EDITORIAL COMMENTARY

Preoperative FDG PET/CT in breast cancer patients: where are we going?

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Breast cancer remains the commonest female malignancy in Western countries and the second leading cause of cancer mortality in women [1].

Accurate staging at the time of the initial diagnosis plays a major role in the choice of therapeutic modalities for an optimal management of these patients [2]. Breast cancer staging includes assessment of cancer spread to regional lymph nodes and also to distant sites. Being a whole-body procedure, PET/CT is able to assess all these data in a single test, providing morphological information and also evaluating the metabolic activity of the disease.

However, FDG PET/CT is not currently indicated for primary breast cancer diagnosis, mainly due to its poor spatial resolution. Indeed, diagnostic accuracy depends on primary breast tumour size as reported by Cermik et al. In this series the sensitivity of FDG PET to detect nonpalpable, small (<10 mm) invasive malignancies ranged from 53 to 63 % for T1mic/T1a and T1b tumours, respectively [3]. In addition, PET imaging accuracy is affected by tumour histology: invasive lobular carcinomas are detected with less sensitivity than ductal carcinomas [4, 5]. Conversely, the detection of high intensity, focal FDG uptake in the breast has a strong positive value for cancer [6].

In practice the main contribution of PET in local tumour assessment consists in measuring FDG uptake by the standardized uptake value (SUV), which is useful to evaluate early response to neoadjuvant therapy in those cases not submitted to surgery directly. Indeed, while morphological changes due to therapy activity are not detectable until 4–6 months of treatment, metabolic changes occur earlier and are assessable even after one or two cycles of systemic therapy [7, 8]. This allows the oncologist to anticipate surgery, if needed.

According to several studies FDG PET/CT could provide some important clinical and biological information about the disease aggressiveness [9–11], even if the degree of FDG uptake in the primary tumour has not proven to be an independent predictor of outcome [12, 13].

In addition to tumour size, the status of the axillary lymph nodes is the most reliable prognostic indicator for recurrence and survival in early breast cancer.

None of the current imaging procedures has sufficient sensitivity to substitute the sentinel node biopsy (SNB) in the histopathological evaluation of the axilla. In particular, PET/CT showed poor sensitivity for axillary staging, with values as low as 20 % in some series [14, 15]. This is especially true for breast cancer patients with very restricted disease spread to the axilla, because of the limited spatial resolution of the technique and the presence of few FDG-avid cells in case of micrometastases.

Vinh-Hung et al. reconfirmed these data with their paper published in the present issue of the *European Journal of Nuclear Medicine and Molecular Imaging*. The authors retrospectively evaluated 104 patients, who underwent preoperative FDG PET/CT for breast cancer staging and surgery as part of planned primary therapy. The diagnostic utility of the preoperative PET scan in the assessment of axillary lymph node involvement was reported: among 63 PET node-negative patients, 26 were histopathological node-positive and among 41 PET node-positive patients, 36 were histopathological node-positive. These data confirm

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that preoperative PET scan is not adequate in the classification of lymph node involvement [16], but it can be useful in differentiating low versus high burden nodal disease [17].

A false-negative result generally represents a very small number of lymph node metastases, with very limited invasion of the lymphatic structures. On the contrary a node-positive PET scan has high specificity and positive predictive value for axillary staging and indicates a higher disease spread to this region [18]. Therefore PET/CT could guide the choice of surgical treatments on the axilla. Direct axillary lymph node dissection (ALND), avoiding SNB, could be proposed in PET node-positive patients, while SNB actually remains the best staging procedure in PET node-negative cases.

Increasing data suggest that surgical management of the axilla by SNB or ALND has no influence on recurrence-free and overall survival in all breast cancer patients. However, sample size and length of follow-up are substantially different among studies, so definitive conclusions are not available [19]. In this setting PET/CT could be mainly useful for its ability in differentiating low from high axillary involvement, and for the prognostic information it can provide.

Indeed, Vinh-Hung et al. found that PET positivity in axillary lymph nodes was the only unequivocal preoperative predictor of disease-free survival (DFS), overriding the other conventional prognostic factors and providing prognostic information second only to histological lymph node involvement [17]. Inoue et al. reported that the prognosis for breast cancer patients with high SUV_{max} in the primary tumour and concomitant PET-positive axillary lymph nodes was significantly poorer than that of the other patients, with a 5-year DFS of 44.4 vs 96.8 % [12]. Song et al. demonstrated that axillary lymph node SUV_{max} on preoperative PET was an independent prognostic factor for disease recurrence in a population of 65 women with invasive ductal carcinoma [20].

PET/CT is therefore standing out as a risk stratification modality in patients with breast tumours, as it could distinguish aggressive from indolent forms of cancer. This evaluation may become more important in the future, in case axillary surgery is not performed and no prognostic information is available [21]. Consequently PET/CT could provide the basis for a better management of breast cancer patients, avoiding overtreatment in low-risk cases.

PET/CT can also define the real aim of the therapeutic strategy in newly diagnosed breast cancer. Indeed, as a whole-body modality, it is able to detect unknown distant metastases, changing the therapeutic purpose from curative to palliative.

FDG PET/CT performs better than conventional imaging to demonstrate occult metastases in breast cancer patients [22–24]. It is a valuable tool in locally advanced breast cancer, but also in early-stage disease [25–28]. In particular, Groheux et al. demonstrated that PET/CT had a non-negligible yield in

patients with stage IIB and primary operable stage IIIA breast cancer. In these patients with T3 N0, T2 N1 or T3 N1 disease the overall yield was 13 % with a change in therapeutic management due to the finding of N3 disease or distant metastases. Even 2 of 36 patients with stage IIA disease were upstaged due to the discovery of internal mammary lymph node (1 patient) and contralateral supraclavicular and mediastinal nodal disease (1 patient) [26]. Extra-axillary lymph node involvement was also detected in almost one third of stage II-III breast cancer patients in the study of Aukema et al. PET/CT upgraded the TNM stage in 17 % (10/60) of the patients, leading to a change in the radiotherapy plan in 12 % (7/60) [29].

The above-mentioned studies indicate that FDG PET/CT imaging is applicable to a patient population with a wide range of tumour stages, from T1 to T4 carcinomas. Patients with more aggressive and FDG-avid histopathological subtypes are more likely to have distant metastases, but also patients not fulfilling these criteria could present a stage IV disease at the initial diagnosis.

Breast cancer is indeed an heterogeneous disease in terms of histology, dissemination modality, therapeutic response and prognosis. The tumours can be classified into subtypes distinguished by pervasive difference in their gene expression patterns [30, 31]. The decision to perform an FDG PET/CT scan in the initial evaluation of patients with breast cancer should probably take into account these biological differences.

Actually some uncertainties remain about the exact characteristics (clinical stage and histopathological features) of newly diagnosed breast cancer for which PET/CT should be systematically performed with a favourable cost-effectiveness balance. Moreover, standard characteristics of the equipment to be used need a clear definition; a combination of state-of-the-art PET/CT plus a dedicated breast PET device with a single FDG injection could be indicated. Targeted prospective studies with a large number of patients are therefore necessary to better define these points.

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