ANTICANCER RESEARCH *38*: 4145-4148 (2018)
doi:10.21873/anticanres.12706

Low-dose High-resolution ^{18}F-FDG-PET/CT Using Time-of-flight and Point-spread Function Reconstructions: A Role in the Detection of Breast Carcinoma Axillary Lymph Node Metastases

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Abstract. *Aim: to evaluate the performance of N-staging assessment in clinically-proven T1 breast carcinoma by high-resolution ^{18}F-fluorodeoxyglucose-positron-emission tomography/computed tomography (^{18}F-FDG-PET/CT) using time-of-flight with point-spread function reconstruction. Patients and Methods: In 30 women with clinically proven T1 breast carcinoma, imaging before surgery was performed using ^{18}F-FDG-PET/CT. The results of PET/CT in detection of lymph node metastases were compared with those obtained after pathological investigation of axillary biopsy. A four-ring PET subsystem with image reconstruction using time-of-flight and point-spread function was used with the radiopharmaceutical dose reduction to 2.5 MBq/kg. Results: Axillary lymph node metastasis was confirmed by histology in 13 patients, but metastasis was suspected based on PET/CT in 12 of those patients, the absence of metastasis was surgically confirmed in 17 women, 15 of which were suspected based on PET/CT. The sensitivity for detection of axillary lymph node metastasis was 93.3%, with a specificity of 88.2% in the whole patient cohort. Additionally, distant metastatic spread was found in 13.3% of patients. Conclusion: The reconstruction of PET images with time-of-flight and point-spread function enabled the improvement of diagnostic performance in N-staging of breast carcinoma, even when the dose of radiopharmaceutical was reduced to 2.5 MBq/kg*

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Key Words: PET/CT, FDG, breast cancer, N-staging, time-of-flight, point-spread function reconstruction.

Accurate preoperative staging is critical when deciding on further treatment for breast cancer, and it is of crucial importance for predicting the prognosis. In addition to primary breast imaging using mammography, ultrasound scanning or magnetic resonance imaging, other imaging modalities are also used to determine the stage of the disease, such as computed tomographic (CT) scan of the chest, ultrasound liver imaging and skeletal scintigraphy. Ultrasound or magnetic resonance imaging is used when assessing the presence of metastatic infiltration of the axillary nodes (1). The standard procedure for assessing N-staging is sentinel node biopsy by radioguided excision and subsequent histopathological examination. The vast majority of ductal or lobular breast cancers, predominantly higher grade and triple-negative phenotypes, are known to accumulate ^{18}F-fluorodeoxyglucose (^{18}F-FDG) relatively well and therefore positron-emission tomography (PET)/CT can also be used to stage the disease (1-3). Although the use of ^{18}F-FDG-PET/CT has already been established for locally advanced tumors and restaging of the disease (1, 2), its benefit has not been fully evaluated for the detection of axillary node involvement. The decision to perform radical surgery or to plan neoadjuvant therapy primarily depends on the presence of axillary node involvement or the presence of occult distant metastases when the breast carcinoma is triple-negative, even when of size T1.

In our work here, we evaluated the benefit of whole-body ^{18}F-FDG-PET/CT for the detection of distant metastases and secondary findings, but especially for the assessment of axillary node involvement. The analysis includes an assessment of the diagnostic benefits of PET/CT imaging using a 128-row CT and a four-ring PET subsystem with data reconstruction using time-of-flight (TOF) and point-spread function (PSF) with reduced dosing of ^{18}F-FDG to 2.5 MBq/kg.

Materials and Methods

A total of 30 examinations were carried out in women with triple-negative breast carcinoma already confirmed by biopsy up to 2 cm in size (T1 according to TNM classification) (4) and ranging in age from 29 to 71 years, with an average age of 47.2 years. All examinations were indicated due to the high-risk phenotype of the breast carcinoma, and all procedures were performed after informed consent was obtained; the study was carried out to the according Helsinki declaration. All examinations were performed after at least 6-hour fasting, and a check of blood glucose level prior to and 60-75 minutes after administration of ^{18}F-FDG (UJV, Rez u Prahy, Czech Republic) at a dose of 2.5 MBq/kg. Iodine contrast agent 80 ml iopromide, Ultravist 370; Bayer Healthcare, Berlin, Germany) was administered intravenously at a flow rate of 4 ml/s to all patients; no contraindications for the administration of the contrast agent were found in any of the examined patients.

The examinations were performed with the use of PET/CT scanner equipped with 128-row CT subsystem and 4-ring PET subsystems (Biograph mCT 128; Siemens Healthcare, Knoxville, TX, USA) after the administration of ^{18}F-FDG at 2.5 MBq/kg. CT data were obtained using a 100 kV voltage protocol with the possibility of reducing the voltage in asthenic patients to 80 kV with automatic dose correction. Data were reconstructed into diagnostic images using SAFIRE iterative data reconstruction at a 0.75 mm image width with a 0.6 mm reconstruction increment and a soft-tissue algorithm. PET data were reconstructed in a 400 × 400 matrix in transaxial field-of-view with 46 cm diameter using the ultraHD algorithm, which combines the TOF and PSF algorithms, and also 2 mm. Data acquisition was performed by step-and-shoot techniques using five to six positions with an acquisition time of 1.5 minutes per position.

Image fusion was used to evaluate all aspects of potential metastatic involvement, including the presence of hypermetabolic involvement in the axillary and mediastinal lymph nodes, the presence of other possible metastases in the lung tissue, liver and skeleton, as well as the presence of other important findings, such as further manifestations of a secondary primary malignancy. Breast carcinoma was not found as a second malignancy in any of the women. The following lymph nodes were considered as being infiltrated by metastasis: short diameter larger than 10 mm (according the TNM staging manual) (4), and/or the accumulation of FDG of 3 SUV_{max} (maximum standardized uptake value within the lymph node).

Histological verification of axillary findings was performed in all patients using lymph node excision or biopsy. In patients who had their primary breast tumor removed, a biopsy of the sentinel node was performed followed by histological examination, or subsequently removed lymph nodes were subjected to histological examination after demonstrating positivity of the sentinel node. In five patients, biopsy only was performed because treatment with neoadjuvant therapy had been started.

Results

Axillary lymph node metastasis was confirmed by histology in 13 patients, and metastasis was suspected based on PET/CT in 12 patients. In one false-negative lymph node, microscopic metastatic involvement was found by the pathologist. In one patient, metastases were found additionally in internal thoracic lymph nodes, assigned as N3. Seventeen women had axilla free of metastases, two of them suspicion of metastases in supraclavicular or internal mammary lymph nodes, which were not removed and not confirmed by biopsy. Total sensitivity in detection of lymph node metastases using PET/CT was 92.3% and specificity was 88.2%; the negative predictive value was 93.8% and the positive predictive value was 85.7%; Table I details the results.

Table I. *Axillary lymph nodes detected using positron-emission tomography/computed tomography (PET/ CT) versus biopsy findings.*

	Biopsy *versus* PET/CT
Total, n	30
True positives, n	12
False negatives, n	1
True negatives, n	15
False positives, n	2
Sensitivity	0.9231
Specificity	0.8824
Positive predictive value	0.8571
Negative predictive value	0.9375

Other significant findings were four cases (13.3%) of distant metastatic spread: one to the skeleton, one to the lungs, and two to mediastinal lymph nodes. Both patients with metastases to the mediastinal lymph nodes had carcinoma of the axillary accessory mammary gland. Accidental findings of second primary tumors in four different patients, namely lung adenocarcinoma, papillary renal carcinoma, sigmoid colon carcinoma and chronic lymphatic leukemia, were also important for further treatment.

Discussion

Staging of breast carcinoma currently involves multiple imaging methods in several steps. This process is complicated and relatively time consuming. Given a relatively high level of glycolysis in almost all breast carcinomas (1-3), ^{18}F-FDG-PET/CT has a good chance of becoming a method that can replace other examinations and ensure that all organs are evaluated with sufficient accuracy, except for micrometastases in the brain tissue.

Major studies have reported that distant metastases are found by PET in up to one-fifth of breast cancer cases. The studies mainly concerned patients who were not classified by tumor size, and they included tumors from T1 to T4 (3, 5). Four cases of distant dissemination were found in our group of tumors of T1 size. Multiple metastatic involvement was found in only two cases of invasive ductal carcinoma. Secondary findings of secondary primary malignancies are of great importance, as they lead to modifications of the breast cancer treatment strategy and require further surgical or conservative treatment of the additional malignancy.

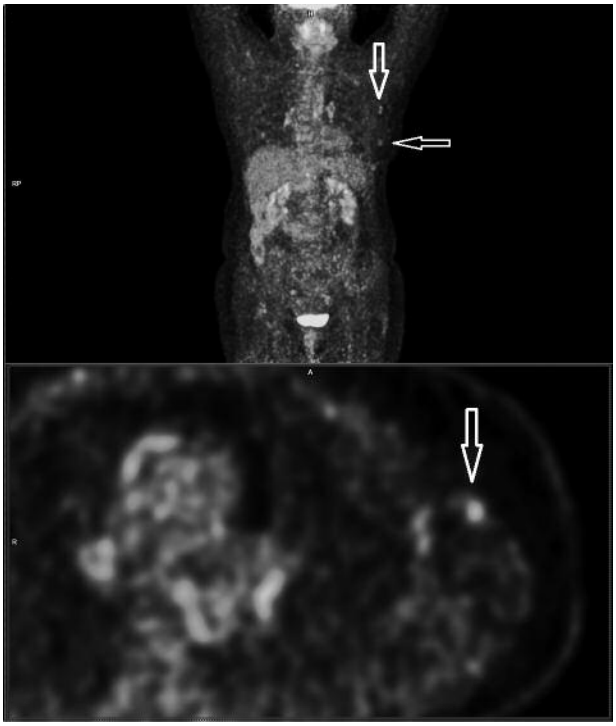

Figure 1. *Whole-body (A) and transverse (B) images of positron-emission computed tomography using. ^{18}F-fluorodeoxyglucose. Multifocal lobular invasive carcinoma (estrogen and progesteron receptor-positive, grade 2), exhibiting moderate ^{18}F-fluorodeoxyglucose accumulation in the primary site (horizontal arrow), and in axillary level I metastases (vertical arrows).*

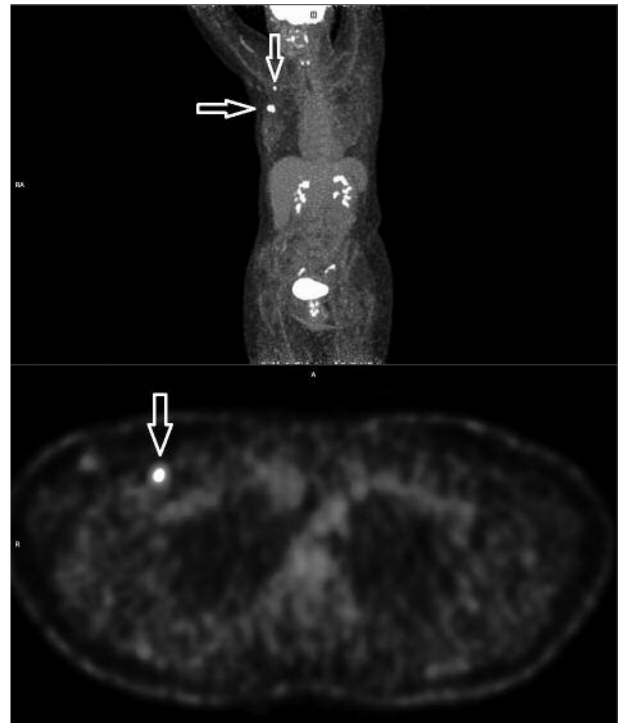

Figure 2. *Whole-body (A) and transverse (B) images of positron-emission computed tomography using ^{18}F-fluorodeoxyglucose. Triple-negative invasive ductal carcinoma (grade 3), exhibiting extreme ^{18}F-fluorodeoxyglucose accumulation in the primary site (horizontal arrow), and in axillary level II metastases (vertical arrows).*

However, the most important outcome of our study is the evaluation of the reliability of assessment of the involved axillary lymph nodes. The current standard is radioguided sentinel node biopsy. However, this is not a diagnostic imaging modality for the presence of metastatic lymph node involvement, but only a sign of the degree of lymphatic drainage. In contrast, ^{18}F-FDG-PET/CT is a method that directly evaluates metastatic infiltration (2, 3, 5) and is also relevant for prognosis of the disease (5, 6). When evaluating axillary nodes, false-negative and false-positive findings may be obtained. False-positive findings are often caused by sinus hyperplasia or activation after previous puncture biopsy, and cannot basically be eliminated by a more accurate acquisition method or PET data reconstruction. In contrast, false-negative findings can be caused by micro-metastases that are below the resolution limit of PET acquisition. A higher spatial and contrast resolution can be achieved by further refinement of reconstruction parameters, and in particular by using refined algorithms. In our population, we clearly demonstrated a high quality in the diagnostic performance of the ^{18}F-FDG-PET/CT method when using high-resolution reconstruction algorithms with TOF and PSF (7-9), and reconstruction with a high matrix size in a smaller reconstructed field.

PSF is an image reconstruction method based on the analysis of the Airy Disk distribution function, which is derived from applications used in astrophysics to identify objects in the sky. PET data reconstruction relies on a more accurate identification of coincident lines, known as line of response. It helps achieve better reconstruction of places where coincidence occurs, especially in the marginal parts of the field of vision, which means just in the axillary region. PSF technology is significant in enabling the possibility of identifying focal areas of radiopharmaceutical uptake and better identification of minor metastases, thus achieving better detection of axillary metastases and the complete elimination of false-negative findings (10). Examples of the reconstruction used in detection of metastases are displayed in Figures 1 and 2. The images document the possibility to identify tmetastases (bright objects) regardless of its intensity and background noise.

TOF technology contributes greatly to better contrast resolution by enabling detection of multiple coincidences through differentiation of time differences in the coincidence of quantum effects. Improved efficiency of the system can be used to reduce the acquisition time or the required radiopharma-ceutical activity, or both. In our population, we successfully used both options and reduced the dose delivered and thereby the radiation load from PET by one-third. At the same time, the time for data acquisition per bed was shortened (also partly due to the wide PET detector system) without reducing the diagnostic yield, which may even have been increased.

The axial width of the PET detector system is also an important contributor to increasing the quality of the examination. An increase to a 22 cm-wide four-ring detector from the original 15 cm-wide three-ring detector resulted in a shorter length of examination by reducing the number of required positions, as well as by increasing the detection efficiency of the whole system.

However, the CT protocol also has a significant impact on the assessment of axillary lymph nodes. Using a contrast agent with a higher iodine concentration in conjunction with a 100 kV or even 80 kV protocol, and the use of iterative data reconstruction help visualize minor hypervascularized lesions with higher contrast, including very small nests of tumorous tissue inside the axillary lymph nodes. This technique also helps to reduce the number of false-negative and false-positive results. The combination of iterative reconstruction with active dose-modulation components on the voltage and current side contributes to reduction of the radiation dose from the CT scan: it was possible to reduce the CT-related dose to two-thirds or to one-half of without use of dose-modulation.

Compared to other studies, our study achieved well-balanced sensitivity and specificity, and the results of PSF and TOF techniques are virtually identical to those in the published populations (2-3, 5). The results of the evaluation of axillary lymph nodes are comparable to those of PET and magnetic resonance imaging (MRI) studies. The use of integrated PET/MRI scanning (10), achieved higher accuracy, in particular with higher resolution of lesions in the breast tissue. In addition, PET/MRI also enables the complete elimination of the radiation dose from morphological imaging.

Conclusion

^{18}F-FDG-PET/CT, when using high-resolution reconstruction algorithms with PSF and TOF, and higher-size matrix reconstruction in a smaller reconstructed field, achieve high accuracy in breast cancer staging and significantly reduced the examination time, while also reducing the dose of radiopharmaceuticals by one-third. The ^{18}F-FDG protocol at 2.5 MBq/kg and an acquisition time of 1.5-minute per position is fully diagnostic, and the high diagnostic value in detection of metastatic involvement of axillary nodes was documented in this study. Dose reduction using a low kilovoltage CT protocol seems to be an important additional advantage of better contrast resolution of the iodine uptake, besides the effect of the dose reduction itself.

Acknowledgements

This study was supported by a project of the conceptual development of the Czech Ministry of Health - University Hospital Plzen 00669806 and a project of the Charles University - Progress Q39

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Received April 17, 2018
Revised May 14, 2018
Accepted May 16, 2018