented by 1940, but was overlooked until the 70s.[69] Since this period, therapies using Samarium-153, Strontium-89 or Rhenium-186 have been used in the management of bone pain from metastatic cancers of many origins, including BC.[4,70] Generally, it is indicated in patients with painful, multifocal, and osteoblastic metastatic lesions, who did not respond to other therapeutic options and have more than 3 months of life expectancy. Response rate is approximately 75%, and 25% of the patients may even become pain-free.[70] The majority of patients are able to reduce or withdraw opioid analgesics and continue using non-steroidal anti-inflammatory medication. Despite the good results reported in literature, there are no clinical trials or other well-designed studies to corroborate its usefulness and impact on patient's outcome. Therefore, these therapeutic options are not included in the current clinical recommendations. The number of therapies performed worldwide seems to be decreasing and this may lead to its disappearance.

RECENT DEVELOPMENTS AND FUTURE PERSPECTIVES

Diagnostic radiopharmaceuticals

[^{18}F]-anti-1-amino-3-fluorocyclobutane-1-carboxylic acid (FACBC - Fluciclovine)

[^{18}F]Fluciclovine (Axumin^{TM}) is a leucine analogue PET tracer that depicts amino acid transport into cells. It is already FDA (2016) and [71]EMA (2017 - EMA/240225/2017)-approved for clinical use in patients with biochemically recurrent prostate cancer. As amino acid transport is upregulated in BC malignancies by comparison with normal breast epithelium, this PET radiotracer can also be useful in BC imaging.[72] Indeed, preliminary results showed higher avidity for [^{18}F]Fluciclovine than for 2-[^{18}F]FDG in the primary tumour and axillary lymph nodes of patients with ILC, although 2-[^{18}F]FDG performed better for imaging of no special type BC.[72] Also, decrease in [^{18}F]Fluciclovine uptake between pre- and post-neoadjuvant systemic therapy strongly correlated with percent reduction of tumour on pathology in BC patients.[73]

[^{68}Ga]/[^{18}F]-Fibroblast activation protein inhibitor (FAPI)

Fibroblast activation protein (FAP) is highly expressed in cancer associated fibroblasts of multiple cell types, including in BC, but not in quiescent fibroblasts.[74] In 2021, it was submitted for FDA-approval to study pancreatic cancer. Preliminary results using the FAP-targeted PET tracer [^{68}Ga]FAPI in BC patients revealed significantly higher tracer uptake compared with 2-[^{18}F]FDG in primary tumour as well as in metastatic disease, including the ILC subtype.[74] Moreover, it showed higher target-to-background ratios in the primary and metastatic lesions compared with 2-[^{18}F]FDG, which may be particularly advantageous in the detection of brain metastatic lesions, due to the low physiologic uptake of [^{68}Ga]FAPI.[75]

Human epidermal growth factor receptors (HER) agents

HER2-targeted agents (*e.g.* [^{89}Zr]Trastuzumab, [^{89}Zr]Pertuzumab, [^{68}Ga]Trastuzumab F(ab′)two fragments) are radiolabelled antibodies or antibody fragment ligands of HER2 receptors. As patients with HER2-positive tumours receive HER2-targeted therapies that reduce the risk of death, the possibility of identifying patients most likely to benefit from such directed therapies is of uttermost interest.[76] Considering that BC patients may have spatial and temporal heterogeneity of HER2 receptor expression, HER2-targeted PET agents offer the opportunity of *in vivo* whole-body mapping of HER2 expression, helpful to select patients for HER2-targeted treatments, even in cases of unsuspected HER2-positive lesions (in patients with HER2-negative primary tumours).[76,77]

Radionuclide therapies

Despite Radium-223 (Xofigo®) being FDA-approved since 2013 for treating patients with castration-resistant prostate cancer and bone metastases, some clinical trials are being performed in BC also, *e.g.* to evaluate the addition of radium-223 to an aromatase inhibitor (NCT02258451) or chemotherapy (ISRCTN92755158). The results of these studies are awaited to better understand the role of Radium-223 in BC.

Several pre-clinical studies about theranostics with radiopharmaceuticals Lutetium-177-labelled HER2, prostate-specific membrane antigen (PSMA) and FAPI have been published. These radionuclide therapies have already been administered in patients, and few case reports have described the use of targeted therapies in patients with BC.[78–80]

Concerning liver metastases in BC, some patients have been treated by radioembolisation (Yttrium-90 embedded in either glass or resin-based microspheres), nevertheless, the position of radioembolisation in this setting is not yet well stablished.[81]

PET/MRI

PET/MRI fuses the functional information of PET with the functional and anatomic information obtained with MRI.

For breasts evaluation, PET/MRI should be performed in prone position, using a breast-dedicated coil. It presents a modest increase in specificity compared to MRI alone,[71,82,83] but improves the diagnostic performance when assessing response after neoadjuvant therapy.[84] For nodal staging, 2-[^{18}F]FDG PET/MRI outperforms MRI alone,[85,86] but shows similar results compared to 2-[^{18}F]FDG PET/CT.[87] 2-[^{18}F]FDG PET/MRI has higher sensitivity for brain, hepatic and bone metastases compared to PET/CT.[88,89] Currently, CT still outperforms MRI for the evaluation of lung parenchyma, and consequently assessment of lung metastases is more difficult with PET/MRI than with PET/CT.

Radiomics/quantification

Textural features that measure tumour heterogeneity and changes in the surrounding stroma are emerging as potential prognostic imaging biomarkers in BC studies.[90,91] Recent studies suggest that imaging features reflecting tumour heterogeneity in BC are associated with more aggressive molecular phenotypes, reduced response to neoadjuvant treatment, and worse prognosis.[92,93]

Nevertheless, despite encouraging results, studies are far from providing definitive conclusions. The use of harmonisation programs (*e.g.* EARL certification for PET scanners and Image Biomarker Standardisation Initiative[94] for RADIOMICS analysis) will certainly help providing stronger evidence in the near future.

CONCLUSION

The general advantage of nuclear medicine imaging is the ability to document changes in a molecular structure or physiological processes, differently from radiological imaging modalities that show mainly morphological modifications.

Nuclear medicine provides information representative of function in patients with BC and it is a fundamental tool for disease diagnosis, staging, treatment guidance and prognostication. Both gamma-camera and PET/CT studies are considered first-line modalities in multiple clinical scenarios, recommended in imaging and clinical guidelines. Technical developments in both single-photon and positron emission-based systems, mostly becoming hybrid techniques nowadays, as well as the development of breast-dedicated molecular devices, significantly improved spatial resolution, sensitivity, examination duration and radiation exposure.

Although some tracers have been used for more than 50 years, new radiopharmaceuticals have been developed in recent years for diagnostic and therapeutic purposes in BC. Despite some not being routinely used in clinical practice yet, preliminary results are promising and it is expected that new PET radiopharmaceuticals will be used in clinical practice in the near future, increasing the role of nuclear medicine in BC.

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