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EDITORIAL

The EANM-SNMMI guideline on the role of [18F]FDG-PET/CT in breast cancer: Important milestones and perspectives for the future

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The Joint EANM-SNMMI guideline on the role of [18F]FDG PET/CT in breast cancer (BC) of no special type (NST), previously known as invasive ductal carcinoma, is important for the nuclear medicine and oncology communities [1]. Sofia Carrilho Vaz and co-authors discuss the utility of this imaging modality in different situations, from baseline staging to assessing treatment response and recurrence. For each scenario, the level of evidence, grade of recommendation (following NICE criteria), and percentage of agreement is provided. Contemporary BC management involves a multidisciplinary approach. The inclusion of the perspectives from medical oncologists, surgeons, radiologists and radiation oncologists, in addition to nuclear medicine specialists, provides a more complete view of the clinical implications and decision-making process.

In women, BC is the most frequent type of cancer and is still the leading cause of cancer death [2]. Substantial advancements in BC management occurred, however. Mortality from BC in the US declined from 48/100,000 women in 1975 to 27/100,000 women in 2019 [3]. Interestingly, 47% of this reduction resulted from improved treatment of stage I to III BC, 29% from improved treatment of metastatic disease and 25% from mammography screening [3].

Based on hormone receptors (HR), including oestrogen receptor (ER) and progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status, BC is typically divided into HR+/HER2- subtype, HER2+ disease (HR + or HR-) and triple-negative BC (TNBC) [4, 5]. Histological and biological features influence FDG avidity [1, 6], which is typically higher in NST BC than in invasive lobular carcinoma (ILC); in grade 3 cancers compared to lower-grade malignancies; in ER- tumours, notably TNBC, than in ER+ tumours [6]. BC without HER2 overexpression or amplification (HER2-) is now further divided into HER2-low and HER2-zero, as the antibody-drug conjugate trastuzumab deruxtecan has shown efficacy in HER2-low patients [7], offering an additional line of treatment to some patients within the ER+/HER2- and TNBC subtypes [5]. The guideline focuses on NST [1], excluding BC of special types, notably ILC which represents about 10% of invasive BC.

A large part of the EANM-SNMMI guideline document is devoted to baseline staging and to the emerging role of [18F]FDG PET/CT to assess the response to neoadjuvant therapy (NAT) in patients with high-risk early BC. With a focus on these two applications, in this editorial I will discuss areas of uncertainty and provide perspectives for the future.

Systemic staging requires careful selection of patients

[18F]FDG PET/CT is an established modality of tumour staging. In the multicentre study PETABC, 369 patients with invasive ductal carcinoma and clinical TNM stage III or IIB were randomly assigned to receive either [18F]FDG PET/CT imaging or "conventional staging" consisting in contrast-enhanced computerized tomography (ceCT) of the chest/abdomen and pelvis plus a bone scintigraphy [8]. A significantly larger percentage of patients imaged with PET/CT were upstaged to stage IV, compared to those imaged

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with traditional conventional imaging (23% vs. 11%; $p = 0.002$) [8].

Appropriate selection of patients that require [18F]FDG PET/CT is very important. With a 100% agreement between authors, the EANM/SNMMI guideline recommend [^{18}F]FDG PET/CT for baseline staging of BC patients with clinical stage IIB and stage III, but not for stage I. In the case of stage IIA (T1N1, T2N0), the evidence is less clear. Moreover, [18F]FDG PET/CT can be done instead of, and not in combination with, conventional imaging modalities [1]. Table-2 of the guideline shows the percentage of upstaging with [18F]FDG PET/CT for each initial clinical stage [1]. Upstaging can result from detection of distant metastases or regional nodes. Regarding more specifically the rates of distant metastases, two prospective studies [9, 10], and one retrospective study [11], provided results by initial clinical TNM substages in populations that were not selected by age or BC categories [1]. The mean upstaging to stage IV is already 10% for patients with clinical stage IIB (T2N1, T3N0) and further increases to 20% in stage IIIA, 25% in stage IIIB, and 32% in stage IIIC [1].

For clinical stage IIA (mostly represented by T2N0 patients [9, 10]), studies disagree on the percentage of upstaging with [18F]FDG PET/CT, including the three studies mentioned above [9–11]. Importantly, the study by Groheux considered only distant metastases or unknown N3 disease (infraclavicular, supraclavicular, or internal mammary nodes), which translated into an upstaging in 4.5% (2/44) of stage IIA patients (2.3% distant metastases; 2.3% N3 disease) [9]. By applying the same criteria to the three studies above the mean yield in clinical stage IIA patients would be, for distant metastases 3% (3/104), and for N3 disease 4% (4/104) [9–11]. However, the last two studies further took into account stage modification from IIA to IIB (i.e. T2N0 to T2N1 from suspicious axillary foci) (Cochet: 6/22; Ko: 6/38) [10, 11]. While the role of [18F]FDG PET/CT in clinical T2N0 patients deserves further investigation, its utility might be greater in the context of NAT, as these patients often have high-risk BC subtypes. In addition, since axilla management has shifted towards sentinel node biopsy (SNB) performed after NAT [4], prior information on FDG-avid nodes can be relevant. Also, a baseline study is needed if response with [18F]FDG PET/CT during NAT is deemed helpful. The role of [18F]FDG PET/CT in clinical T1N1 patients, and the criteria for post-surgery staging in SNB-positive patients, are not clearly established yet.

The impact of [18F]FDG-PET/CT staging is high – However, optimal management of patients with oligometastases deserves further investigation

The presence of distant metastases on [18F]FDG PET/CT, with biopsy confirmation as appropriate, has a clear impact on survival [9]. The 3-year disease-specific survival was 57% when metastases were seen on [18F]FDG PET/CT, vs. 88% in M0 patients ($p < 0.001$) [9]. The impact with short-term follow-up was even more pronounced in TNBC patients, in whom only few treatments are effective [12]. In the study by Dayes et al., treatment was changed from the initially planned combined modality treatment (neoadjuvant therapy, surgery, and regional radiation), to palliative therapy, in 35 (81.3%) of the 43 patients upstaged to stage IV on [18F]FDG PET/CT [8]. Identification of distant metastatic disease thus directly affects management, potentially preventing the morbidity associated with aggressive local therapies or inappropriate intensive systemic therapies [8, 13]. So far, clinical trials have failed to demonstrate improvement in overall survival (OS) with multimodality therapy in metastatic BC [14–16]. In the EA2108 trial, adding surgery and locoregional radiotherapy to the primary site did not result in improved OS [14]. In the NRG-BR002 trial, adding metastasis-directed therapy to standard-of-care systemic therapy did not improve PFS or OS [15]. The CURB trial found benefit from adding stereotactic ablative body radiotherapy (SABR) to the standard-of-care in oligoprogressive metastatic non-small-cell lung cancer, but not in BC patients [16].

Importantly, however, patients upstaged to stage IV on [18F]FDG PET/CT are often oligometastatic [9]. With the wide adoption of [18F]FDG PET/CT, many patients will be diagnosed with de-novo synchronous oligometastatic BC. Prospective randomized studies are needed to see if, for this unique subset of patients, outcomes could be improved through multimodality therapy plus metastasis-directed therapy [17].

Response assessment with [18F]FDG PET/CT during neoadjuvant therapy – a growing evidence

The authors of the EANM/SNMMI guideline reached 100% agreement that "[18F]FDG PET/CT may be used to assess early metabolic response in non-metastatic breast cancer, particularly in TNBC and HER2+". The conditional tense is appropriate, as this is still an emerging indication that is not backed yet by an exhaustive level of evidence.

Neoadjuvant therapy (also called primary systemic therapy) was previously used to increase the probability of performing breast-conserving surgery, or to render locally advanced disease operable, but it is now employed with a wider scope [4]. Notably, NAT is proposed to any patient with TNBC or HER2 + BC, with tumour ≥ 2 cm or clinical N + disease. A large analysis showed that pathological complete response (pCR) at the end of NAT was associated with improved OS and this association was stronger in TNBC and HER2+/HR- BC [18]. Importantly, the prognosis in case of residual disease can now be modified with additional adjuvant therapies, for example capecitabine in patients with TNBC [19], or trastuzumab emtansine (T-DM1) in patients with HER2 + BC [20], or through pursuing some treatments beyond NAT, such as pembrolizumab in TNBC [21], or olaparib in patients with germline *BRCA1* or *BRCA2* mutation [22]. However, although information can be obtained after surgery, the best timing to optimize outcomes is probably during the course of NAT. Interim PET might allow therapy intensification in poor responders, or also de-escalating therapy in early responders, with the understanding that management can then be additionally refined after surgery.

Early studies with mixed BC subtypes showed that response measured by [18F]FDG PET after only one or two cycles of NAT was correlated with the degree of pathological response at surgery [23–25]. However, response considerably differed between subtypes [26]. Subsequent studies showed that, through the use of subtype-specific criteria, interim PET can predict pathology outcomes (pCR vs. residual disease) in TNBC [27, 28], as well as in HER2 + BC [29–31]. In HR+/HER2- BC, pCR is rare, but baseline FDG uptake and early modification of PET parameters during NAT were predictive of event-free survival [32, 33]. Response criteria are subtype-specific, but also depend on the timing of evaluation (e.g., after 1 or 2 cycles) and the type of treatment. For example, response in HER2 + disease differs based on whether NAT started with chemotherapy first [29], or with HER2-targeted therapy [30], or both [31].

Evaluation by interim PET would be helpful clinically only if valid alternative therapies were available [34]. In the Avataxher study, interim PET identified HER2 + BC patients who responded poorly to docetaxel plus trastuzumab, and introducing bevacizumab to poor-responders improved pCR rates. However, this strategy did not modify disease-free survival [35]. Pérez-García and colleagues recently reported updated results from the randomised phase 2 trial PHERGain [36]. This trial investigated a chemotherapy-free treatment approach based on a dual HER2-blockade with trastuzumab and pertuzumab in patients with HER2-positive, stage I-IIIA operable BC. The trial design is interesting, with treatment decisions made on interim PET, then adapted according to pathology findings. The two primary endpoints, pCR rate in PET-responders of the experimental arm, and 3-year invasive disease-free survival (iDFS) in the experimental arm overall, were both met [36]. With this "PET-based, pCR-adapted" strategy, the 3-year iDFS was 94·8%, and about a third of patients could avoid chemotherapy [36]. This trial opens the way to the use of interim PET in clinical practice in carefully selected patients, with the possibility to further refine therapy after surgery [20]. An alternative to the chemotherapy-free approach is adapting the total number of NAT cycles based on response, as in the TRAIN-3 study (NCT03820063) that uses MRI monitoring during NAT.

TNBC accounts for approximately 15% of BC and has poor prognosis [3]. Recently, the Keynote-522 trial showed that the addition of pembrolizumab to neoadjuvant chemotherapy, and followed by adjuvant pembrolizumab after surgery, led to a higher pCR rate and a longer event-free survival as compared with neoadjuvant chemotherapy alone [21]. However, a non-negligible proportion of patients experience serious adverse events. Early response assessment during NAT might allow to offer immuno-chemotherapy combination only to patients with predicted poor response to chemotherapy alone. More generally, poor-responders identified early during NAT with [^{18}F]FDG PET/CT would constitute a target population when testing for the effect of new drugs in clinical trials [37].

Now that [18F]FDG PET/CT stands as the imaging modality of choice for staging, the use of the same modality for response assessment during NAT becomes more and more appealing. Criteria need to be developed for specific clinical situations, akin to the situation in lymphomas, where Deauville score is used with various cut-offs depending on whether aiming de-escalation in excellent responders or therapy intensification in poor responders.

[18F]FDG-PET/CT in the settings of suspected recurrence and for response assessment in metastatic BC

[18F]FDG PET/CT is useful to detect the site and extent of recurrence when conventional imaging methods are equivocal and when there is clinical and/or laboratorial suspicion of relapse [1]. A prospective study in 100 patients with suspected BC recurrence showed higher overall diagnostic accuracy of [^{18}F]FDG PET/CT compared to ceCT and bone scintigraphy [38]. The guideline also notes that [18F]FDG PET/CT is useful in patients with oligometastatic disease, particularly to exclude other metastatic sites prior to curative intent radioablation [1]. [^{18}F]FDG PET/CT imaging can indeed help the management of oligometastases (de-novo,

repeat, or induced), by providing accurate information on the exact number and sites, but also activity, of metastases [39, 40].

According to the EANM/SNMMI guideline, [^{18}F]FDG PET/CT may play a role in monitoring treatment response in metastatic BC, and may be particularly useful to assess bone metastases and enable early response to treatment evaluation [1]. For bone disease, [^{18}F]FDG PET/CT provides combined metabolic information and morphologic information. These recommendations were graded C, as the authors state that more evidence is needed [1].

Additional tracers widen the scope of molecular imaging in breast cancer

The guideline also includes considerations of other tracers [1]. Importantly, receptor-specific tracers, such as 16α-18F-fluoro-17β-Fluoroestradiol ([18F]FES), or HER2-trageting tracers, are able to predict response before the start of therapy and could be helpful in the advanced disease setting, where tumours are more heterogeneous.

[18F]FES offers a noninvasive whole-body evaluation of the presence and functionality of ER in tumour lesions [41]. The ET-FES trial in ER+/HER2- metastatic BC patients showed that [18F]FES PET/CT can predict endocrine responsiveness [42]. This evaluation could be particularly helpful when a patient has already been exposed to hormonal therapy in combination with a CDK4/6 inhibitor, as the risk of heterogeneous disease and loss of target expression is then high. [^{18}F]FDG PET can be combined with [18F]FES PET for complete assessment of active lesions [43].

In the ZEPHIR trial, HER2 imaging with 89Zr-trastuzumab PET/CT, in combination with early metabolic response assessment on [18F]FDG PET/CT after 1 cycle, predicted lack of response to trastuzumab emtansine in patients with advanced HER2-positive BC [44]. A small pilot study recently suggested that [68Ga]Ga-ABY-025 might be used for the non-invasive assessment of disease heterogeneity in HER2-low patients [45]. It remains to be determined if HER2 PET imaging can help select appropriate candidates for trastuzumab deruxtecan therapy [7], and which HER2 tracer is optimal for that purpose.

The successful application of antibody-drug conjugates targeting HER2 [7, 20], or targeting the human trophoblast cell-surface antigen 2 (Trop-2) [46], should stimulate research for similar developments with targeted radionuclide therapy (TRT). Different targets are overexpressed in BC tumour cells, such as GRPR in ER + BC [47], or in the microenvironment or neovasculature, such as FAP or PSMA [48], that can be targeted with available radioligands.

As stated in the guideline, ILC has lower FDG uptake than NST and distinct patterns of metastatic dissemination [1]. Prospective studies are needed to see if [18F]FDG PET/CT is superior to ceCT plus bone scintigraphy, also in ILC. Because ILC is very often ER-positive, [18F]FES PET/CT could offer higher sensitivity compared to [18F]FDG PET/CT [49]. More recently, FAPi tracers also showed superiority over FDG in small series [50]. Potential advantages with FAPi tracers over [18F]FES would be better visualization of liver metastases and peritoneal metastases that might be obscured by hepatic uptake and biliary excretion of [18F]FES, and treatments with ER modulators/ER degraders would not need to be interrupted. Prospective studies comparing [18F]FES, FAPi tracers and [18F]FDG are needed to assess which tracer is better for ILC, and if there is a benefit from combining more than one tracer.

Finally, the guideline also includes considerations of emerging technologies, such as PET/MRI, positron emission mammography (PEM) and dedicated breast PET (dbPET), PET LINAC, and analysis of textural features on [^{18}F]FDG PET/CT images.

Undoubtedly, these guideline will contribute to properly use [^{18}F]FDG PET/CT in BC and improve the management of patients.

Declarations

Competing interest The author has declared that no competing interest exists.

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