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EDITORIAL COMMENTARY

What is the role of FDG-PET in the initial staging of breast cancer?

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In an era of increasingly available fludeoxyglucose positron emission tomography (FDG-PET) and its hybrid with computed tomography (FDG-PET/CT), these modalities are entering new fields of possible utilization. The power of FDG-PET can be shown in the example of a 57-year-old female with fever of unknown origin (Fig. 1). A high FDG uptake is clearly apparent in the large arteries because of vasculitis—the cause of the fever. Vasculitis probably represented a secondary paraneoplastic sign of breast cancer, missed by mammography due to the dense breast tissue. The diameter of the surgically confirmed cancer was only 4 mm. The patient was followed-up for 4.5 years and has been found to be free of disease after the appropriate treatment.

In this issue of EJNMMI, Tevfik Çermik et al. [1] address the role of FDG-PET in the initial staging of breast cancer. As the introductory example shows, under certain circumstances, FDG-PET is easily able to depict breast cancer less than 5 mm in diameter. Unfortunately, the concentration gradient of the FDG uptake between tumour and the surrounding background is not high enough in all breast cancers to be able to discover even small lesions, where the partial volume effect applies negatively. Moreover, dense breast tissue usually exhibits higher FDG uptake [2] in comparison to adipose breast, which further worsens the tumour contrast. Çermik et al. have found 53% sensitivity for primary lesions <5 mm and 92% for lesions >20 mm.

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The design of the study is ethically justified because it follows routine clinical steps: first, biopsy of the suspected breast lesion, then, if positive, staging modalities including PET and, finally, surgery or systemic therapy depending on the results of the staging. For the purpose of evaluating FDG-PET, this brings a certain number of problems. To some extent, core needle biopsy reduces the tumour mass, and together with the partial volume effect, this negatively influences PET sensitivity, especially in small lesions. On the other hand, the inflammatory reaction caused by the biopsy can facilitate the imaging of primary neoplasms. A secondary inflammatory reaction can be also present in lymph nodes, and this may lower the specificity of any lymph node evaluation. Thus, Çermik et al. have found 89% specificity in axillary lymph node assessments.

PET has not yet approached its theoretical physical limits in spatial resolution. PET is still improving, and the progress is apparent each year. It might be expected that in the future, substantially smaller primary cancers, smaller nodal and distant metastases, and tumours with a lower concentration gradient will be detected. It would be interesting to compare the results of Çermik's study with those of the same study conducted using the latest PET/CT scanner of 2 mm FWHM. In addition, a better assessment of the infiltration of the chest wall or skin would be achieved if a prone position using a special underlay enabling the breasts to hang freely were used [3]. The majority of PET scanners currently installed do not achieve the sensitivity of magnetic resonance imaging (MRI) when the lesions are very small, e.g., multicentric tumours. On the other hand, FDG-PET seems to be more specific compared to MRI in detecting primary tumours.

PET still remains "only" a macroscopic imaging modality—thus, a negative FDG-PET cannot exclude the presence of microscopic metastases. Therefore, histologic exploration

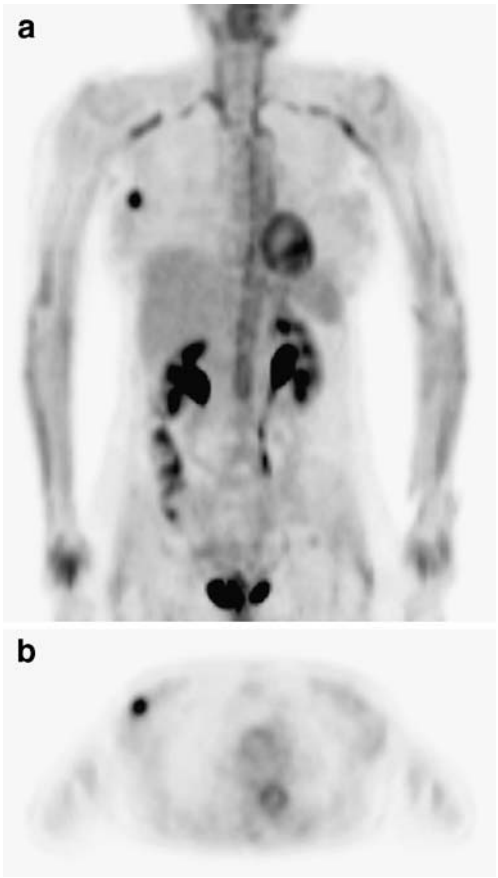

Fig. 1 A 57-year-old female with fever of unknown origin. Maximum intensity projection (**a**) and transverse slice (**b**) show diffuse high FDG uptake in the aorta and large vessels as well as very intense focal uptake in a 4-mm large cancer in the right breast

of sentinel lymph nodes cannot be avoided after FDG-PET negative findings, except for in situ carcinoma. Çermik et al. bring evidence for this statement—they found sensitivity of only 41% at the pN1 and 67% at the pN2 axillary lymph node stage. Their findings are in concordance with another large series [4]. In addition to FDG-PET, neither contrast-enhanced CT (CE-CT) nor MRI help in the diagnosis of lymph node involvement because their lower sensitivity is limited by the assessment of lymph node size only.

Thus, the role of contemporary FDG-PET or, rather, PET/CT in initial staging lies in proving that the disease is more extensive than originally expected. How can this knowledge be used? In the first place, it represents an important prognostic factor, and in the second, it is crucial for determining the optimal tailoring of the therapy. The discovery of distant metastasis results in the postponement or cancellation of surgery that is usually considered as the therapy of the first choice. Systemic therapy is indicated instead of surgery when a distant metastasis is present. The choice of an optimal diagnostic method or their sequence is based on their sensitivity and specificity, especially with regard to the most frequently occurring metastases in the lung, liver, bones and soft tissues. The choice of methods is also influenced by their availability and the social and financial situation of the patient and/or the community (when insured). It is clearly apparent that CT is much more accurate than plain radiography in the same way as SPECT is in comparison to planar scintigrams. On the other hand, the various imaging modalities complement each other, and each of them brings more or less different information. Hypothetically, if no financial limits existed, radiation protection would be the only reason for not using all of them. After all, FDG-PET represents a very accurate method in liver metastases, but it fails in small lesions due to respiratory motion and partial volume effect. In addition to FDG-PET, CE-CT and/or MRI can, under specific conditions, identify additional liver lesions. CE-CT is currently unrivalled in the discovery of lung metastases. In terms of bone metastases, FDG-PET has the potential to diagnose them when they infiltrate the bone marrow, i.e., before they initialize bone remodelling apparent using bone SPECT or CT, but not all bone metastases are FDG avid. Thus, MRI comes forward with help to localize subtle changes in the material composition of the bone marrow. To diagnose focal, even minimal changes in mineral turnover, [18F]fluoride PET is optimal, and when not available, bone SPECT with diphosphonates can assist. It is not possible to define an optimal diagnostic algorithm, which would be acceptable under different social and economic conditions. The reason is the rapid and continuous development of all imaging modalities and the different generation/age of instruments used in the trials. The results of any clinical trial performed in one period using a single technology are not transferable to a different period, when more advanced technology is available.

In individual cases, when the cancellation of surgery would be based on a FDG-PET finding of distant metastases, one must take into consideration that this modality does not have 100% specificity. The most important contribution of FDG-PET is to alert the examiner to a present pathology that should then be specified by another modality. For example, focal FDG uptake in the rib may not always represent a metastasis but can also be the sign of a recent fracture. In this case, it is important to take a detailed history and to perform a spiral CT. Slightly increased FDG uptake in mediastinal lymph nodes can be confusing because the most common reason is their inflammatory activation. Similarly, grossly inhomogeneous FDG uptake simulating foci of minimal contrast in the liver or bone marrow without structural changes may cause decision-making problems. In the knowledge that PET is not able to discover microscopic metastases, it is a lesser evil to report a "non-diagnostic result" rather then to report a false-positive finding that leads to the cancellation of surgery. This type of patient should be treated as free-of-metastases, or preferably, he/she should undergo additional imaging (e.g., an MRI of the liver or bone marrow).

At present, the hybrid FDG-PET/CE-CT seems to represent the optimal staging modality, when the PET part of the scanner is equipped with a high-resolution detector and the CT part with a multislice detector. This state-of-the-art equipment has great potential not only to discover macroscopic lung, liver, bone and soft tissue involvements, but also to specify and localize them. In the case of an indeterminate finding, it targets MRI or even biopsy. The combination of a whole body MRI and the hybrid FDG-PET/"low-dose" CT was newly proposed as being highly accurate. This will force the development of new hybrid PET/MRI scanners. Nevertheless, at the current state of knowledge, the negative results of these macroscopic imaging modalities do not allow us to avoid the histological exploration of sentinel lymph nodes with the aim of excluding their microscopic involvement.

Even in a hypothetical case of unlimited financial sources and unlimited availability of PET/CT, the question also arises of whether to expose all patients with breast cancer to the radiation risk originating from FDG-PET/CT or only to expose those at a more advanced stage of the disease and a higher risk of distant metastases. To date, it has not been possible to answer this question because there is no clear evidence of the degree of risk coupled with low-dose irradiation [5]. There is still the question of whether the 7.5% of cases of distant metastases discovered by Çermik et al. using FDG-PET are enough to conclude that this investigation is essential for the initial staging of breast cancer. The answer is not a purely medical one and can be found in individual decision of the patient who pays for this investigation, which means in his/her priorities and social and economic situation. When he/she is insured, the answer should be found in the group of clients of insurance company, i.e., whether they are willing to pay a high enough amount of money to cover this type of investigation. Cost-benefit studies should serve as a guiding rule to enable insurance companies to prepare well-balanced insurance options. Let each reader try to answer the question of whether he/she would be willing to pay for FDG-PET/CE-CT if they were suffering from breast cancer. My experience with this modality leads me to believe that I would undergo this investigation as one of first choice, except in the case of an in situ carcinoma. Another question is why FDG-PET/CE-CT should be indicated at an apparently advanced stage of the disease, when systemic treatment is the first choice (e.g., advanced inflammatory breast cancer). In this situation, the value of imaging lies not in its input for staging but as a comparison with future investigation to assess the effect of the therapy.

As a result of improved breast care (education, life style, self-examination, regular mammographic screening in combination with ultrasonography), breast cancer can be screened out at earlier stages, and thus, the probability of diagnosing the disease at more advanced stages diminishes. Çermik et al. found that FDG-PET upstaged 9.2% of cases. In other social and economic conditions, when preselecting patients or using a different scanner, this proportion might be significantly more or less. For example, Keller and Subramaniam [6] upstaged 34% of 62 premenopausal patients with T2 breast cancer using FDG-PET/CT. This means that published proportions of upstaged cases are tightly coupled to the group of patients examined, and it is not possible to generalize results beyond this group.

From the point of view of community affairs, breast care is the most important means of screening out cancer at as early a stage as possible. What additional impact routine initial staging by FDG-PET/CE-CT has on the quality of life, overall survival and costs at the community level, still remains the question to be answered.

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