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EDITORIAL COMMENTARY

FDG-PET/CT for systemic staging of patients with newly diagnosed breast cancer

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Breast cancer (BC) is the most common cancer in women. 92,600 deaths from BC are predicted in the European Union in 2017 [1]. Several weapons (surgery, radiation therapy, chemotherapy, targeted therapy, endocrine therapy) are available to treat BC. To use optimal treatment for a given patient, the biological characteristics of the tumour and the precise staging of the disease should be known. In particular, the presence or not of distant metastases should be assessed.

In recent years, FDG-PET/CT has gained an increasing role in the pre-treatment staging of BC. PET/CT has shown a high accuracy to detect extra-axillary lymph nodes and distant metastases [2]. Given the high incidence of BC and known inconvenience of FDG imaging (such as high cost, radiation exposure, potential false positive findings and risk for delaying care), PET should be used in specific sub-groups only, especially in patients with high risk of distant metastases. Several teams investigated in which sub-groups of women with BC FDG-PET/CT should be offered with a favourable ratio advantage/disadvantage.

Many studies have pointed out the lack of utility for FDG-PET/CT in staging patients with early detected cancer, i.e. tumours ≤2–3 cm and no palpable nodes that represent the majority of BC cases [3, 4]. The low sensitivity of PET, compared to the sentinel node technique, in assessing axillary lymph node involvement is well-established [3] and the risk of distant metastases is low in early-stage disease. The case is different in higher-risk BC patients in whom initial workup would usually comprise several imaging studies including ultrasonography of accessible lymph node basins, CT of the thorax and abdomen (or liver ultrasonography) and bone scan. In many studies, FDG-PET/CT outperformed conventional imaging for examining extra-axillary nodes, chest, abdomen and bone in a single session [5, 6]. The larger evaluations have been performed in locally advanced and inflammatory BC [6–8] which are usually regarded as equivalent to stage III cancer of the AJCC classification [9]. More recent studies have suggested that PET/CT could also be valuable in stage II patients, especially in stage IIB [2, 10, 11]. In 254 patients with BC of mixed phenotypes, we detected distant metastases with PET/CT in 2.3% (1/44) of clinical stage IIA, 10.7% (6/56) of stage IIB, 17.5% (11/63) of stage IIIA, 36.5% (27/74) of stage IIIB and 47.1% (8/17) of stage IIIC patients [11]. Among 189 patients with clinical stage IIB or higher and adequate follow-up, disease-specific survival was significantly shorter in the 47 patients which scored M1 on 18FDG-PET/CT in comparison to M0 patients, with a 3-year disease-specific survival of 57% vs 88% ($P < 0.001$) [11].

In order to optimize PET/CT indications, several teams evaluated the performance of PET/CT in sub-groups for which prognosis is poor based on patient and tumour characteristics. Young BC patients have more aggressive tumours with potential for earlier metastases than older patients. In 134 BC patients younger than 40 years, the team from the Memorial Sloan Kettering Cancer Center in New York detected stage IV disease with PET/CT in 1 of 20 (5%) patients with initial clinical stage I, 2 of 44 (5%) stage IIA, 8 of 47 (17%) stage IIB, 4 of 13 (31%) stage IIIA, 4 of 8 (50%) stage IIIB, and 1 of 2 (50%) stage IIIC [12]. There data suggested that PET/CT might be valuable in young patients with stage IIB and III disease. The yield of PET/CT in younger patients was not

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compared with the yield in older patients [12]. In a study from the Institut Curie in Paris, no significant difference in the distant metastasis rate was observed between the <40 years group and the ≥40 years group (107 patients in each group; distant metastases rate: 21% and 22%, respectively; $P = 1$) [13].

Clinical stage and patient's age are not the sole criteria that have been used to define sub-groups in which the yield of PET/CT has been evaluated. Some criteria taking into account the breast tumour characteristics have also been tested. BC is a heterogeneous disease with different response rates to chemotherapy, different risks of relapse, different treatment options, and different prognoses. In current practice, three specific tumour sub-groups based on immunohistochemistry analysis are differentiated: triple-negative BC (TNBC), oestrogen receptor-positive/human epidermal growth factor receptor-negative (ER+/HER2-) BC, and HER2+ BC [14]. Of those, TNBC has the worst prognosis while outcome is the best in the case of ER+/HER2- BC. FDG uptake differs significantly between these phenotypes with higher FDG uptake in TNBC than in ER+ tumours [15, 16]. Therefore, it has been suggested that the TNBC sub-group is the most adequate sub-group for PET imaging. In 232 patients with TNBC, Ulaner et al. detected distant metastases in 15% of patients with stage IIB TNBC [17]. Findings of PET/CT were not compared to findings observed in non-TNBC. In this issue of the European Journal of Nuclear Medicine and Molecular Imaging, Ulaner and his colleagues from the Memorial Sloan Kettering Cancer Center report on the role of FDG-PET/CT in patients with ER+ and HER2+ BC [18]. In this large retrospective study, 238 patients with ER+/HER2- and 245 patients with HER2+ were evaluated [18]. FDG-PET/CT revealed distant metastases in 14% of patients with stage IIB ER+/HER2- and HER2+ BC, which is similar to up-staging rates previously seen in patients with stage IIB triple-negative BC (15%) [17]. The majority of distant metastases was pathologically proven, giving credit to the results [18]. In our study of 254 women, we also observed that the rates of distant involvement did not differ significantly according to the BC phenotype: TNBC (16%), HER2+ (26%), ER+/HER2- (22%) ($P = 0.419$). However, the sites of involvement differed. TNBC patients and HER2+ patients had a high proportion of extra-skeletal metastases.

It is also well-known that prognostic value decreases in the case of high-grade tumours. We observed that extra-axillary lymph nodes were more frequent in patients with grade 3 tumours in comparison with lower grades (29% vs. 13%, $P = 0.004$) but the rate of distant metastases did not differ (17% vs. 21%, $P = 0.418$) [11].

Concerning the histology, invasive lobular carcinoma (ILC) shows currently faint or no FDG uptake [15]. Therefore, ILC is considered as a poor candidate for staging with PET imaging. In a retrospective study, the team from the Memorial Sloan Kettering Cancer Center detected unsuspected distant metastases with PET/CT in 12 of 146 (8%) ILC patients; 10 of 88 (11%) stage III [19]. The yield of distant metastases was higher in a comparison stage III invasive ductal carcinoma (IDC) cohort: 22% (20/89). Some ILC patients were up-staged by non-FDG-avid lesions visible only by the CT component [19]. ILC differs in its patterns of metastatic spread when compared with IDC. ILC demonstrates a predilection for metastases to the peritoneum and hollow viscera. Non-FDG-avid sclerotic osseous metastases are more common in patients with ILC than in patients with IDC [20].

In conclusion, based on available literature, PET/CT appears to perform better than conventional modalities in the initial work-up of BC patients. There is now current evidence that PET/CT has substantial yield in BC patients with clinical stage IIB or higher, and findings from this examination have prognostic value. The high accuracy of PET/CT in stage IIB or higher stage is observed whatever the BC cancer phenotypes (TNBC, HER2+ and ER+/HER2-), whatever the tumour grade and whatever the patient's age. FDG imaging is more limited in the case of ILC. Patterns of the metastatic spread in ILC should be known for optimal analysis.

Compliance with ethical standards

Conflicts of interest The author declared no conflicts of interest.

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