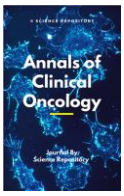

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Case Report

Response Evaluation with Dynamic FDG PET/CT during the Primary Systemic Therapy of Breast Cancer - A Case Report

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ABSTRACT

18-fluorine-fluorodeoxyglucose (FDG) positron emission tomography (PET) and mainly combined with computed tomography (CT), abbreviated as FDG PET/CT is a useful and accurate tool for staging and restaging in locally advanced breast cancer. In daily practice static images are prepared during the PET/CT examinations. However, despite the success of static PET and PET/CT imaging, the role of precise quantification of FDG-uptake – measured by dynamic acquisition – is ambiguous in the staging and management of different malignancies. In this case report, we described our experience with staging, interim and restaging dynamic PET/CT examinations of a woman suffering from breast cancer. Based on the described case we concluded that dynamic PET/CT is suitable for accurate quantification of FDG-uptake in primary breast tumors. However, performing dynamic PET/CT examinations is time-consuming, therefore, it is important to define the group of patients where their use is with the most favourable benefit/risk ratio. Furthermore, using of interim PET/CT scan is recommended in cases with clinically controversial baseline tests. Based on literature *in vivo* biomarkers of the dynamic PET/CT are predictive of more favourable tumor response and longer disease-free survival, as confirmed by our own results.

Introduction

Current guidelines recommend 18-fluorine-fluorodeoxyglucose (FDG) positron emission tomography (PET) combined with computed tomography (CT), (abbreviated as FDG PET/CT) as a useful and accurate tool for staging and restaging in locally advanced breast cancer. Additionally, its role is also coming into view in the response evaluation during neoadjuvant systemic treatment [1]. In daily practice static images are prepared during PET and PET/CT examinations: the amount of the accumulated radiotracer is examined at one predefined time-point after injection and characterized by Standardized Uptake Value (SUV), which is a calculated, semi-quantitative parameter. FDG-uptake of breast tumors shows strong correlation with their clinicopathological characteristics, such as histological tumor type, biological subtypes, grading and proliferation rate [2, 3].

However, despite the success of static PET and PET/CT imaging, the role of precise quantification of FDG-uptake – measured by dynamic acquisition – is emerged in the staging and management of different cancers. In our two earlier studies we used dynamic PET/CT imaging to accurately quantify the radiotracer uptake by the kinetic analysis of FDG-accumulation over a period of time, in staging of breast cancers [4, 5]. We assessed the correlations between the kinetic parameters measured by dynamic PET examinations (i.e., K1, k2, k3, Ki) and the routinely used predictive and prognostic factors of breast cancers − such as clinical TNM, histological tumor type, tumor grade, proliferation rate and receptor status (i.e., hormone-receptor (HR) and human epidermal growth factor receptor 2 (HER2) expression). In addition to dynamic imaging, also static imaging was performed for all patients. We found that the parameters of the dynamic measurements are also showed correlations with the clinicopathological features of the tumors [5]. As a

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part of a pilot study, we planned to evaluate the role of dynamic PET/CT imaging in the early response evaluation to primary systemic therapy (PST), which could be crucial in the clinical management of locally advanced breast tumors. We performed an additional interim PET/CT scan (after 3 cycle of systemic chemotherapy) and a restaging PET/CT scan (after the completion of PST) in case of a patient with locally advanced breast cancer and assessed the response to the therapy on the dynamic data and with static imaging, as well.

Materials and Methods

All three FDG PET/CT examinations – staging examination before the initiation of the therapy, interim PET/CT after 3 cycles of chemotherapy and restaging at the end of the PST - were performed at the Pozitron PET/CT Center, Budapest, Hungary. The examinations were carried out on a TruePoint HD PET/CT scanner (Siemens, Knoxville, TN). In case of dynamic breast PET/CT imaging, data collection lasted constantly for 60 minutes, right directly after the tracer injection of 214.6, 218.3 and 236.8 MBq (5.8, 5.9 and 6.4 mCi) FDG according to body weight (3.7 MBq/ kg), respectively. Collected dynamic data were analysed by using PMOD software (v3.310, Zürich, Switzerland). The compartment modelling of FDG-distribution is used to evaluate the data acquired by dynamic imaging. Using the FDG-two-compartment model we could estimate the important rate parameters of the tracer flow between the blood-pool (first, "plasma compartment") and the investigated tissue compartments (i.e., a "transfer compartment", where FDG is intracellular and a "metabolic compartment" where FDG is in FDG-6-phosphate form). The estimated rate constants describe the influx and efflux of the FDG between these compartments: K1 and k2 are the rate constants representing carrier-mediated transport of FDG from plasma to tissue (K1, unit: ml/ccm/min) and back from tissue to plasma (k2, unit: 1/min), in the transfer compartment. k3 (unit: 1/min) represents the rate constant for phosphorylation of the FDG by the hexokinase enzyme in the metabolic compartment. Based on the above listed parameters the net tracer influx constant (Ki, unit: ml/ccm/min) and the FDG metabolic rate in the tissue (MRFDG; unit: µmol/min/100g tissue) could be calculated [4-7]. Relationships of these parameters are defined by the following equations: Ki = (K1 x k3) / (K2+k3) and MRFDG = Cglc x Ki, where Cglc is the plasma glucose concentration (mmol/L).

The static examinations were performed as usual in clinical practice, according to the following. Scans were acquired at a range: 63, 61 and 62 min, respectively, after the intravenous injection of FDG. The patient fasted for a minimum of six hours before the injection of FDG. The blood glucose levels of the patient were 82.8, 108.0 and 81.0 mg/dl (4.6, 6.0 and 4.5 mmol/l) respectively, before the injection of FDG. PET data were acquired in three-dimensional mode and were reconstructed using CT data for attenuation correction with ordered subsets expectation maximization (OSEM) algorithm (4 iterations/8 subsets). The static scans were performed from the base of the skull to mid-thigh.

Case Presentation

A 45-year-old patient was admitted to our oncological ward, after she had discovered a lump in her left breast by self-examination. The patient was in premenopausal status, she had no history of contraceptive medication; however, she participated in an *in vitro* fertilization programme (four times), which resulted in one successful pregnancy at the age of 29. During the diagnostic imaging workup, she participated in a complex breast examination, whereas a 2.5 cm sized lump was palpated in the upper-outer quadrant of the left breast by the radiologists. X-ray mammography described a 3 cm sized lesion in the border of the upper-inner and upper-outer quadrant of the left breast, whilst breast ultrasound described a 22x28x24 mm sized lobulated, hypoechogenic lesion, without any involvement in the axillary region. Ultrasound-guided core-biopsy was performed from the breast lesion, which indicated a grade 2 invasive lobular carcinoma which was estrogen and progesterone receptor positive and Her2 negative. The Ki-67 proliferation index was 15% and the lesion was p53 positive and CK5/6 positive. The intrinsic subtype of the tumor was luminal B-like (Her2 negative).

Results

Before initiating any treatment, we decided to perform a PET/CT scan with dynamic PET/CT imaging (Figure 1), due to the controversial clinicopathological features of the tumor – in case of an ILC with intermediate or high grade and Ki-67 index FDG-PET/CT could be advised in the daily routine, due to the fact that with additional imaging, up-staging is quite frequent, which could result in a different treatment approach in these tumor types [8, 9]. K1, K2, K3, Ki and MRFDG were 0.1211, 0.1846, 0.0338, 0.0187 and 8.2764, respectively based on the staging dynamic PET/CT (Table 1). Maximum of SUV (SUVmax) was calculated, and morphological data were measured for the primary tumor and left axillary lymph node region based on the staging static PET/CT scan (Table 2). In the upper-outer quadrant of the left breast FDG PET/CT has shown metabolically active, multiplex breast lesions (SUVmax 6.2, in a region sized 50x20x35 mm). Additionally, a metastatic lymph node with pathologic FDG-uptake was also detected in the left axilla (SUVmax 2.3, sized 13x6 mm,). There was no sign of distant metastasis, therefore clinical TNM stage was established as cT3N1M0, which was an upstaging compared to the routine imaging modalities. Based on the clinical and pathological evaluation the multidisciplinary team decided to administer primary systemic therapy.

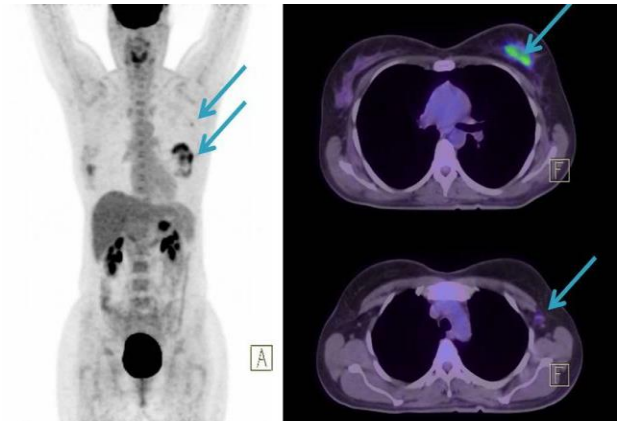

Figure 1: Staging PET/CT. Maximum intensity projection (MIP) presentation (left side) and transaxial sections (right side) of the staging FDG PET/CT examination demonstrating primer tumor in the left breast and lymph node metastasis in the left axilla (blue arrows).

Table 1: Measured and calculated kinetic parameters of staging, interim and restaging dynamic PET/CT examinations.

DYNAMIC	**Staging**	**Interim**	**Restaging**
K1(ml/ccm/min)	0.1211	0.1241	0.0924
k2(1/min)	0.1846	0.1430	0.1360
k3(1/min)	0.0338	0.0155	0.0114
Ki(ml/ccm/min)	0.0187	0.0121	0.0072
MRFDG(µmol/min/100g tissue)	8.2764	6.9926	3.1135

Table 2: Parameters of staging, interim and restaging static PET/CT examinations.

STATIC	**Staging**		**Interim**		**Restaging**	
	SUVmax	size (mm)	SUVmax	size	SUVmax	size
Primer tumor	6.2	50×20×35	4.6=PR	SD	3.7=PR	PR
Axilla	2.3	13×6	CR	SD	CR	CR

SUVmax: maximum of Standardized Uptake Value; PR: Progressive Disease; SD: Stable Disease; CR: Complete Response.

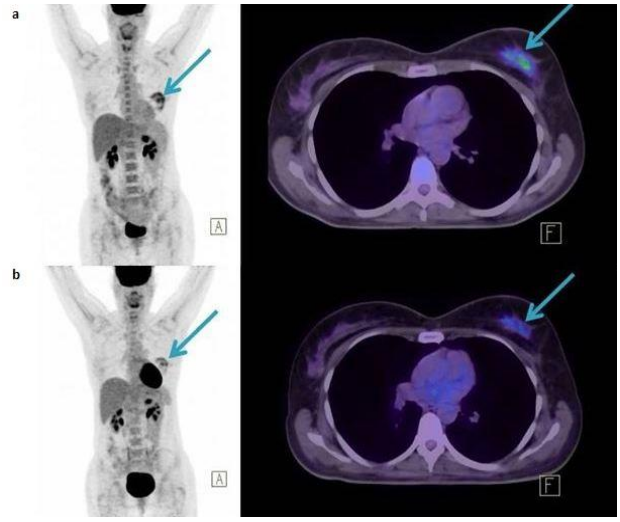

Figure 2: a) Interim PET/CT and **b)** restaging PET/CT. a) Maximum intensity projection (MIP) presentation (left side) and transaxial section (right side) of the interim FDG PET/CT examination demonstrating primer tumor in the left breast (blue arrows). b) Maximum intensity projection (MIP) presentation (left side) and transaxial section (right side) of the restaging FDG PET/CT examination demonstrating primer tumor in the left breast (blue arrows).

The patient received 3 cycles of FEC regimen (5-fluorouracil-epirubicin and cyclophosphamide combination) per protocol, thereafter interim PET/CT imaging was performed (Figure 2a). K1, K2, K3, Ki and MRFDG were 0.1241, 0.1430, 0.0155, 0.0121 and 6.9926, respectively based on the interim dynamic PET/CT (Table 1). The tumor of the left breast showed a mild metabolic remission but was still viable. According to PERCIST criteria a stable disease was detected (SUVmax 4.6 – based on the interim static scan). The axillary lymph node displayed complete metabolic remission. The patient received 3 additional cycles of chemotherapy, with a different regimen (TXT protocol, containing docetaxel).

At the restaging dynamic PET K1, K2, K3, Ki and MRFDG were 0.0924, 0.1360, 0.0114, 0.0072 and 3.1135, respectively (Table 1). Based on the restaging static PET/CT scan (Figure 2b) the primary tumor showed further remission (SUVmax 3.7) and defined as partial metabolic remission by PERCIST. We did not detect any FDG-avid lesion in any other examined regions on the whole-body scans. Based on these results, the multidisciplinary tumor board suggested performing a mastectomy and a 1st level ABD, due to the fact that the tumor did not showed a complete remission metabolically, as well as a retromamillar invasion was still detectable, which could have jeopardized breast conserving approach. The final histological examination of the surgical specimen provided a multifocal, grade 2 invasive lobular carcinoma, with luminal B-HER2 negative subtype. In the axillary lymph nodes macro-metastases were detected. In conclusion, according to the pathological staging, the patient was in ypT3ypN1a, the pathological response rate was established as TR3, NR4.

After surgery, the patient received radiation therapy (46,8 Gy +14 Gy) for the left breast and axillary region, with hormonal doublet therapy (GnRH analogue and tamoxifen). As of writing this paper the patient has been in complete remission, disease-free survival (DFS) was 53 months. Overall survival (OS) from the diagnosis was 60 months.

Discussion

Regarding the static PET/CT examinations, it is well-known, that the metabolic response precedes and predicts the expected morphological remission in the primary breast tumor. Furthermore PET/CT scan does not replace the sentinel lymph node biopsy, because false negativity is quite frequent in the axillary region. Regarding the dynamic PET/CT examinations, there are promising opportunities to define new predictive markers during staging and even more to measure therapeutic effect. This can be inferred from the rate constants, especially the initial value of the FDG influx (Ki) and the rate of phosphorylation (k3), as well as their changes. In breast cancers, Mankoff *et al.* already found correlation between the rate of the FDG influx and the achieving of partial complete remission, as well as the rate of the FDG influx and the longer DFS and OS [10-14].

In case of the presented case, the processes characterized by K1 and k2 (FDG-uptake into the cell and FDG-release from the cell) were dominant in the primary tumor at all three PET/CT scans, in addition to low k3. Based on the study of Mankoff *et al.* prevalence of K1 and k2 is predictive of favourable tumor response (otherwise, typically correlates with tumor grade and proliferation activity) [14]. In case of our patient the Ki/K1 ratio was 0.15, 0.097 and 0.078, calculated from staging, interim, and restaging PET/CT, respectively. If the Ki/K1 ratio is close

to zero (i.e., the rate of FDG flux is determined primarily by the phosphorylation step), it is also predictive of a more favourable tumor response according to result of Mankoff *et al.* [14]. We found MRFDG values 8.2, 6.9 and 3.1 µmol/min/100g calculated from staging, interim, and restaging PET/CT, respectively. Based on results of Mankoff *et al.*, if MRFDG is less than 20 µmol/min/100g, it is predictive of favourable therapeutic response and prognostic to the longer DFS [14]. In our case, the patients' tumor showed MRFDG under 20 µmol/min/100g in every performed scan, with decreasing value during the therapeutic course, and she also experienced a favourable clinical outcome with 53 months DFS.

However, our case underlined that PET/CT imaging is still not able to accurately predict the tumor response in the axillary region, as was already stated by several earlier studies [2]. Due to the small tumor burden in the axillary region, our scans showed metabolic complete remission after the PST, despite the pathologically proved lymph node involvement in the finally removed axillary block.

Conclusion

Based on the described case we can conclude that dynamic PET/CT is suitable for accurate quantification of FDG-uptake also in primary breast tumors. However, performing dynamic PET/CT examinations is time-consuming; therefore, it is important to define the group of patients where their use is with the most favourable benefit/risk ratio. Furthermore, using of interim PET/CT scan is recommended for clinically controversial baseline tests. Based on literature, *in vivo* biomarkers of the dynamic PET/CT exams are predictive of more favourable tumor response and longer DFS, as confirmed by our own results.

Ethical Approval

Ethical approval for the study was given by the Semmelweis University Institutional Review Board (SE-TUKEB No.119/2013; date of approval: 24 June 2013).

Consent

Patient was informed personally and written informed consent form was signed before the enrollment.

Conflicts of Interest

None.

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