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Positron emission tomography (PET) in the diagnostic of breast tumors

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Summary

The article is a review of current knowledge in the field of positron emission tomography and breast cancer diagnostics. It presents in a comprehensive way the physiological background of (18F) fluorodeoxyglucose (FDG) use in the diagnostics. The paper presents FDG study rules. The author discusses the indications for the PET studies in the field of breast cancer diagnostics, the current knowledge and some present prospects of PET development.

Key words: PET/CT • FDG • breast cancer

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Positron emission tomography (PET) involves functional imaging of the whole body, the trunk or a selected organ (e.g. the brain, liver or heart) after intravenous administration of a radiopharmaceutical labeled with positron isotope. The P E T method is applied for imaging of tissues and organs utilizing the substances occurring physiologically in the organism (or their precursors), labeled with radioactive elements with low atomic mass, emitting positrons as a result of their disintegration. After leaving the atom orbits, the positrons collide with negatively charged electrons, which results in the annihilation phenomenon and emission of two quanta of gamma radiation of 511,9 keV energy, which is recorded by PET apparatus. Disintegrating fluorine isotope ^{18}F is one of the components of fluorodeoxyglucose – FDG.

The use of fluorodeoxyglucose allows to visualize the tissues demonstrating increased glucose demand. Because of the common metabolic pathway of 18 FDG and glucose up to the level of glucose phosphorylation, 18FDG falls into the "metabolic trap".

As early as in the 1920's-30's, Warburg observed increased glucose demand presented by tumors. He also demonstrated that „In tumor cells thirteen glucose molecules undergo „fermentation" and only one oxidation." The above indicates manifold higher demand for this metabolite in most tumor tissues, including breast cancers.

Thus, PET, or more precisely PET/CT technique (as 90% of newly installed devices are hybrid scanners at present) is an examination with a potential to differentiate malignant tumor tissue from benign lesions. Its application in breast cancer diagnostics ranges from examinations of the primary tumors, through staging of the hyperplastic process, treatment monitoring, to prediction of the course of the disease.

Preparation of the patient

- The patient should be fasting (min. 6 h prior to the examination) but hydrated, exclusively with PURE mineral water
- Serum glucose level should not exceed 150 mg%
- After FDG administration, no physical exertion, talking, chewing gum allowed
- The procedure should be performed with caution in patients with renal insufficiency
- The patient brings:
  - 1 l still mineral water
  - A social security document
  - Results of imaging diagnostics

Diagnostics of primary lesions

The first results concerning the application of PET in breast cancer diagnostics were encouraging. Adler et al. [1] demonstrated in a group of 124 patients with high risk of breast cancer a sensitivity of 97% and specificity of 100%. Their results were confirmed by the study by Utech et al. [2] demonstrating 100% sensitivity and the same specificity in a group of 79 patients with breast cancer < 3 cm. However, further studies were not so optimistic. PET sensitivity was found to be significantly reduced in tumors less than 1 cm in diameter. In the largest-scale study the sensitivity of detection for tumors < 1cm was 57%, for tumors > 1 cm – 91%. We do not have currently any representative data concerning the sensitivity, specificity and accuracy of PET/CT performed using the latest generation equipment in the preliminary diagnostics of breast cancers below 8 mm in diameter. Tumor size (> 10 mm) and low differentiation are two independent factors causing false negative results. No effect of such factors as: the patient's age, tumor type, estrogen and progesterone receptors, parenchyma density, metastases to sentinel lymph node and distant metastases, as well as single or multiple primary lesions has been noted.

There are hopes for overcoming the lesion size barrier owing to new equipment combining a mammograph with PET and fusion images combining the functional images provided by PET and morphological images obtained by mammography. This technique is referred to as PEM (positron emission mammography). The results obtained with this method are excellent: sensitivity 91%, specificity 93%, PPV 95%, NPV 88%, accuracy 92%, if assessed in combination with clinical and mammographic data – 94.9% [3]. It should be remembered that these figures concern only the assessment of the mammary gland, and not the whole body, as it is the case with classic PET technique. However, in diagnostics of small diameter lesions, and consequently, at early stages of progression, a technique of this type can become very useful in future, enabling to differentiate benign and malignant lesions on the basis of metabolic activity at the site of an "abnormality" revealed by mammography.

Staging of the disease

In assessment of post-augmentation mammoplasty conditions, PET belongs to the leading diagnostic techniques. Such infrequent cases, whose interpretation is difficult for classic diagnostic methods, have been classified correctly by functional imaging utilizing [4, 5]. Staging of the disease and diagnostics of relapses or distant metastases is the area in which PET technique has been unquestionably successful since its introduction to the medical market. The results obtained with PET and FDG are significantly superior to those obtained with classic imaging techniques. For instance: PET and CT of the thorax were compared in a group of 73 patients with breast cancer relapses and metastases.

Method	sensitivity	specificity
PET:	85%	90%
CT:	50%	85%

In 33% of patients, PET results led to a change in staging and treatment method.

In another group of patients – 39 subjects with elevated tumor markers, PET diagnosed relapses correctly in 94% of cases, in contrast to conventional imaging techniques (CT and MRI) – 18%.

In assessment of bone metastases, PET FDG detects lesions of osteolytic character, overlooked by standard bone scintigraphy, whereas it may not visualize the lesions of osteoblastic character detected by BS. The overall sensitivity and specificity of PET utilizing FDG and classic BS are comparable, but it should be emphasized that these two techniques are complementary to each other [6]. PET with sodium fluoride (^{18}F)NaF seems to be a solution. The sensitivity of this technique approximates 100% with similar specificity [7].

The accuracy of PET and sentinel node scintigraphy are similar. PET inadequately identifies the number of involved lymph nodes, but it visualizes the mediastinal lymph nodes generally inaccessible with other techniques. Micrometastases cannot be visualized by PET but their significance in clinical practice has not been determined. In the largest-scale study in a group of 124 patients, PET visualized correctly metastases to the lymphatic system in 100%, ie. 44 patients. In another study, sensitivity, specificity and accuracy reached, respectively, 85%, 91% and 89% [8, 9].

PET technique utilizing FDG has a significant impact on staging, affecting it in 36% of cases, as well as on the management of patients with breast cancer, which is modified in 56% [10]. In another study, in comparison with classic imaging modalities, PET led to staging alteration in 67% (43% – increase, 24% – decrease). The management of the patients was modified in 32% of cases [11].

Assessment of the therapy

Another application, finding increasing support in scientific evidence, is the assessment of efficacy of the adopted therapeutic regimen. Significant decreases of metabolic activity (to 72 %) were observed in the group of patients responding to treatment, in contrast to no such effect in the group of non-responders. The changes were visible as early as after the first course of treatment [12]. In another study, a decrease by 28% after the first cycle and by 46% after the second one was reported in „responders". The conclusions from the latter study provide strong evidence that PET FDG can predict the effectiveness even after one chemotherapy cycle [13, 14, 15]. The decrease of metabolic activity by 55% in comparison with baseline values differentiated „responders" from „non-responders" with 100% sensitivity, 85% specificity and 88% accuracy [16]. Monitoring breast cancer patients with PET seems to be more accurate and reliable than classic imaging modalities.

Classic imaging methods (X-ray mammography, US, CT, MRI and bone scans) were compared with PET in a study group of 62 patients after surgical breast cancer resection [17].

	Sensitivity	Specificity	NPV	PPV	Accuracy
PET	97%	82%	92%	87%	90%
CI	84%	60%	75%	73%	74%

In meta-analysis of 16 out of 28 studies, including 808 breast cancer patients, the obtained sensitivity was 92.7%, and specificity 81.6% for PET FDG applied in assessment of tumor relapse and metastases [18]. Because of false positive results of PET with FDG used, due to inflammatory conditions or other non-neoplastic changes enhancing focally glucose metabolism, studies concerning utilization of other markers are presently under way. Promising results have been obtained with ^{18}F fluorothymidine as a marker of enhanced DNA replication process. In 8 out of 10 patients with breast cancer, 18F-FLT PET visualized correctly the presence of a malignant process [19]. There were no additional foci of marker metabolism. In another study, 13 out of 14 primary breast tumors and 7 out of 8 metastases to axillary lymph nodes were diagnosed correctly using 18F-FLT PET [20].

Summing up the presented study, the following areas of application can be indicated for PET technique in breast cancer diagnostics:

1. Screening in the group of patients with mammographically „dense" mammary glands (limited area, PEM).
2. Screening in the group of patients with implants and after reconstruction surgery (limited area, PEM).
3. „Lymph node staging" in patients with high probability of thoracic lymph nodes involvement (limited area).
4. Staging in patients with high risk of metastatic lesions (whole-body PET).
5. Metabolic characteristics of suspicious lesions in conventional diagnostics (whole-body PET).
6. Re-staging in the group of patients in which numerous repeated conventional tests are necessary (whole-body PET).
7. Monitoring chemotherapy effects in order to determine the patient's response to treatment and assess its effects (limited or whole-body PET).

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