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Groheux, David; Vaz, Sofia C.; Ulaner, Gary A.; Cook, Gary J.R.; Mann, Ritse M.; Poortmans, Philip; Jacene, Heather; de Geus-Oei, Lioe Fee; More Authors

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EDITORIAL

Joint EANM-SNMMI guidelines on the role of 2-[^{18}F]FDG PET/CT in no special type breast cancer: differences and agreements with European and American guidelines

David Groheux[1,2,3] · Sofia C. Vaz[4,5] · Gary A. Ulaner[6,7] · Gary J. R. Cook[8,9,10] · John Patrick Pilkington Woll[11] · Ritse M. Mann[12] · Philip Poortmans[13,14] · Fatima Cardoso[15] · Heather Jacene[16,17] · Stephanie L. Graff[18,19] · Isabel T. Rubio[20] · Marie-Jeanne Vrancken Peeters[21,22] · Elizabeth H. Dibble[23] · Lioe-Fee de Geus-Oei[5,24,25]

Breast cancer (BC) is the most commonly diagnosed cancer worldwide. Recently, 2-[^{18}F]FDG PET/CT has become indispensable in the care of patients with BC. In this issue of the *European Journal of Nuclear Medicine and Molecular Imaging*, the Joint EANM-SNMMI guideline on the role of 2-[^{18}F]FDG PET/CT in no special type breast cancer [1] is published. This is the first guideline with the nuclear medicine societies' participation in this topic endorsed by the following relevant societies in this field: the American College of Radiology (ACR), the European Society of Surgical Oncology (ESSO), the European Society for Radiotherapy and Oncology (ESTRO), the European Society of Breast Imaging/European Society of Radiology (EUSOBI/ESR), and the European Society of Breast Cancer Specialists (EUSOMA). In these guidelines, updated information about 2-[^{18}F]FDG PET/CT procedures is summarized, and the current evidence of the role of 2-[^{18}F]FDG PET/CT in the initial staging, assessment of treatment response, and assessment of recurrence in patients with BC is presented and organized into recommendation boxes (and summarized in Table 5 of the EANM/SNMMI guidelines). All recommendations were scored in terms of level of evidence and grade of recommendation, with a percentage of agreement of at least 85% by a group multidisciplinary team of experts. Finally, other developments and future applications are discussed [1].

We, hereafter, discuss the difference and agreement of these guidelines in comparison to the guidelines from the European Society for Medical Oncology (ESMO) and from the American National Comprehensive Cancer Network (NCCN) (Table 1). The ESMO guidelines for *early breast cancer* were first published in 2019 [2] and updated in 2024 [3], and the ESMO c*linical practice guideline for metastatic breast cancer* was published in 2021 [4] and is regularly updated on the ESMO website [5]. NCCN guidelines for breast cancer are updated topic-wise several times each year, and we refer to the version "Clinical Practice Guidelines in Oncology—Breast Cancer—Version 2.2024" [6].

Baseline staging

2-[^{18}F]FDG PET/CT is highly accurate in detecting extra-axillary lymph nodes and distant metastases, particularly in locally advanced breast cancer (LABC) or inflammatory BC (T4d) (for stage and TNM classification, see Table 4 of the EANM/SNMMI guidelines). More recently, several studies have shown that 2-[^{18}F]FDG PET/CT may also be useful in "intermediate-risk" patients. Given the high incidence of BC, the costs of PET/CT imaging, the radiation exposure, and the inconvenience associated with potential false-positive results, it is important to determine in which patient subgroups 2-[^{18}F]FDG PET/CT staging would be beneficial and should be performed.

EANM/SNMMI and ESMO guidelines do not recommend systemic staging for stage I BC, whatever the BC molecular subtype classification—clinical T1 (T < 2 cm) N0 M0. Taking into account the BC molecular subtype classification, NCCN considers that systemic staging can be performed for T1c N0 TNBC and HER2 + BC (stage I BC of more than 1 cm) [6]. In the NCCN guidelines, systemic staging can also be performed for stage IIA and higher, whatever the BC subtype, and this workup is based on a panel of conventional imaging modalities. According to the NCCN, "2-[^{18}F]FDG PET/CT is most beneficial and accurate for

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Extended author information available on the last page of the article

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Table 1 Summary of the recommendation of the EANM-SNMMI, ESMO, and NCCN guidelines in the different clinical scenarios

		EANM-SNMMI	ESMO	NCCN
Baseline systemic staging	Stage I	Not recommended	Not recommended	If $T > 1$ cm, BSS can be performed for HER2 + BC and TNBC
	Stage IIA	[^{18}F]FDG PET/CT is optional	BSS can be performed in T1 N1 BC	BSS can be performed
	Stages IIB–III	**2-[^{18}F]FDG PET/CT is recommended**	- BSS is recommended with CM - **2-[^{18}F]FDG PET/CT is indicated in equivocal findings or can replace CM in high-risk patients**	- BSS is recommended with CM - **2-[^{18}F]FDG PET/CT is indicated in selected circumstances mostly to complement CM**
	Stage IV	**2-[^{18}F]FDG PET/CT is recommended**	**CM or 2-[^{18}F]FDG PET/CT alone is recommended**	- CM is recommended - **2-[^{18}F]FDG PET/CT is useful in certain circumstances**
Treatment response	PST setting	- **2-[^{18}F]FDG PET/CT may predict early pCR, especially for TNBC and HER2 + BC** - 2-[^{18}F]FDG PET/CT is not very sensitive in identifying residual primary tumour after PST	2-[^{18}F]FDG PET/CT has no indication in the PST setting	2-[^{18}F]FDG PET/CT has no indication in the PST setting
	M + setting	2-[^{18}F]FDG PET/CT is accurate in assessing the response of BM	**2-[^{18}F]FDG PET/CT might provide earlier guidance in monitoring BM,** but prospective trials are needed	CT is recommended for assessing the response
Assessment of recurrence		**2-[^{18}F]FDG PET/CT is recommended when CM is equivocal and when there is clinical or laboratorial suspicion of recurrence**	- In the suspicion of **oligometastatic disease**, systemic imaging is recommended, **preferably with 2-[^{18}F]FDG PET/CT** - For **known metastatic disease**, imaging is recommended, with CM or 2-[^{18}F]FDG PET/CT	- For known metastatic disease, systemic imaging with CM is recommended - **2-[^{18}F]FDG PET/CT is useful in certain circumstances**

The relevant statements about the use of 2-[^{18}F]FDG PET/CT are marked in bold

BSS baseline systemic staging, *BM* bone metastases, *CM* conventional modalities, *PST* primary systemic treatment, *pCR* pathological complete response, *M* + metastatic

advanced disease (stage III) and invasive ductal (compared to lobular) histology but may be useful in selected circumstances of earlier stage disease (stage IIA disease: T1N1 and T2N0) such as equivocal CT and bone scan results and suspicion of undetected nodal and/or distant disease" [6].

In ESMO guidelines, a workup based on a CT of the chest, abdominal imaging (US, CT, or MRI), and a bone scan is indicated for T0/T1 N1 disease of stage IIA and for all stages IIB–III BC. For ESMO, 2-[^{18}F]FDG PET/CT may be useful in the staging of early BC when conventional methods are inconclusive and can also replace traditional imaging for staging in high-risk patients [3]. EANM/SNMMI recommends baseline staging with 2-[^{18}F]FDG PET/CT (without conventional imaging) for stage IIB and higher. In patients with clinical stage IIA (T1N1 or T2N0), EANM/SNMMI considers there are not enough strong data to recommend routine use of 2-[^{18}F]FDG PET/CT in this subgroup at this time [1].

For stage IV disease, EANM/SNMMI recommends 2-[^{18}F]FDG PET/CT for determining the precise extent of metastatic disease (outside the brain) and improving treatment planning [1]. ESMO recommends a minimum imaging work-up with CT of the chest and abdomen and a bone scan or with 2-[^{18}F]FDG PET/CT alone [4, 5]. NCCN recommends a panel of different conventional imaging modalities and states that 2-[^{18}F]FDG PET/CT is useful in "certain circumstances" [6].

Assessment of treatment response

Primary systemic treatment (PST) is used in most stage II–III BC patients. This strategy allows more patients to undergo breast-conserving surgery and increases the likelihood of surgery in cases of initially inoperable primary disease. A complete pathological response (pCR) at the end of PST is associated with better survival, namely in aggressive breast cancer subtypes [7]. Early assessment of response to PST is potentially useful information, as it can theoretically reduce the toxicity of ineffective therapy or allow for refinement of treatment. A number of studies have demonstrated the potential effectiveness of 2-[^{18}F]FDG PET/CT to predict early (after one of two cycles of PST) pCR and patient outcomes, especially for TNBC and HER2 + BC. In contrast, several studies showed that 2-[^{18}F]FDG PET is not very sensitive in identifying residual primary tumor tissue when performed at the end of the PST; hence, MRI is the preferred modality in this situation.

EANM/SNMMI guidelines consider that 2-[^{18}F]FDG PET/CT may be used to assess early metabolic PST response, particularly in TNBC and HER2 + BC. Furthermore, EANM/SNMMI considers that 2-[^{18}F]FDG PET/CT can be useful at the end of PST to exclude metabolically active regional lymph nodes or distant metastases before breast surgery. For NCCN and ESMO, 2-[^{18}F]FDG PET/CT has no indication in the PST setting. NCCN considers that the accurate assessment of breast tumors or regional lymph node response to PST should include physical examination and breast imaging studies.

Early response to treatment is also important in the metastatic setting in order to use the most effective drugs and to stop ineffective therapy early. Moreover, local treatments such as surgery, radiation therapy, and radiofrequency may also be used, especially in patients with oligometastatic disease. It is of utmost importance to provide these treatments at the most appropriate time and to be able to evaluate their effectiveness at an early stage. Considering that changes in metabolic activity usually occur earlier than changes in tumor size, 2-[^{18}F]FDG PET/CT has a relevant role to play due to its effectiveness in assessing the response of patients with metastatic BC. Compared with conventional imaging, 2-[^{18}F]FDG PET/CT has been shown to be very accurate, especially in assessing the response of bone lesions. EANM/SNMMI guidelines state that 2-[^{18}F]FDG PET/CT may play a role in monitoring treatment response in metastatic patients and may be particularly useful to assess bone metastases and enable an early response to treatment evaluation using PERCIST or EORTC criteria. For ESMO, 2-[^{18}F]FDG PET/CT might provide earlier guidance in monitoring bone-only/predominant metastases, but prospective trials are needed to evaluate the impact on treatment decisions and overall survival. NCCN recommends CT for response assessment, using the RECIST or the WHO criteria.

Assessment of recurrence

Early detection and staging of recurrence are essential for optimal therapeutic management. 2-[^{18}F]FDG PET/CT offers high sensitivity in detecting locoregional and distant metastases with higher performance than conventional imaging, whether suspected by clinical examination, conventional imaging, or elevation of a tumor marker.

In the absence of clinical signs and symptoms suggestive of recurrent BC, NCCN, and ESMO, do not recommend imaging studies for metastases screening. If there is suspicion of oligometastic disease, ESMO recommends systemic imaging staging, preferably with 2-[^{18}F]FDG PET/CT [5]. For known metastatic disease, ESMO recommends a minimum imaging work-up with CT of the chest and abdomen and bone scan, or with 2-[^{18}F]FDG PET/CT. NCCN recommends a panel of different conventional imaging modalities and states that 2-[^{18}F]FDG PET/CT is useful in "certain circumstances". For EANM/SNMMI, 2-[^{18}F]FDG PET/CT is useful in detecting the site and extent of recurrence when conventional imaging methods are equivocal. Furthermore, 2-[^{18}F]FDG PET/CT can also be

recommended in patients with signs or symptoms suggestive of metastatic disease and in patients with rising serum tumor markers to guide the site of biopsy and improve RT planning. 2-[^{18}F]FDG PET/CT can substitute for CT and/or bone scan in the detection of bone metastases.

Final considerations

2-[^{18}F]FDG PET/CT is widely used in patients with breast cancer, with a proven impact on its clinical management. Overall, although there are similarities among EANM/SNMMI, ESMO, and NCCN recommendations, many differences exist, being specific to each guideline. The Joint EANM/SNMMI guidelines more often recommend the use of 2-[^{18}F]FDG PET/CT in patients with BC. ESMO has specific indications for 2-[^{18}F]FDG PET/CT and when it can replace conventional imaging modalities. However, NCCN provides less specific recommendations regarding the use of 2-[^{18}F]FDG PET/CT and usually states that it is indicated/useful in certain circumstances.

It is expected that the evidence to support the use of 2-[^{18}F]FDG PET/CT will increase with future studies, particularly regarding the metabolic response criteria and the role of 2-[^{18}F]FDG PET/CT in assessing treatment response in the metastatic setting.

The relevance of the "Joint EANM-SNMMI guideline on the role of 2-[^{18}F]FDG PET/CT in no special type breast cancer" is related to the fact of being the first imaging guidelines summarizing up-to-date information with the participation of both international nuclear medicine societies and endorsed by several other medical societies relevant to this subject. This may help foster appropriate utilization of 2-[^{18}F]FDG PET/CT in patients with breast cancer and lead to greater harmonization of imaging and clinical guidelines in the future.

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Authors and Affiliations

David Groheux[1,2,3] · Sofia C. Vaz[4,5] · Gary A. Ulaner[6,7] · Gary J. R. Cook[8,9,10] · John Patrick Pilkington Woll[11] · Ritse M. Mann[12] · Philip Poortmans[13,14] · Fatima Cardoso[15] · Heather Jacene[16,17] · Stephanie L. Graff[18,19] · Isabel T. Rubio[20] · Marie-Jeanne Vrancken Peeters[21,22] · Elizabeth H. Dibble[23] · Lioe-Fee de Geus-Oei[5,24,25]

✉ David Groheux
dgroheux@yahoo.fr

1 Nuclear Medicine Department, Saint-Louis Hospital, Paris, France

2 University Paris-Diderot, INSERM U976, Paris, France

3 Centre d'Imagerie Radio-Isotopique (CIRI), La Rochelle, France

4 Nuclear Medicine-Radiopharmacology, Champalimaud Clinical Center, Champalimaud Foundation, Lisbon, Portugal

5 Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands

6 Molecular Imaging and Therapy, Hoag Family Cancer Institute, Newport Beach, CA, USA

7 University of Southern California, Los Angeles, CA, USA

8 Department of Cancer Imaging, King's College London, London, UK

9 King's College London and Guy's & St Thomas' PET Centre, London, UK

10 School of Biomedical Engineering and Imaging Sciences, King's College London, London, UK

11 PET-CT Department, Clinica Delgado AUNA, Lima, Perú

12 Radiology Department, Radboud UMC, Nijmegen, The Netherlands

13 Department of Radiation Oncology, Iridium Netwerk, Antwerp, Belgium

14 University of Antwerp, Wilrijk, Antwerp, Belgium

15 Breast Unit, Champalimaud Clinical Center, Champalimaud Foundation, Lisbon, Portugal

16 Dana-Farber Cancer Institute/Brigham and Women's Hospital, Boston, MA, USA

17 Harvard Medical School, Boston, MA, USA

18 Lifespan Cancer Institute, Providence, RI, USA

19 Legorreta Cancer Center at Brown University, Providence, RI, USA

20 Breast Surgical Oncology, Clinica Universidad de Navarra, Cancer Center Clinica Universidad de Navarra, Madrid, Spain

21 Department of Surgical Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands

22 Department of Surgery, Amsterdam University Medical Center, Amsterdam, The Netherlands

23 Department of Diagnostic Imaging, The Warren Alpert Medical School of Brown University, Providence, RI, USA

24 Biomedical Photonic Imaging Group, University of Twente, Enschede, The Netherlands

25 Department of Radiation Science & Technology, Delft University of Technology, Delft, The Netherlands