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EDITORIAL COMMENTARY

Is ^{18}FDG uptake useful to decide on chemotherapy in ER+/HER2- breast cancer?

David Groheux[1,2] · **Elif Hindié**[3]

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Dear Sir,

Primary operable breast cancers (BCs) (clinical stage I-II and T3N1 of stage IIIA) are currently treated by surgery followed by radiation therapy [1]. Adjuvant systemic therapy is given according to the risk of locoregional or distant breast cancer recurrence (BCR). Breast carcinoma is a heterogeneous class of tumours; gene-expression profiling has led to the identification of five different subtypes with clinical implications (i.e., luminal A, luminal B, basal-like, HER2-like and normal-like subtypes) [2]. To some degree, these molecular subtypes can be distinguished using immunohistochemistry (IHC) tests [1]. Estrogen receptor-positive/human epidermal growth factor receptor 2-negative (ER+/HER2-) BCs regroup the majority of luminal A and B tumours. This important group is characterized by potential hormonosensitivity and relatively good prognosis, mainly for luminal A subtype [3].

Besides IHC classification, several prognostic factors are currently used to predict the risk of BCR. The strongest clinico-biological factors are patient age, tumour size, lymph node status and tumour grade [1]. Algorithms can be used to estimate the rates of recurrence and online computer-based models have been developed. These tools aid the clinician in estimating the benefits expected from adjuvant chemotherapy in primary operable BC, regarding the toxicities and benefits of the treatment.

More recently, gene-based assays appeared as potential tools to predict prognosis, the most used tests being the 21-gene assay "Oncotype DX", the 50-gene assay "PAM50" and the 70-gene expression profile "Mammaprint" [1]. Oncotype DX has been best validated for its use as a prognostic test as well as in predicting who is most likely to respond to systemic chemotherapy [1]. This test analyses a group of 21 genes found in breast cancer and results are reported as a Recurrence Score (RS) ranked between 0 and 100. Based on the observations of previous studies, three risk groups are defined: a low risk of recurrence at 10 years after surgery for a RS < 18, an intermediate risk for a RS of 18–30 and a high risk for a RS ≥ 31. Patients with a high RS benefit from chemotherapy, whereas patients with a low RS do not appear to benefit from the addition of chemotherapy. The additional benefit from adjuvant chemotherapy in addition to endocrine therapy is currently unclear for intermediate-risk patients. According to the American Society of Clinical Oncology clinical practice guideline, Oncotype DX can be used by the clinician to guide decisions on adjuvant systemic chemotherapy, only in ER+/HER2- and node-negative BC [4].

Oncotype DX test is expensive and not readily available in some institutions. Association between high baseline tumour SUV_{max} measured by ^{18}FDG-PET/CT and some poor prognostic factors such as high tumor grade is well known [5, 6]. In this issue of the *European Journal of Nuclear Medicine and Molecular Imaging*, Lee and colleagues report on a potential new role of ^{18}FDG-PET/CT in early stage BC patients: prediction of the results of the Oncotype DX RS [7]. In a retrospective analysis of 38 patients with small (only one patient had a tumor > 3 cm) and node-negative breast cancer, partial-volume corrected tumour SUV_{max} (PVC-SUV_{max}) had significant association with the

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✉ David Groheux
dgroheux@yahoo.fr

[1] Department of Nuclear Medicine, Saint-Louis Hospital, Paris, France

[2] University Paris-Diderot, INSERM/CNRS UMR944/7212, Paris, France

[3] Department of Nuclear Medicine, Bordeaux University Hospital, Bordeaux, France

Oncotype DX RS; a PVC-SUV_{max} higher than a cutoff value of 4.96 predicted intermediate-to-high RS. The authors conclude that ^{18}FDG-PET/CT can be used to predict the Oncotype DX RS in early-stage, ER+/HER2- BC patients. As explained by the authors, the study has some limitations (eg. retrospective design, limited number of patients, multifocal/multicentric BC excluded from the analysis). Intermediate and high Oncotype DX RS were predicted as a single group, while prognosis is potentially different between these groups. However, to offer credit to the results of Lee et al., several recent studies showed that high baseline tumour SUV values were associated with shorter survival in patients with early stage ER+/HER2- BC. In 305 patients with hormone receptor-positive BC, Ahn et al. reported that SUV_{max} was correlated with recurrence-free survival (SUV_{max} cutoff value of 4) [8]; 174 women (57 %) had T1 tumour (size≤2 cm). In a recent preliminary report, the same team also suggested that SUV_{max} of 4 to be used as a cutoff value to estimate the Oncotype DX RS (to separate low-to-intermediate from high RS) [9]. In the study by Aogi et al. [10], 262 stage I–III luminal BC patients (187 with T1 tumour) had ^{18}FDG-PET/CT before initial therapy. In the univariate and multivariate analyses, SUV_{max} was identified as the only significant factor for overall survival (SUV_{max} cutoff value of 6). Patient's age, Clinical T score, clinical N score and nuclear grade were not predictive for overall survival [10].

The studies from Lee [7], Ahn [8, 9] and Aogi [10] are focused on early stage BC. Partial volume effect can affect SUV values. Lee et al. did not include BC with tumour size<8 mm. Even with this precaution, when SUV values were not corrected for partial volume effect, results were not significant [7].

Most oncology societies do not recommend the use of systemic staging in patients with early-detected BC, given the low risk of distant metastases and the risk of false-positive PET/CT findings [1, 11]. On the contrary, PET/CT is currently used for the staging of stage IIB and stage III locally advanced breast cancer (LABC) [12–15]. Additional information that can be gained from baseline SUV of the primary tumour can be of interest. Large tumours are less affected by imprecision in SUV measurements than small tumours. Patients with large or locally advanced ER+/HER2- BCs usually receive neoadjuvant treatment before surgery (neoadjuvant chemotherapy or hormone therapy). Chemotherapy is mostly given to women with the luminal-B subtype, but the precise group who drives benefit from neoadjuvant chemotherapy (NAC) remains unclear. Several studies focusing on LABC showed that high baseline tumour SUV_{max} before NAC was associated with recurrence and poorer outcome [16–18].

In 61 patients treated by NAC for ER+/HER2- BC of stage II-IIIA, Humbert and colleagues found that patients with hypermetabolic tumours (SUV of breast tumour>liver SUV) had a higher risk of relapse compared to tumours with weak ^{18}FDG uptake ($p=0.04$) [16]. In the study from Garcia Vicente et al., high ^{18}FDG uptake at baseline was associated with shorter survival in ER+/HER2- and in HER2+ BCs patients, but not in triple negative BC patients [17]. In our own study of 84 patients with ER+/HER2- BC of stage II-III (primary tumour size>2 cm), we also observed that a high SUV_{max} or a high total lesion glycolysis at baseline was associated with shorter event-free survival ($p<0.001$ and $p=0.032$, respectively). Twelve patients had a tumour SUV_{max} of 10 or greater and a 3-year EFS of 49 % (vs. 92 % in patients with baseline $SUV_{max}<10$) [18].

Finally, in small tumours before breast surgery, as well as in large tumours before NAC, several studies showed that high SUV_{max} values at baseline PET were associated with poorer patients' outcomes. Unfortunately, the SUV_{max} cutoff values differed between studies and still need to be defined. Probably a panel of criteria (in which ^{18}FDG-PET could be included) is needed to guide treatment in luminal BC patients, especially in the neoadjuvant setting. ^{18}FDG-PET could be used in addition to other predictive factors such as the Oncotype DX test. Of note, some PET tracers other than ^{18}FDG could also be of interest in luminal tumors, in particular, 16α-^{18}F-fluoro-17β-oestradiol (^{18}FES) [19].

In conclusion, there is current evidence that high metabolic activity of the primary tumour is correlated with poorer outcome in the ER+/HER2- breast cancer subtype. These patients could be better candidates for systemic chemotherapy. Thus, the level of ^{18}FDG uptake might be helpful in ER+/HER2- BC to guide treatment, especially in the neoadjuvant setting, when ^{18}FDG-PET/CT imaging is currently performed for disease staging.

Compliance with ethical standards

Conflict of interest The author declared no conflicts of interest.

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