GENERAL REVIEW

UDC: 616-006-073-037::618.19-006-037
https://doi.org/10.2298/VSP151018110M

The ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography in breast cancer

Pozitronska emisiona tomografija/kompjuterizovana tomografija primenom ^{18}F-fluorodeoksiglukoze kod karcinoma dojke

Jasna Mihailović*†, Milan Ubavić‡§

Oncology Institute of Vojvodina, *Department of Nuclear Medicine, Sremska Kamenica, Serbia; University of Novi Sad, †Technical Faculty "Mihajlo Pupin", Zrenjanin, Serbia; ‡Health Care Institution for Laboratory Diagnostics "Medlab", Novi Sad, Serbia; European University, §Faculty of Pharmacy, Novi Sad, Serbia

Key words:
breast neoplasms; tomography, emission-computed; tomography, x-ray computed; radiopharmaceuticals; sensitivity and specificity.

Ključne reči:
dojka, neoplazme; tomografija, kompjuterizovana, emisiona; tomografija, kompjuterizovana, rendgenska; radiofarmaci; osetljivost i specifičnost.

Introduction

Breast cancer is the most common malignancy diagnosed in women. A number of 231,840 new cases of breast cancer was expected in 2015, and 40,290 women were estimated to die from breast cancer in 2015 [1]. In 2012 in Central Serbia, 3,186 new cases of breast cancer in women were registered and 1,175 cause-related deaths [2, 3]. There is an increasing incidence and mortality of breast cancer in Vojvodina, a northern part of Serbia (Figure 1) [3].

Positron emission tomography (PET) is a modern imaging method which plays an important role in oncology. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is a radiolabelled glucose analogue presenting a glucose metabolism marker. Since glucose uptake is increased in malignant tumors, ^{18}F-FDG PET has a major performance in oncology. A quantitative measurement of FDG uptake is expressed by the standardized uptake value (SUV) and is used mostly for diagnosis and response to treatment assessment. In fact, the SUV represents a relative measure of FDG uptake in tissue and is automatically calculated by PET and PET/computed tomography (CT) scanners as follows: SUV= r/(a/w), where *r* is the radioactivity measured within the region of interest (ROI) in kilobecquerels *per* millimeter (kBq/mm), *a* is the decay-corrected amount of injected radiolabeled FDG (kBq), and *w* is the weight of the patient (g). There are several factors that affect the SUV, such as plasma glucose concentration, the amount of injected FDG, the patient size and, the time from injection to imaging which is perhaps one of the most important factor [4, 5].

^{18}F-FDG PET imaging is a so-called metabolic imaging because of the ability to detect malignant metabolism changes. These changes in fact, precede morphologic changes which are visualized by conventional anatomic imaging such as CT and magnetic resonance (MR).

In the last decade, PET and combined PET/CT were introduced in imaging of breast cancer. The CT part provides exact anatomic information and is used for attenuation correction of PET images. Comparing these two imaging modalities, PET/CT has been accepted to have better diagnostic accuracy than PET itself [6–8].

General considerations

Several authors have studied intensity of FDG uptake in different types of breast cancer. In comparison to ductal carcinoma, the lower FDG uptake was detected in infiltrating lobular carcinoma [9–13]. This phenomenon might be explained by several reasons: lower tumor cell density, a diffuse infiltration of surrounding tissue, a low level of glucose transporter 1 (GLUT1) expression and a decreased proliferation rate in infiltrating lobular carcinoma [10, 14, 15].

Correspondence to: Jasna Mihailović, Oncology Institute of Vojvodina, Department of Nuclear Medicine, Put dr Goldmana 4, 21 000 Sremska Kamenica, Serbia. Phone: +381 21 480 5459.

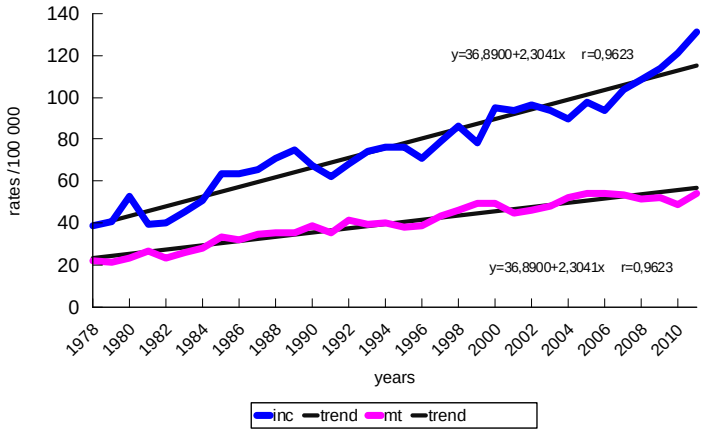

Fig. 1 – The crude incidence and mortality rates for breast cancer in females in Vojvodina in a period from 1985 to 2011 (inc – incidence; mt – mortality).

It has been reported that FDG uptake strongly correlates with high tumor proliferation index (Ki67 expression measured by immunohistochemical analysis) [9, 13, 14, 16] and p53 factor status [9, 12]. The relation between ^{18}F-DG uptake and steroid hormone receptor status is still controversial. Some authors reported no correlation between hormone receptor status and SUV values [11–13, 16]. Several studies detected a higher SUV in estrogen receptor negative (ER−) than in estrogen receptor positive (ER+) tumors [9, 17–19]. In contrast to Osborne et al. [19] who detected no correlation between the SUV and progesterone receptor status, Groheux et al. [20] documented a significant difference in ^{18}F-FDG uptake in progesterone receptor negative (PR−) tumors *vs* progesterone receptor positive (PR+) tumors ($p = 0.003$). Triple-negative breast tumors (negative for estrogen and progesterone receptors, and no human epidermal growth factor receptor-HER 2/neu overexpression) present a great subject to investigate because of their aggressiveness, poor prognosis and lack of targeted regimens. They are characterized with significantly higher SUV values than non-triple negative tumors [21].

Indications

Primary tumor

^{18}F-FDG PET or ^{18}F-FDG PET/CT plays an important role in the diagnostic workup of breast cancer. However, it has no role in breast cancer screening due to limited spatial resolution (disability to detect tumors less than 10 mm) and the low sensitivity in less FDG-avid low-grade breast tumors. In a comparison study, Kumar et al. [22] concluded that tumor size and tumor grade are independent factors associated with false negative results. The eight times higher chances of obtaining false negative results were detected in smaller (< 10 mm) tumors *vs* larger (>10 mm) tumors. Results from another study showed that breast carcinomas were identified with an overall sensitivity of 64.4% and 80.3%, respectively. ^{18}FDG-PET detected only 68.2% breast cancer at stage T1, compared to 91.9% of breast malignancy stage T2 [10]. Analyzing 13 different studies, Samson et al. [23] reported that ^{18}FDG PET was 88% sensitive and 80% specific for detection of primary breast cancer showing false negative results in 12% cases. In another PET study done by Danforth et al. [24], the primary breast cancer was accurately imaged with 90% sensitivity in early staged breast cancer (stage I, II). Moreover, ^{18}FDG-PET is able to image locally advanced skin changes in locally advanced tumors (stage III, IV). In the same study, ^{18}FDG-PET sensitivity for detection of the primary tumor, skin, and axillary lymph node metastases was 96%, 77%, and 83%, respectively. However, in comparison to MR, ^{18}FDG-PET is less sensitive and accurate in the assessment of the primary tumor and screening for tumor multifocality (54% *vs* 77%, respectively) [25].

With the aim to overcome the low spatial resolution of ^{18}FDG-PET, a high-resolution PET scanners dedicated to breast imaging, so-called "positron emission mammography (PEM)" has been recently introduced. There are several publications based on clinical performance of PEM. In comparison to conventional whole-body PET, PEM is favorable in detection of ductal carcinoma *in situ* and lesions ≤ 1.0 cm. The advantages of ^{18}FDG-PEM include: reduced attenuation, improved geometric sensitivity, higher spatial resolution, shorter acquisition time (4−10 min), easy feasibility, device mobility, gentle breast immobilization, possible PEM-guided biopsy. The limitation of the study includes imaging of posterior lesions and variable ^{18}FDG uptake in small tumors [26–30]. In a recent study done by Berg et al. [31], the efficacy of PEM was compared to MR imaging. At the lesion-level, PEM was more specific than MR (79.9% *vs* 65.6%) which helps in avoiding unnecessary biopsies. However, in detection of additional malignant lesions MR imaging was more sensitive than PEM which results in better assessment of disease extent and less frequent mastectomy (53% *vs* 41%) [31].

As generally accepted, ^{18}FDG-PET has no clinical role in diagnostic algorithm of suspicious breast lesions. How-

ever, if there is inconclusive or suspicious mammography, ^{18}FDG PET may be useful. If ^{18}FDG PET unexpectedly detects FDG avid breast foci, patient needs additional conventional imaging and biopsy [32].

Axillary staging

The status of axillary lymph nodes remains one of the most important prognostic indicators in patients with breast cancer. Sentinel lymph node biopsy (SLNB) and axillary lymph node dissection (ALND) are standard procedures that are used for axillary staging. If axillary metastases are identified on SLNB, ALND is necessary. However, patients with negative SNB results may avoid ALND [33].

Despite high diagnostic accuracy, both SLNB and ALND are invasive procedures associated with morbidity, including lymphedema. Therefore, a non-invasive ^{18}FDG-PET imaging has been introduced for axillary staging in breast cancer. It is a metabolic radionuclide imaging technique that detects higher glycolytic rate of cancer cells in comparison to normal cells. The axillary lymph node involvement is shown at ^{18}F-FDG PET/CT (Figure 2).

Veronesi et al. [34] compared SLNB and ^{18}FDG-PET imaging, in detection of occult axillary metastases. Sensitivity of ^{18}FDG-PET scan was low (37%). However, specificity and positive predictive values were high (96% and 88%, respectively). The high specificity of PET imaging indicates that patients with a PET-positive axilla should have an ALND without SLNB for axillary staging. On the contrary, poor sensitivity of PET scan suggests the need for SLNB in patients with a PET-negative axilla.

A recent meta-analysis reported about lower sensitivity and specificity of PET in comparison to SLNB. Analysis of 7 PET/CT studies on 862 patients showed the mean sensitivity and specificity of 56% and 96%, respectively. Across 19 PET studies on 1,729 patients the mean sensitivity was 66% and the mean specificity 93%. In terms of evaluation of axillary extension, ^{18}FDG-PET cannot replace SLNB [35]. In another study, Gil-Rendo et al. [36] reported about 84.5% sensitivity and 98.5% specificity of FDG-PET in detecting axillary involvement. Avril et al. [37] performed FDG PET in women with suspected breast cancer in preoperative staging. They reported the sensitivity of 79% and specificity of 96% for detection of axillary lymph node metastases. Sensitivity increased to 94% in patients with primary breast tumors sized more than 2 cm. Similarly, Danforth et al. [24] suggested that sensitivity of PET in detection of axillary metastases increases with the stage of the disease. He reported sensitivity of 43% for stage I/II and 83% in stage III/IV.

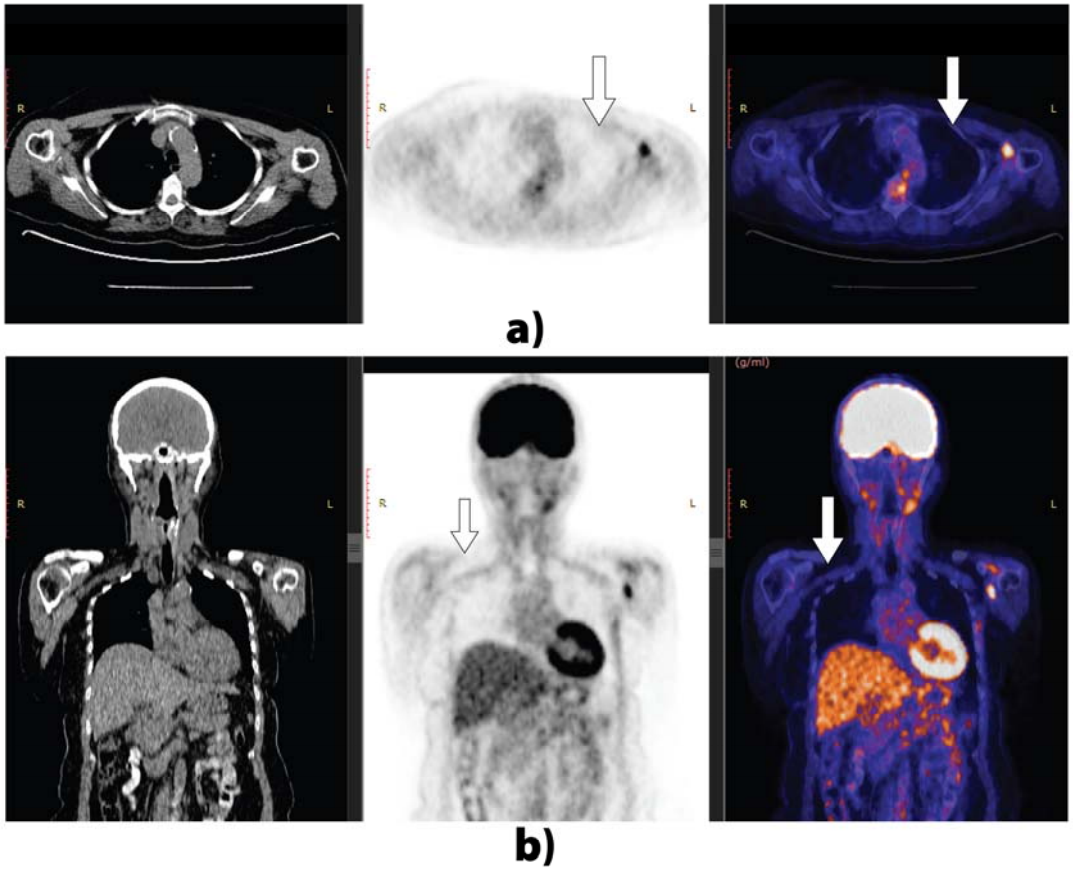

Fig. 2 – a) A 61-year-old woman with right invasive ductal breast cancer, stage pT1, underwent mastectomy, chemotherapy and radiation followed by tamoxifen and trastuzumab (Herceptin®). Transaxial sections (a) and coronal sections (b) detect hypermetabolic lymph node in the left axilla 1.7 cm in size, SUVmax = 10, consistent with axillar involvement.
SUV – standardized uptake value.

A review by Rosen et al. [30], suggests that ^{18}FGD-PET has no clinical role in a routine axillary staging of early stage breast cancer. However, preoperative ^{18}FDG-PET may be worthwhile in locally advanced and inflammatory breast cancers. In a multicentric study, detection of axillary nodal metastases by ^{18}FDG-PET was evaluated in 360 patients with newly diagnosed invasive breast cancer. The reported sensitivity and specificity were 61% and 80%, respectively [38].

Distant metastases

^{18}FDG-PET is also important for detection of occult distant metastases. In high stage breast cancer, Alberini et al. [39] discovered more distant lesions by PET/CT than by conventional diagnostic procedures (31% *vs* 10%). Some authors reported advantage of PET/CT over conventional staging and detecting metastatic involvement of internal mammary chain nodes in patients with stage II and stage III breast cancer [40, 41]. In a work by Carkaci et al. [42], out of 41 studied patients with inflammatory breast cancer, 24% of mediastinal nodal metastases and 15% of liver metastases were correctly identified by PET/CT. Figure 3 shows a patient with breast cancer and liver metastasis.

In the evaluation of metastatic bone involvement, PET is complementary to bone scintigraphy which remains the standard imaging procedure [30]. PET is superior for the detection of osteolytic and mixed bone metastases, but often fails to demonstrate blastic lesions. In contrast, bone scintigraphy is better for depicting sclerotic (blastic) lesions [43]. In a comparison study of bone scintigraphy *versus* PET/CT, Nakai et al. [44] reported on different detection rate for blastic, mixed and lytic type of lesions (100% *vs* 56% ; 84% *vs* 95% ; and 70% *vs* 100%, respectively).

In terms of accurate detection of bone metastases, ^{18}F sodium fluoride PET seems to be better than bone scintigraphy and ^{18}F-FDG PET/CT [45].

Recurrent cancer and restaging

Current diagnostic strategy for the detection of recurrent disease in patients with breast cancer includes physical examination and imaging tests such as mammography, ultrasonography (US), CT, MR and bone scintigraphy. These diagnostic tests are part of routine clinical monitoring during the course of breast cancer. In patients without clinical symptoms and with rising levels of tumors markers PET imaging alone or combined with CT (PET/CT) is useful in detection of recurrent disease. Additionally, in proven recurrent disease or in suspicious recurrence by using conventional imaging, PET/CT helps to distinguish between isolated and multiple metastatic disease.

In a recent study by Aukema et al. [46], additional lesions not visible at conventional imaging were detected by PET/CT in 45% cases. Results of one meta-analysis indicated that MR and PET (including PET and PET/CT) had higher sensitivity than US or CT, which resulted in higher detection rate of recurrent breast cancer. However, there was no difference in sensitivity between PET and MR [47]. Accross 28 studies included in the review Pennant et al. [48] found that PET had a significantly higher sensitivity (89% *vs* 79%) and significantly higher specificity (93% *vs* 83%) compared with conventional imaging tests. In addition, PET/CT had a significantly higher sensitivity compared with CT (95% *vs* 80%) but without a significant increase in specificity (89% *vs* 77%). Furthermore, PET/CT had a significantly higher sensitivity compared with PET (96% *vs* 85%) but no significant increase in specificity (89% *vs* 82%). There were no significant differences in the sensitivity or specificity of PET *versus* MRI, and PET/CT *vs* MRI, respectively.

In another study by Piperkova et al. [49] PET/CT and contrast enhanced CT were compared for initial staging in patients with breast cancer. They reported better diagnostic accuracy for PET/CT than contrast-enhanced CT (CE-CT): the sensitivity, specificity, accuracy, positive productive value, and negative productive value for PET/CT were 97.8%, 93.5%, 97.3%, 99.1%, and 85%, respectively, and for CE-CT were 87.6%, 42%, 82.1%, 91.6%, and 31.7%, respectively. The staging of the disease was changed in 65% of cases: 36% of patients were down-staged and 64% of patients were upstaged. PET imaging is important in restaging of breast cancer, because it might affect treatment management. An example of patient upstaging after ^{18}FDG PET/CT is shown in Figure 4.

In a study by Eubank et al. [50] PET revealed more lesions than CT and consequently altered therapeutic manage-

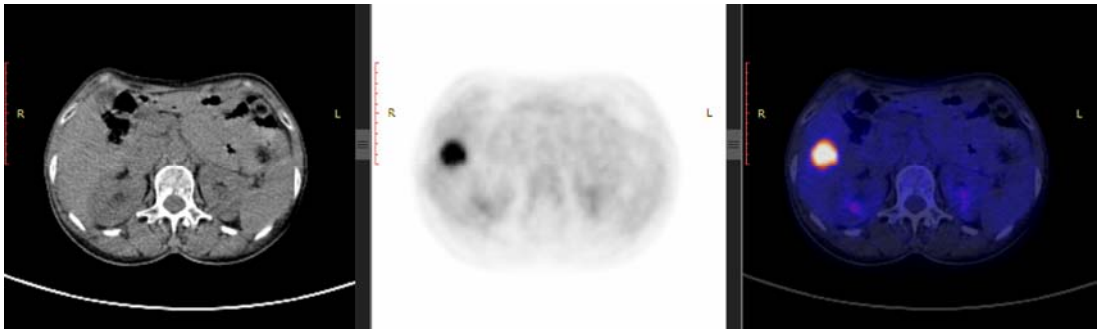

Fig. 3 – A 57-year-old woman with invasive ductal carcinoma of the left breast. The patient underwent mastectomy followed by adjuvant chemotherapy, paclitaxel (Taxol®) and trastuzumab (Herceptin®). Transaxial images show a hypermetabolic liver mass in S6 segment, 3.1cm in size, SUVmax = 12.5 corresponding to hepatic involvement. SUV – standardized uptake value.

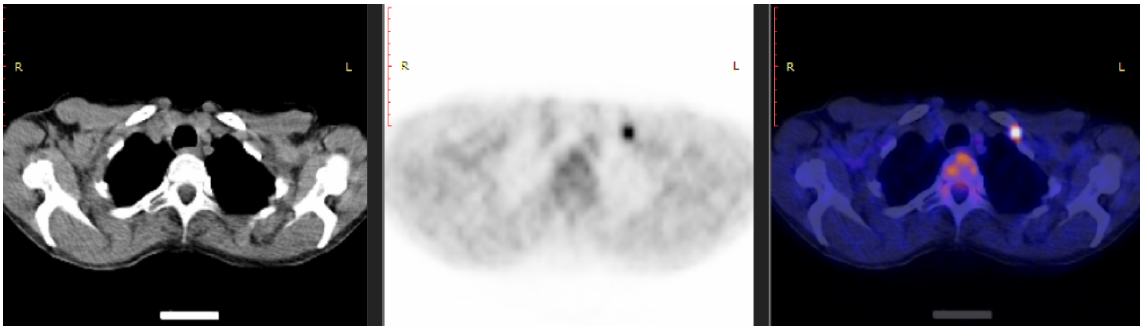

Fig. 4 − A 58-year-old female patient in the postsurgery status and post-adjuvant chemotherapy due to invasive ductal carcinoma of the left breast. The patient presents for restaging after completion of chemotherapy. Transaxial images show left retroclavicular lymph node 1.5 cm in size, SUVmax = 5.64 consistent with metastatic involvement.
FDG – ^{18}F-fluorodeoxyglucose; SUV – standardized uptake value.

ment in up to 44% of patients with suspected locoregional recurrent disease. ^{18}F-FDG PET/CT may have a potential role in clinically asymptomatic patients with rising markers and negative conventional imaging (US, X-mammography, CT and MR). Radan et al. [51] reported about 90% sensitivity of ^{18}FDG-PET in detection of recurrent disease. Consequently, treatment management was changed in 51% of patients. Additionally, if compared to contrast-enhanced CT, PET/CT showed better sensitivity (85% *vs* 70%), specificity (76% *vs* 47%), and accuracy (81% *vs* 59%). Similar results were obtained in a recent study by Dirisamer et al. [52]. They studied 52 patients and detected suspicious recurrence and rising tumor markers levels in 62%. PET/CT had better patient-based accuracy than CE-CT (96% *vs* 73%, respectively), and lesion-based sensitivity and specificity (93% *vs* 66% and 100% *vs* 92%, respectively). Grasseto et al. [53] studied patients with post-treatment rising tumor serum levels of Ca 15−3 but negative clinical examination and conventional imaging. ^{18}F-FDG PET/CT was able to detect cancer lesions in 45% of cases. Finally, there are reports that ^{18}F-FDG PET/CT imaging in patients with rising CA15-3 levels alters treatment management in up to 50% [54–56].

Monitoring of the treatment response

Neoadjuvant or so-called preoperative chemotherapy is the initial standard treatment for patients with locally advanced breast cancer. This treatment results in a reduction of the tumor volume and is followed by conservative surgery and radiotherapy. The assessment of treatment response includes conventional methods such as physical examination, radiography, ultrasound and mammography. However, these methods are usually evaluated after completion of three cycles of chemotherapy. In addition, clinical response does not necessarily reflect the pathological response [57]. Due to the fact that changes in tumor metabolism precede the tumor shrinkage, ^{18}FDG PET is able to detect tumor response at an earlier stage than conventional imaging methods [58, 59].

Evaluation of changes in FDG uptake at different time points of the systemic treatment is based on comparison between the baseline (pretherapy) PET scan and postherapy PET scan. Some authors performed PET imaging early, after only 1 or 2 cycles, or during midtherapy, or at treatment completion. In the settings of early stage at chemotherapy, PET imaging is capable of predicting the pathologic response. In addition, PET is possible to distinguish between patients who respond to treatment (responders) and those who do not (non-responders) [30]. Approximately 70% of patients demonstrate clinical response to neoadjuvant chemotherapy, but only 20% achieve pathological complete response. Since the SUV decline early in the course of chemotherapy predicts a treatment failure, the regimen should altered with aim to avoid unnecessary toxic side effects [60, 61]. Jung et al. [62] suggested that the reduction rate of SUV has a prognostic value after the completion of the fourth cycle of chemotherapy before surgery. They detected 70% of sensitivity and specificity when 84.8% SUV reduction was used as a cutoff value for the pathologic complete response.

In another study, Schelling et al. [63] studied the role of ^{18}F-FDG PET in the assessment of early response to neoadjuvant chemotherapy in locally advanced and inflammatory breast cancer. Decline in SUV values by more than 55% after one cycle, was predictive of a good response with sensitivity of 100% and specificity of 85%. In addition, after one and two cycles pathologic response was predicted with accuracy of 88% and 91%, respectively.

In nonmetastatic, non-inflammatory breast cancer, Kolesnikov-Gouthier et al. [64] detected < 15% of SUV decline after the first chemotherapy course which was used as a strong predictor for inefficient neoadjuvant chemotherapy. Additionally, a 4-year recurrence free survival rate was significantly longer in metabolic responders than non-responders (85% *vs* 44%, respectively).

Park et al. [65] used diffusion weighted imaging (DWI) MR and PET/CT to predict pathologic complete response to preoperative neoadjuvant chemotherapy in patients with invasive breast cancer. PET/CT showed the same sensitivity of 100% as DWI MR, but better specificity (77.8% *vs* 70.4%). A study by Andrade et al. [66] indicated that decrease of SUV values after the second course of neoadjuvant chemotherapy (NAC) can predict pathological response in ductal breast carcinomas, and potentially identify a subgroup of non-responding patients. Keam et al. [67] analyzed the relation between changes in ^{18}FDG uptake and different molecular phenotype of breast cancer treated with neoadjuvant chemotherapy. During the early metabolic response, they detected that the estrogen receptor negative phenotype showed

a higher pre-chemotherapy SUV (8.6 *vs* 6.4) and reduction rate of SUV (48% *vs* 30%) than estrogen receptor positive phenotype. In triple negative breast cancer, the pre-chemotherapy SUV was higher than in not triple-negative breast cancer (9.8% *vs* 6.4%).

In another study, Rousseau et al. [68] demonstrated the efficacy of ^{18}F-FDG PET in the assessment of early response to neoadjuvant chemotherapy in I/II staged breast cancer. They also analyzed the variation of SUV values after the first, second, third and six chemotherapeutic cycles. After 1 cycle of chemotherapy, using a 60% decline in baseline SUV as their threshold for response, PET was 61% sensitive and 96% specific with 68% predictive negative value. After 2 cycles, PET showed better sensitivity, specificity and negative predictive value (89%, 95%, 85%, respectively). After 3 courses of chemotherapy, if compared to values obtained after the second cycle, lower sensitivity, specificity and negative predictive value of PET were detected (88%, 73%, 83%, respectively). These results may suggest possible prediction of final response to treatment.

However, if ^{18}F-FDG PET is performed after the completion of chemotherapy residual FDG uptake may predict residual disease. In contrast, the absence of FDG uptake does not exclude residual microscopic malignancy and may not indicate pathologic response [69, 70]. In patients with large residual disease, ^{18}F-FDG PET is complementary to MR to define the degree of residual mass [71]. Moreover, if ^{18}F-FDG PET is performed after the chemotherapy it has a prognostic value. Cachin et al. [72] showed that negative PET scan was an indicator for a significantly better survival than PET positive scan. Additionally, ^{18}F-FDG PET scan was the most powerful and independent predictor of survival. Patients with negative post-treatment ^{18}F-FDG PET had a longer median survival than patients with positive ^{18}F-FDG PET (24 months *vs* 10 months).

The examples of PET/CT imaging in the assessment of the treatment response are shown in Figures 5a and b, and Figures 6a and b.

New positron emission tomography/ computed tomography tracers in breast cancer imaging

FDG is specific for increased metabolism of glucose and ^{18}F- FDG-PET/CT is able to detect the presence of viable tumor tissue in the human body. However, the new agents that are able to target the cellular processes have been recently developed. These agents are still under investigation and are not available in the routine clinical practice. The recent development of radiolabeled-thymidine compounds allows measurement of the exact tumor proliferation. According to some authors, the ^{18}F-fluoro-thymidine PET (^{18}FLT-PET) imaging has a role in the assessment of therapeutic response and prediction of response to therapy [73–76]. Regarding recently published data, PET is also able to evaluate estrogen (ER) expression by using estrogen receptor ligand, 16α-[18F]-fluoro-17β-estradiol (^{18}F-FES). While increased up-

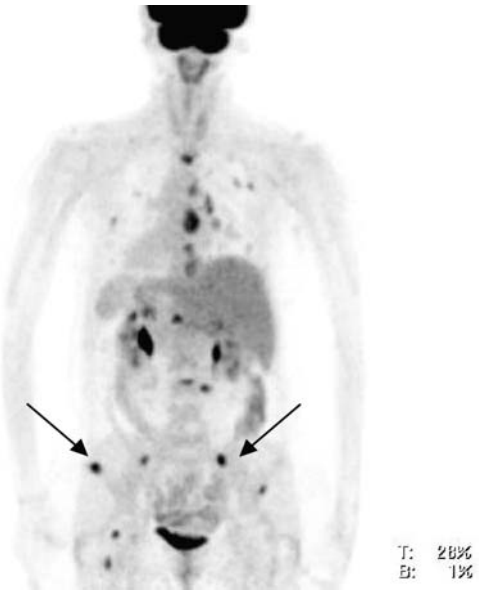

Fig. 5a – A patient presents after mastectomy, before chemotherapy. Maximal Intensity Projection (MIP) image shows multiple mediastinal FDG avid foci (pre- and paratrachealis, aortopulmonalis, subcarinealis, esophageal and hilar) on the right with multiple lung hypermetabolic foci bilaterally. There are multiple FDG avid foci in the skeleton: spine (thoracic V2 and V12, and lumbar V3), iliac bones (SUVmax = 9.47 on the left, and SUVmax = 10.10 on the right) and proximal left femur.
FDG – ^{18}F-fluorodeoxyglucose; SUV – standardized uptake value.

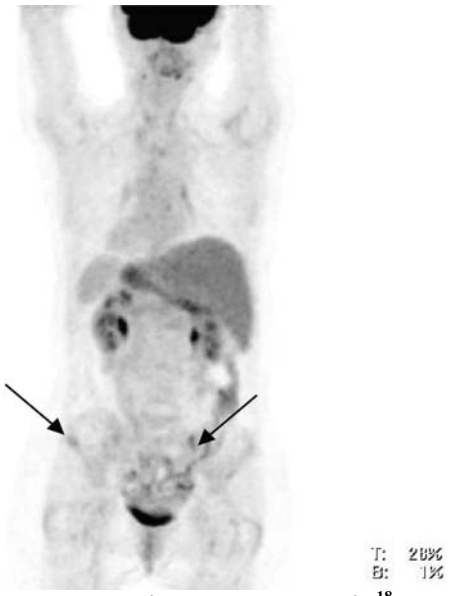

Fig. 5b – The same patient, posttherapeutic ^{18}F-FDG PET/CT scan. MIP image shows restitution of most of the hypermetabolic foci previously seen. There are only two FDG avid foci in the right iliac bone, SUVmax = 4.05 and in the left iliac bone, SUVmax = 2.84. This is an example of partial response to treatment and partial remission.
PET/CT – positron emission tomography/ computed tomography.
FDG – ^{18}F-fluorodeoxyglucose; SUV – standardized uptake value.

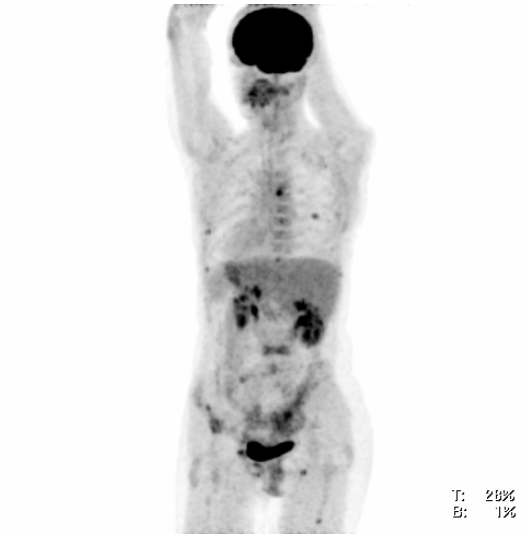

Fig. 6a − A 54-year-old woman with right invasive ductal breast cancer.
Hormone receptor ER, PR positive; HER2 negative. She underwent breast quadrectomy, chemotherapy and external radiation therapy. This is the pretherapeutic PET/CT scan. The MIP image shows multiple hypermetabolic foci in the skeleton located in the spine (cervical level 2, thoracic level 6, 8 and 10, lumbal level 1, 4 and 5), 8th rib on the right and 8th rib and 10th on the left, both iliac and ischiadic bones bilaterally, left pubic bone, and right femoral diaphysis).
MIP – maximal intensity projection; PET/CT – positron emission tomography/computed tomography .

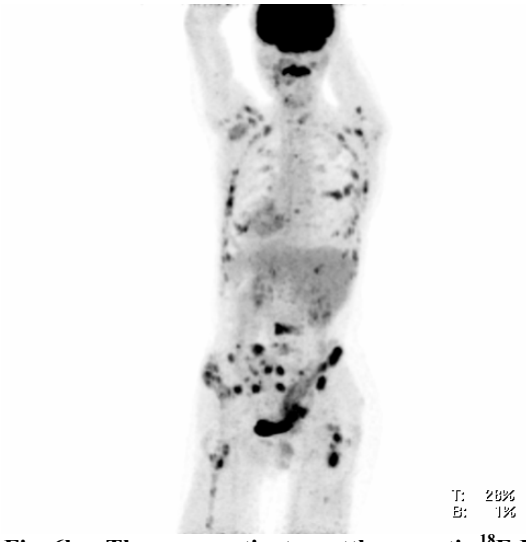

Fig. 6b − The same patient, posttherapeutic ^{18}F-FDG PET/CT scan patient.
After the completion of chemotherapy, MIP image shows persistent FDG avid foci and new hypermetabolic foci spread all over the skeleton wich indicates progressive disease. This is an example of patient, who is non-responder or shows no response to the treatment.
^{18}F-FDG − ^{18}F-fluorodeoxyglucose. PET/CT – positron emission tomography/computed tomography;
MIP – maximal intensity projection.

take of ^{18}F-FES can reliably detect ER-positive lesions, its low uptake seems to be a strong predictor for failure of antihormonal therapy [77–81]. Another important feature of malignant disease is hypoxia. Numerous studies have been done on malignant tumors, mostly head and neck and lung cancers, but less in breast cancer. The results of these studies indicate that tumor hypoxia is important prognostic factor that influences the response to therapy and overall survival. In addition, hypoxia increases the risk of invasion and metastasis, as well as the resistance to chemo- and radio-therapy. Hussain et al. [82] correlated the hypoxia-regulated carbonic anhydrase (CA) IX expression with the outcome in patients with invasive breast cancer. They indicated that CA IX expression is a predictor of poor survival which may subsequently lead to better patient selection for adjuvant treatment. Additionally, hypoxia-related gene expression may present a basis for novel targeted therapies. In head and neck cancers, [^{18}F]fluoromisonidazole (^{18}FMISO-PET) is proven to be a promising agent for detection and localization of significant hypoxia, delineation for external radiation, and for selecting treatment strategy [83]. In another study, Rajendran et al. [84] compared ^{18}FDG-PET to the ^{18}FMISO-PET in different malignant tumors, including breast cancer. They found that despite the fact that hypoxia influences glucose metabolism, some highly metabolic tumors are not hypoxic. They suggested that different tracer uptake in examined tumors can be tumor type-specific. The future will bring the results of currently ongoing studies with new, ^{18}FDG-PET, PET tracers ^{18}FMISO-PET evaluating tumor angiogenesis, chemo resistance and metastatic potential of malignant tumors.

Conclusion

^{18}F-FDG PET/CT is new non-invasive whole-body imaging of breast cancer. In particular, it helps in staging of recurrent or metastatic cancer and in evaluating the treatment response in patients with locally advanced and metastatic disease. Besides evaluation of increased glucose metabolism by FDG-PET, recently developed radiotracers have the ability to assess receptor expression, tumor cell proliferation and tumor viability in patients with breast tumors. However, future molecular imaging studies are necessary for better understanding of tumor biology and behavior. This is directly connected with the development of new PET agents and their introduction in clinical practice.

R E F E R E N C E S

1. *Siegel RL, Miller KD, Jemal A.* Cancer statistics, 2015. CA Cancer J Clin 2015; 65(1): 5−29.
2. Institute of Public Health of Serbia "Dr Milan Jovanović Batut". Cancer incidence and mortality in central Serbia 2012. 2015. [cited 2015 Aug 17]. Available from: http://www.batut.org.rs/index.php.
3. Cancer registry data of Oncology Institute of Vojvodina [unpublished database]. Sremska Kamenica, Serbia: Oncology Institute of Vojvodina; 2010.
4. *Beaulieu S, Kinahan P, Tseng J, Dunnwald LK, Schubert EK, Pham P,* et al. SUV varies with time after injection in (18)F-FDG PET of breast cancer: characterization and method to adjust for time differences. J Nucl Med 2003; 44(7): 1044−50.
5. *Kinahan PE, Fletcher JW.* Positron emission tomography-computed tomography standardized uptake values in clinical practice and assessing response to therapy. Semin Ultrasound CT MR 2010; 31(6): 496−505.
6. *Eubank WB, Mankoff DA, Schmiedl UP, Winter TC, Fisher ER, Olshen AB*, et al.. Imaging of oncologic patients: benefit of combined CT and FDG PET in the diagnosis of malignancy. AJR Am J Roentgenol 1998; 171(4): 1103−10.
7. *Tatsumi M, Cohade C, Mourtzikos KA, Fishman EK, Wahl RL.* Initial experience with FDG-PET/CT in the evaluation of breast cancer. Eur J Nucl Med Mol Imaging 2006; 33(3): 254−62.
8. *Fueger BJ, Weber WA, Quon A, Crawford TL, Allen-Auerbach MS, Halpern BS,* et al. Performance of 2-Deoxy-2-[F-18]fluoro-d-glucose Positron Emission Tomography and Integrated PET/CT in Restaged Breast Cancer Patients. Mol Imaging Biol 2005; 7(5): 369−76.
9. *Gil-Rendo A, Martínez-Regueira F, Zornoza G, García-Velloso MJ, Beorlegui C, Rodriguez-Spiteri N.* Association between [18F]fluorodeoxyglucose uptake and prognostic parameters in breast cancer. Br J Surg 2009; 96(2): 166−70.
10. *Avril N, Rosé CA, Schelling M, Dose J, Kuhn W, Bense S,* et al. Breast imaging with positron emission tomography and fluorine-18 fluorodeoxyglucose: use and limitations. J Clin Oncol 2000; 18(20): 3495−502.
11. *Avril N, Menzel M, Dose J, Schelling M, Weber W, Jänicke F*, et al. Glucose metabolism of breast cancer assessed by 18F-FDG PET: histologic and immunohistochemical tissue analysis. J Nucl Med 2001; 42(1): 9−16.
12. *Crippa F, Seregni E, Agresti R, Chiesa C, Pascali C, Bogni A,* et al. Association between [18F]fluorodeoxyglucose uptake and postoperative histopathology, hormone receptor status, thymidine labelling index and p53 in primary breast cancer: a preliminary observation. Eur J Nucl Med 1998; 25(10): 1429−34.
13. *Buck A, Schirrmeister H, Kühn T, Shen C, Kalker T, Kotzerke J,* et al. FDG uptake in breast cancer: correlation with biological and clinical prognostic parameters. Eur J Nucl Med Mol. Imaging 2002; 29(10): 1317−23.
14. *Bos R, van Der Hoeven JJ, van Der Wall E, van Der Groep P, van Diest PJ, Comans EF,* et al. Biologic correlates of (18)fluorodeoxyglucose uptake in human breast cancer measured by positron emission tomography. J Clin Oncol 2002; 20(2): 379−87.
15. *Buck AK, Schirrmeister H, Mattfeldt T, Reske SN.* Biological characterisation of breast cancer by means of PET. Eur J Nucl Med Mol Imaging 2004; 31(Suppl 1): S80−7.
16. *Shimoda W, Hayashi M, Murakami K, Oyama T, Sunagawa M.* The relationship between FDG uptake in PET scans and biological behavior in breast cancer. Breast Cancer 2007; 14(3): 260−8.
17. *Mavi A, Cermik TF, Urhan M, Puskulcu H, Basu S, Yu JQ,* et al. The effects of estrogen, progesterone, and C-erbB-2 receptor states on 18F-FDG uptake of primary breast cancer lesions. J Nucl Med 2007; 48(8): 1266−72.
18. *Ikenaga N, Otomo N, Toyofuku A, Ueda Y, Toyoda K, Hayashi T,* et al. Standardized uptake values for breast carcinomas assessed by fluorodeoxyglucose-positron emission tomography correlate with prognostic factors. Am Surg 2007; 73(11): 1151−7.
19. *Osborne JR, Port E, Gonen M, Doane A, Yeung H, Gerald W*, et al. 18F-FDG PET of locally invasive breast cancer and association of estrogen receptor status with standardized uptake value: microarray and immunohistochemical analysis. J Nucl Med 2010; 51(4): 543−50.
20. *Groheux D, Giacchetti S, Moretti JL, Porcher R, Espié M, Lehmann-Che J*, et al. Correlation of high 18F-FDG uptake to clinical, pathological and biological prognostic factors in breast cancer. Eur J Nucl Med Mol Imaging 2011; 38(3): 426−35.
21. *Basu S, Chen W, Tchou J, Mavi A, Cermik T, Czerniecki B,* et al. Comparison of triple-negative and estrogen receptor-positive/progesterone receptor-positive/HER2-negative breast carcinoma using quantitative fluorine-18 fluorodeoxyglucose/positron emission tomography imaging parameters: a potentially useful method for disease characterization. Cancer 2008; 112(5): 995−1000.
22. *Kumar R, Chauhan A, Zhuang H, Chandra P, Schnall M, Alavi A.* Clinicopathologic factors associated with false negative FDG–PET in primary breast cancer. Breast Can Res Treatment 2006; 98(3): 267−74.
23. *Samson DJ, Flamm CR, Pisano ED, Aronson N.* Should FDG PET be used to decide whether a patient with an abnormal mammogram or breast finding at physical examination should undergo biopsy. Acad Radiol 2002; 9(7): 773−83.
24. *Danforth DN, Aloj L, Carrasquillo JA, Bacharach SL, Chow C, Zujewski J*, et al. The role of 18F-FDG-PET in the local/regional evaluation of women with breast cancer. Breast Cancer Res Treat 2002; 75(2): 135−46.
25. *Heusner TA, Kuemmel S, Umutlu L, Koeninger A, Freudenberg LS, Hauth EA,* et al. Breast cancer staging in a single session: Whole-body PET/CT mammography. J Nucl Med 2008; 49(8): 1215−22.
26. *Murthy K, Aznar M, Thompson CJ, Loutfi A, Lisbona R, Gagnon JH.* Results of preliminary clinical trials of the positron emission mammography system PEM-I: a dedicated breast imaging system producing glucose metabolic images using FDG. J Nucl Med 2000; 41(11): 1851−8.
27. *Rosen EL, Turkington TG, Soo MS, Baker JA, Coleman ER.* Detection of primary breast carcinoma with a dedicated, large-field-of-view FDG PET mammography device: initial experience. Radiology 2005; 234(2): 527−34.
28. *Berg WA, Weinberg IN, Narayanan D, Lobrano ME, Ross E, Amodei L,* et al. High-Resolution Fluorodeoxyglucose Positron Emission Tomography with Compression ("Positron Emission Mammography") is Highly Accurate in Depicting Primary Breast Cancer. Breast J 2006; 12(4): 309−23.
29. *Levine EA, Freimanis RI, Perrier ND, Morton K, Lesko NM, Bergman S,* et al. Positron Emission Mammography: Initial Clinical Results. Ann Surg Oncol 2003; 10(1): 86−91.
30. *Rosen EL, Eubank WB, Mankoff DA.* FDG PET, PET/CT, and breast cancer imaging. RadioGraphics 2007; 27(1): 215−29.
31. *Berg WA, Madsen KS, Schilling K, Tartar M, Pisano ED, Larsen LH,* et al. Breast cancer: Comparative effectiveness of positron emission mammography and MR imaging in presurgical planning for the ipsilateral breast. Radiology 2011; 258(1): 59−72.
32. *Litmanovich D, Gourevich K, Israel O, Gallimidi Z.* Unexpected foci of 18F-FDG uptake in the breast detected by PET/CT: incidence and clinical significance. Eur J Nucl Med Mol Imaging 2009; 36(10): 1558−64.

33. *Lyman GH.* American Society of Clinical Oncology Guideline Recommendations for Sentinel Lymph Node Biopsy in Early-Stage Breast Cancer. J Clin Oncol 2005; 23(30): 7703−20.
34. *Veronesi U, De Cicco C, Galimberti VE, Fernandez JR, Rotmensz N, Viale G,* et al. A comparative study on the value of FDG-PET and sentinel node biopsy to identify occult axillary metastases. Ann Oncol 2007; 18(3): 473−8.
35. *Cooper KL, Harnan S, Meng Y, Ward SE, Fitzgerald P, Papaioannou D,* et al. Positron emission tomography (PET) for assessment of axillary lymph node status in early breast cancer: A systematic review and meta-analysis. Eur J Surg Oncol 2011; 37(3): 187−98.
36. *Gil-Rendo A, Zornoza G, García-Velloso MJ, Regueira FM, Beorlegui C, Cervera M.* Fluorodeoxyglucose positron emission tomography with sentinel lymph node biopsy for evaluation of axillary involvement in breast cancer. Br J Surg 2006; 93(6): 707−12.
37. *Avril N, Dose J, Jänicke F, Ziegler S, Römer W, Weber W,* et al. Assessment of axillary lymph node involvement in breast cancer patients with positron emission tomography using radiolabeled 2-(fluorine-18)-fluoro-2-deoxy-D-glucose. J Natl. Cancer Inst 1996; 88(17): 1204−9.
38. *Wahl RL, Siegel BA, Coleman RE, Gatsonis CG, PET Study Group* . Prospective multicenter study of axillary nodal staging by positron emission tomography in breast cancer: a report of the Staging Breast Cancer with PET Study Group. J Clin Oncol 2004; 22(2): 277−85.
39. *Alberini J, Lerebours F, Wartski M, Fourme E, Le SE, Gontier E*, et al. 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) imaging in the staging and prognosis of inflammatory breast cancer. Cancer 2009; 115(21): 5038−47.
40. *Groheux D, Moretti J, Baillet G, Espie M, Giacchetti S, Hindie E*, et al. Effect of (18)F-FDG PET/CT imaging in patients with clinical Stage II and III breast cancer. Int J Radiat Oncol Biol Phys 2008; 71(3): 695−704.
41. *Segaert I, Mottaghy F, Ceyssens S, De Wever W, Stroobants S, Van Ongeval C*, et al. Additional value of PET-CT in staging of clinical stage IIB and III breast cancer. Breast J 2010; 16(6): 617−24.
42. *Carkaci S, Macapinlac HA, Cristofanilli M, Mawlawi O, Rohren E, Gonzalez AA,* et al. Retrospective study of 18F-FDG PET/CT in the diagnosis of inflammatory breast cancer: preliminary data. J Nucl Med 2009; 50(2): 231−8.
43. *Schirrmeister H.* Detection of bone metastases in breast cancer by positron emission tomography. Radiol Clin North Am 2007; 45(4): 669−76.
44. *Nakai T, Okuyama C, Kubota T, Yamada K, Ushijima Y, Taniike K,* et al. Pitfalls of FDG-PET for the diagnosis of osteoblastic bone metastases in patients with breast cancer. Eur J Nucl Med Mol Imaging 2005; 32(11): 1253−8.
45. *Even-Sapir E, Metser U, Flusser G, Zuriel L, Kollender Y, Lerman H*, et al. Assessment of malignant skeletal disease: initial experience with 18F-fluoride PET/CT and comparison between 18F-fluoride PET and 18F-fluoride PET/CT. J Nucl Med 2004; 45(2): 272−8.
46. *Aukema TS, Rutgers TE, Vogel WV, Teertstra HJ, Oldenburg HS, Vrancken PM,* et al. The role of FDG PET/CT in patients with locoregional breast cancer recurrence: A comparison to conventional imaging techniques. Eur J Surg Oncol 2010; 36(4): 387−92.
47. *Pan L, Han Y, Sun X, Liu J, Gang H.* FDG-PET and other imaging modalities for the evaluation of breast cancer recurrence and metastases: a meta-analysis. J Cancer Res Clin Oncol 2010; 136(7): 1007−22.
48. *Pennant M, Takwoingi Y, Pennant L, Davenport C, Fry-Smith A, Eisinga A*, et al. A systematic review of positron emission tomography (PET) and positron emission tomography/computed tomography (PET/CT) for the diagnosis of breast cancer recurrence. Health Technol Assess 2010; 14(50): 1−103.
49. *Piperkova E, Raphael B, Altinyay ME, Castellon I, Libes R, Sandella N*, et al. Impact of PET/CT in comparison with same day contrast enhanced CT in breast cancer management. Clin Nucl Med 2007; 32(6): 429−34.
50. *Eubank WB, Mankoff D, Bhattacharya M, Gralow J, Linden H, Ellis G*, et al. Impact of FDG PET on defining the extent of disease and on the treatment of patients with recurrent or metastatic breast cancer. AJR Am J Roentgenol 2004; 183(2): 479−86.
51. *Radan L, Ben-Haim S, Bar-Shalom R, Guralnik L, Israel O.* The role of FDG-PET/CT in suspected recurrence of breast cancer. Cancer 2006; 107(11): 2545−51.
52. *Dirisamer A, Halpern BS, Flöry D, Wolf F, Beheshti M, Mayerhoefer ME,* et al. Integrated contrast-enhanced diagnostic whole-body PET/CT as a first-line restaging modality in patients with suspected metastatic recurrence of breast cancer. Eur J Radiol 2010; 73(2): 294−9.
53. *Grassetto G, Fornasiero A, Otello D, Bonciarelli G, Rossi E, Nashimben O,* et al. 18F-FDG-PET/CT in patients with breast cancer and rising Ca 15-3 with negative conventional imaging: a multicentre study. Eur J Radiol 2011; 80(3): 828−33.
54. *Champion L, Brain E, Giraudet A, Le Stanc E, Wartski M, Edeline V,* et al. Breast cancer recurrence diagnosis suspected on tumor marker rising: value of whole-body 18FDG-PET/CT imaging and impact on patient management. Cancer 2011; 117(8): 1621−9.
55. *Filippi V, Malamitsi J, Vlachou F, Laspas F, Georgiou E, Prassopoulos V*, et al. The impact of FDG-PET/CT on the management of breast cancer patients with elevated tumor markers and negative or equivocal conventional imaging modalities. Nucl Med Commun 2011; 32(2): 85−90.
56. *Manohar K, Mittal BR, Senthil R, Kashyap R, Bhattacharya A, Singh G.* Clinical utility of F-18 FDG PET/CT in recurrent breast carcinoma. Nucl Med Commun 2012; 33(6): 591−6.
57. *Baum RP, Przetak C.* Evaluation of therapy response in breast and ovarian cancer patients by positron emission tomography (PET). Q J Nucl Med 2001; 45(3): 257−68.
58. *Wahl RL, Zasadny K, Helvie M, Hutchins GD, Weber B, Cody R.* Metabolic monitoring of breast cancer chemohormonotherapy using positron emission tomography: initial evaluation. J Clin Oncol 1993; 11(11): 2101−11.
59. *Avril N, Dose J, Jänicke F, Bense S, Ziegler S, Laubenbacher C,* et al. Metabolic characterization of breast tumors with positron emission tomography using F-18 fluorodeoxyglucose. J Clin Oncol 1996; 14(6): 1848−57.
60. *Fisher ER, Wang J, Bryant J, Fisher B, Mamounas E, Wolmark N.* Pathobiology of preoperative chemotherapy: findings from the National Surgical Adjuvant Breast and Bowel (NSABP) protocol B-18. Cancer 2002; 95(4): 681−95.
61. *van der Hage JA, van de Velde CJ, Julien JP, Tubiana-Hulin M, Vandervelden C, Duchateau L.* Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol 2001; 19(22): 4224−37.
62. *Jung S, Kim S, Nam B, Min SY, Lee SJ, Park C,* et al. Prognostic Impact of [18F] FDG-PET in operable breast cancer treated with neoadjuvant chemotherapy. Ann Surg Oncol 2010; 17(1): 247−53.
63. *Schelling M, Avril N, Nährig J, Kuhn W, Römer W, Sattler D*, et al. Positron emission tomography using [(18)F]Fluorodeoxyglucose for monitoring primary chemotherapy in breast cancer. J Clin Oncol 2000; 18(8): 1689−95.
64. *Kolesnikov-Gauthier H, Vanlemmens L, Baranzelli M, Vennin P, Servent V, Fournier C,* et al. Predictive value of neoadjuvant chemotherapy failure in breast cancer using FDG-PET after the first course. Breast Cancer Res Treat 2012; 131(2): 517−25.

65. *Park SH, Moon WK, Cho N, Chang JM, Im S, Park IA,* et al. Comparison of diffusion-weighted MR imaging and FDG PET/CT to predict pathological complete response to neoadjuvant chemotherapy in patients with breast cancer. Eur Radiol 2012; 22(1): 18−25.
66. *Andrade WP, Lima EN, Osório CA, Socorro MM, Baiocchi G, Bitencourt AG,* et al. Can FDG-PET/CT predict early response to neoadjuvant chemotherapy in breast cancer. Eur J Surg Oncol 2013; 39(12): 1358−63.
67. *Keam B, Im SA, Koh Y, Han SW, Oh DY, Cho N*, et al. Early metabolic response using FDG PET/CT and molecular phenotypes of breast cancer treated with neoadjuvant chemotherapy. BMC Cancer 2011; 11: 452.
68. *Rousseau C, Devillers A, Sagan C, Ferrer L, Bridji B, Campion L*, et al. Monitoring of early response to neoadjuvant chemotherapy in stage II and III breast cancer by [18F]fluorodeoxyglucose positron emission tomography. J Clin Oncol 2006; 24(34): 5366−72.
69. *Burcombe RJ, Makris A, Pittam M, Lowe J, Emmott J, Wong WL.* Evaluation of good clinical response to neoadjuvant chemotherapy in primary breast cancer using [18F]-fluorodeoxyglucose positron emission tomography. Eur J Cancer 2002; 38(3): 375−9.
70. *Kim S, Kim S, Lee ES, Ro J, Kang Sh.* Predictive value of [18F]FDG PET for pathological response of breast cancer to neo-adjuvant chemotherapy. Annals of oncology 2004; 15(9): 1352−7.
71. *Chen X, Moore MO, Lehman CD, Mankoff DA, Lawton TJ, Peacock S*, et al. Combined use of MRI and PET to monitor response and assess residual disease for locally advanced breast cancer treated with neoadjuvant chemotherapy. Acad Radiol 2004; 11(10): 1115−24.
72. *Cachin F, Prince H, Hogg A, Ware RE, Hicks RJ.* Powerful prognostic stratification by [18F]fluorodeoxyglucose positron emission tomography in patients with metastatic breast cancer treated with high-dose chemotherapy. J Clin Oncol 2006; 24(19): 3026−31.
73. *Dittmann H, Jusufoska A, Dohmen BM, Smyczek-Gargya B, Fersis N, Pritzkow M,* et al. 3'-Deoxy-3'-[(18)F]fluorothymidine (FLT) uptake in breast cancer cells as a measure of proliferation after doxorubicin and docetaxel treatment. Nucl Med Biol 2009; 36(2): 163−9.
74. *Contractor KB, Kenny LM, Stebbing J, Rosso L, Ahmad R, Jacob J*, et al. 18F]-3'Deoxy-3'-fluorothymidine positron emission tomography and breast cancer response to docetaxel. Clin Cancer Res 2011; 17(24): 7664−72.
75. *Lubberink M, Direcks W, Emmering J, Tinteren H, Hoekstra OS, Hoeven JJ,* et al. Validity of simplified 3'-deoxy-3'-[18F]fluorothymidine uptake measures for monitoring response to chemotherapy in locally advanced breast cancer. Mol Imaging Biol 2012; 14(6): 777−82.
76. *Tehrani OS, Shields AF.* PET imaging of proliferation with pyrimidines. J Nucl Med 2013; 54(6): 903−12.
77. *Peterson LM, Kurland BF, Link JM, Schubert EK, Stekhova S, Linden HM,* et al. Factors influencing the uptake of 18F-fluoroestradiol in patients with estrogen receptor positive breast cancer. Nucl Med Biol 2011; 38(7): 969−78.
78. *Linden HM, Kurland BF, Peterson LM, Schubert EK, Gralow JR, Specht JM,* et al. Fluoroestradiol positron emission tomography reveals differences in pharmacodynamics of aromatase inhibitors, tamoxifen, and fulvestrant in patients with metastatic breast cancer. Clin Cancer Res 2011;17(14):4799-805. 17(14): 4799-805. PubMed PMID: 21750198
79. *van Kruchten M, Glaudemans AW, Vries EF, Beets-Tan RG, Schröder CP, Dierckx RA,* et al.. PET imaging of estrogen receptors as a diagnostic tool for breast cancer patients presenting with a clinical dilemma. J Nucl Med 2012; 53(2): 182−90.
80. *Kurland BF, Peterson LM, Lee JH, Linden HM, Schubert EK, Dunnwald LK,* Mankoff DA. Between-patient and within-patient (site-to-site) variability in estrogen receptor binding, measured in vivo by 18F-fluoroestradiol PET. J Nucl Med 2011; 52(10): 1541−9.
81. *Paquette M, Phoenix S, Ouellet R, Langlois R, Lier JE, Turcotte EE,* et al. Assessment of the novel estrogen receptor PET tracer 4-fluoro-11β-methoxy-16α-[(18)F]fluoroestradiol (4FMFES) by PET imaging in a breast cancer murine model. Mol Imaging Biol 2013; 15(5): 625−32.
82. *Hussain SA, Ganesan R, Reynolds G, Gross L, Stevens A, Pastorek J,* et al. Hypoxia-regulated carbonic anhydrase IX expression is associated with poor survival in patients with invasive breast cancer. Br J Cancer 2007; 96(1): 104−9.
83. *Hendrickson K, Phillips M, Smith W, Peterson L, Krohn K, Rajendran J.* Hypoxia imaging with [F-18] FMISO-PET in head and neck cancer: potential for guiding intensity modulated radiation therapy in overcoming hypoxia-induced treatment resistance. Radiother Oncol 2011; 101(3): 369−75.
84. *Rajendran JG, Mankoff DA, O'Sullivan F, Peterson LM, Schwartz DL, Conrad EU,* et al. Hypoxia and glucose metabolism in malignant tumors: evaluation by [18F]fluoromisonidazole and [18F]fluorodeoxyglucose positron emission tomography imaging. Clin Cancer Res 2004; 10(7): 2245−52.

Received on September 14, 2015.
Revised on October 18, 2015.
Accepted on October 22, 2015
Online First May, 2016.