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EDITORIAL COMMENTARY

Concerning pretreatment ^{18}F-FDG PET/CT imaging in patients with large or locally advanced breast cancer

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In this issue of the *European Journal of Nuclear Medicine and Molecular Imaging*, García Vicente and colleagues report on the role of ^{18}F-FDG PET/CT in patients with clinical stage II or III breast cancer (BC). Following PET/CT imaging, the new metabolic stage was stage IV in 38 out of 198 patients (19 %). This had a major prognostic impact. The hazard ratio for death from BC (overall survival) was 0.117 for stage II vs. metabolic stage IV and 0.28 for stage III vs. metabolic stage IV [1]. Although the title of the study refers to locally advanced BC, about half of the included patients had clinical stage II disease [1]. Locally advanced BC is variably defined in the literature; some recommendations such as that of the National Comprehensive Cancer Network refers to patients with N2, N3 or T4 disease, i.e. AJCC clinical stages IIIA (excluding T3N1), IIIB and IIIC (Table 1) [2, 3].

The results of Garcia Vicente and colleagues add to the evidence from a number of recent studies emphasizing the prognostic information offered by ^{18}F-FDG PET/CT in patients with clinical stage II or III BC. In a study by Cochet and colleagues in 142 patients [4], conventional imaging staging was associated with progression-free survival (p=0.01), but PET/CT staging provided much stronger prognostic stratification (p<0.0001) [4]. In our prospective series of 254 patients with clinical stage II/III BC, ^{18}F-FDG PET/CT revealed distant metastases in 53 patients (23 of whom were reported to be negative on unguided conventional imaging work-up) [5]. Riedl and colleagues suggested that ^{18}F-FDG PET/CT be used in staging patients younger than 40 years as these patients are known to be at increased risk [6]. Interestingly, however, in the study by Garcia Vicente patients with occult metastases revealed by PET/CT were not younger than the average patient age in their series (their Table 2). Garcia Vicente and colleagues do not offer information on the yield within substages of clinical stage II/III disease. In our series, the yield of PET/CT was high starting with clinical stage IIB [5]. Among 189 patients with clinical stage IIB or higher, disease-specific survival was significantly shorter in the 47 patients scored M1 on ^{18}F-FDG PET/CT in comparison with M0 patients, with a 3-year disease-specific survival of 57 % vs. 88 % (p<0.001) [5]. Other teams have also found that PET has substantial yield starting with stage IIB BC [6, 7].

Besides staging, the level of ^{18}F-FDG uptake by the primary tumour may have prognostic value. In the study by Garcia Vicente et al., high ^{18}F-FDG uptake (in the breast tumour or in axillary lymph nodes) was associated with shorter survival. It is important to point out, however, that BC comprises different phenotypes which differ in ^{18}F-FDG avidity [8, 9]. In clinical practice, there are three main entities based on immunohistochemical analysis: hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2−) BC, HER2+ BC, and triple-negative BC (TNBC). Specific systemic treatments are used in each subgroup. Because prognosis differs considerably among these phenotypes, if tumour SUV offers "independent" prognostic value, this should be examined within a given subtype. In this respect, the study by Garcia Vicente et al. offers interesting information. SUV has some prognostic value in patients with HR+/HER2− BC and HER2+ BC, but not in patients with TNBC (their Table 5).

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Table 1 TNM stage grouping for breast cancer according to the AJCC Cancer Staging Manual [3]

AJCC stage	TNM			NCCN
I	T1	N0	M0	Primary operable breast cancer
IIA	T0	N1	M0	
	T1	N1	M0	
	T2	N0	M0	
IIB	T2	N1	M0	
	T3	N0	M0	
IIIA	T3	N1	M0	
	T0	N2	M0	Locally advanced breast cancer
	T1	N2	M0	
	T2	N2	M0	
	T3	N2	M0	
IIIB	T4	N0	M0	
	T4	N1	M0	
	T4	N2	M0	
IIIC	Any T	N3	M0	
IV	Any T	Any N	M1	Metastatic disease

AJCC American Joint Committee on Cancer, *TNM* Tumor Nodes Metastasis classification, *NCCN* National Comprehensive Cancer Network

While the number of patients in each subgroup was limited, reducing the power of the analysis, we offer some possible explanations for the findings.

With regard to patients with the HR+/HER2− phenotype, three other studies focusing on this BC subgroup have also found that high baseline tumour SUV_{max} is associated with recurrence and poorer outcome [10–12]. Unfortunately, the cut-offs differ between the studies and still need to be defined; the association between ^{18}F-FDG uptake and prognosis in this subtype might be a continuum.

In patients with the HER2+ phenotype, the reason why high tumour SUV is associated with a higher risk of relapse could be associated with the lower response to chemotherapy of ^{18}F-FDG-avid tumours. In a small pilot series, of HER2+ BC patients treated with neoadjuvant chemotherapy, no patient with a tumour SUV_{max} >9.4 at baseline achieved a pathological complete response (pCR) [13].

Carey and colleagues introduced the term “the triple negative paradox” because although TNBC have higher sensitivity to neoadjuvant chemotherapy than HR+ tumours, patients in this group have a poorer prognosis [14]. With regard to the association between SUV and prognosis, the situation in patients with the TNBC phenotype is also complex with probably two opposing effects. Patients with high basal SUV_{max}, or high SBR tumour grade, are more likely to respond to neoadjuvant chemotherapy and to achieve a pCR [15, 16]. However, when pCR is not achieved, patients with a high tumour grade have a high rate of early relapse [16]. Altogether, although SUV might be associated with prognosis in some subtypes of BC, it seems impossible to determine a *magic* cut-off that could be applied in different centres. Preparation procedures and instrumental factors can also introduce differences in the measurement of SUV. Finally, in the study by Garcia Vicente et al., staging with metabolic PET was an independent factor predicting outcome in multivariate analysis but ^{18}F-FDG tumour uptake was not.

In conclusion, a powerful aspect of PET/CT staging in patients with high-risk BC is that it provides high accuracy in examining extra-axillary nodes, chest, abdomen and bone in a single session. Baseline ^{18}F-FDG tumour uptake might offer additional prognostic information in some subtypes of BC, and this point deserves further investigation.

Compliance with ethical standards

Conflicts of interest None.

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