New aspects of ^{18}F-FDG-PET/CT imaging in cardiology and oncology

Ph.D. thesis

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1 INTRODUCTION

1.1 Modern nuclear medicine

Positron emission tomography (PET) is a non-invasive molecular imaging technique that is highly sensitive in quantitative evaluation of metabolically active processes. Although the first tomography device had been developed as early as the 1950s by David E. Kuhl and Roy Edwards, the real milestone was Tatsui Ido's description of the synthesis of 18F isotope labelled fluorodeoxy-glucose (FDG) in the 1970s. There has been a rapid expansion in the utilisation of FDG PET ever since it was first established in oncological practice over a decade ago. Modern nuclear medicine utilizes tomographic radionuclide imaging do detect picomolar changes in biochemical processes. State of the art PET devices are able to pinpoint metabolic changes with a spatial resolution of 3-4 mm. Conventional tomographic radiology as (CT) computer tomography and magnetic resonance imaging (MRI) on the other hand are capable of a spatial resolution below 1 mm leading to a more detailed morphological characterisation of organs and tissues The efficacy of PET scan has further been improved by the introduction of hybrid imaging techniques, such as the PET/CT, which combines the advantages of both methods. PET provides high functional resolution metabolic information, whereas the CT is responsible for precise morphological imaging, and it also provides accurate information on the correction of the tissue absorption of the imaged gamma photons.

1.2 Clinical applications of 18F-fluoro-deoxi-glucose based imaging

1.2.1 ^{18}F-FDG PET in oncology

The FDG molecule acts as a glucose analogue in the body. Increased glucose metabolism is characteristic to most tumour cells due to the over expression of glucose transporter membrane protein and to the increased vascularisation and high mitotic activity of the tumour tissue. ^{18}F-

FDG is the most common radiopharmaceutical used for the investigation of oncological diseases by nuclear medicine. The wide applicability of FDG imaging in diverse oncological indications can be broadly attributed to the mechanism of uptake of the radiotracer, which acts as a non-specific biomarker of glycolytic metabolism. The incorporation of ^{18}F-FDG-PET/CT in the management pathways of oncological patients, across a broad spectrum of disease, leads to significant management changes in up to 20–40% of patients. Depending on the type tumour ^{18}F-FDG-PET/CT may play a role in detection of unknown primary, staging of disease, irradiation therapy planning, assessment of therapeutic effects (surgery, chemotherapy and irradiation) as well as in restaging of disease after therapy and during follow up.

1.2.1.1 ^{18}F-FDG-PET/CT in head and neck cancer

Head and neck tumours are detected mostly in an advanced stage and have poor prognosis. Due to anatomic complexity of the region complete surgical resection is rarely possible. These in most cases histologically squamous cell- tumours are sensitive to radiation therapy. Precise radiation therapy treatment planning of tumours in this region is especially important as several organs of vital importance are located close to each other in a small area. There is a large amount of evidence proving the efficacy of fluorodeoxy-glucose positron emission tomography (^{18}F-FDG-PET) during detection of unknown primary, staging of disease, restaging after salvage surgery or neck block dissection as well as in assessment of response to therapy in head and neck cancer. There is also growing interest in utilizing ^{18}F-FDG-PET in growth target volume delineation for radiation therapy planning in this sensitive region. According to current guidelines target volume delineation for radiation therapy planning is recommended by CT supplemented by MRI certain cases. Integrated ^{18}F-FDG PET/CT imaging with combined morphological and metabolic information has the potential of improving radiotherapy planning, gross tumour volume (GTV) delineation. However there is currently no

consensus on methods of delineation, volume definition or in regards to overall utility of ^{18}F-FDG-PET/CT scans in radiotherapy planning of in head and neck cancer patients. This field remains an active area of research.

1.2.2 ^{18}F-FDG-PET/CT in inflammatory disorders

Increased glucose metabolism due to high glycolytic activity of inflammatory cells (monocyte, macrophage, lymphocyte) is considered a hallmark of inflammation. Thus with a rapidly expanding body of evidence, it is being increasingly recognised that, in addition to its established role in oncological imaging, ^{18}F-FDG-PET/CT also has clinical utility in suspected infection and inflammation. The use of ^{18}F-FDG-PET/CT is under investigation in a broad spectrum of inflammatory disorders effecting different organs, such as fever of unknown origin, sarcoidosis, large vessel vasculitis, musculoskeletal infections, joint prosthesis infections.

1.2.1 Cardiac ^{18}F-FDG PET/CT imaging

Over the past decades ^{18}F-FDG-PET/CT imaging has been recognized as an indispensable tool in the diagnosis, staging and treatment monitoring of cancer. This modern imaging technique combining functional and morphologic information has approved indications not only in oncology but in clinical cardiology as well.

Cardiac ^{18}F-FDG-PET/CT has special requirements of patient preparation and image acquisition protocol. Because the heart uses a mixture of free fatty acids and glucose for energy production under normal resting conditions, assessment of myocardial inflammation on a background of physiologic myocardial ^{18}F-FDG uptake is challenging. To improve specificity in identifying pathologic glucose uptake, several methods to reduce physiologic myocardial glucose uptake have been implemented including (1) prolonged fasting, (2) dietary modifications and intravenous use of non fractionated heparin.

Historically use of ^{18}F-FDG-PET/CT in cardiology had been restricted to viability and onco-cardiology examinations. Recently however special emphasis has been placed on investigation of inflammatory disorders involving the heart. This relatively newer class of indications includes prosthetic valve endocarditis, cardiac implantable device infection, myocardial inflammation of varying origin such as sarcoidosis where ^{18}F-FDG-PET/CT appears to be particularly useful in differential diagnosis of cases where standard investigation is non-diagnostic or equivocal.

1.2.1.1 ^{18}F-FDG-PET/CT in systemic sclerosis

Systemic sclerosis (SSc) is a rare, chronic, progressive systemic connective tissue disease characterized by microvascular dysfunction, immune-mediated inflammation and fibrosis with multi organ involvement. Cardiac involvement is common for patients with systemic sclerosis, both in diffuse (DcSSc) and limited cutaneous forms (LcSSC) of disease with an estimated clinical prevalence of 15-35%. Cardiovascular disease in SSc may be direct (myocarditis, heart failure, coronary artery disease, valvular and pericardial disease, conduction disturbances) and indirect (pulmonary artery hypertension (PAH) and renal crisis). When heart involvement becomes clinically evident it appears as a bad prognostic factor with a patient mortality rate of up to 70% at 5 years. In the majority of patients (up to 80%), however cardiovascular disease is subclinical for variable duration. Therefore preclinical identification and monitoring of cardiac involvement is pivotal for adequate early management of these patients.

Although diffuse myocardial fibrosis remains the pathologic hallmark of direct myocardial involvement the presence of inflammation is often found in many biopsies of SSc patients suggesting that cardiac inflammation may be more common than originally appreciated. Moreover, the fibrotic process may be secondary to chronic inflammation of the heart. We

hypothesized that ^{18}F-FDG-PET/CT may also be positive in asymptomatic SSc patients with potential subclinical myocarditis.

2 AIMS

- To review the literature of ^{18}F-FDG-PET/CT indications in cardiology, in cases highlighted by own examinations.
- To assess intra- and interobserver variability of manual tumour contouring on ^{18}F-FDG-PET/CT in head and neck cancer patients.
- To compare gross tumour volume delineation for radiation therapy planning by ^{18}F-FDG-PET/CT and the current standard CT scan in head and neck tumour patients.
- To assess the applicability of ^{18}F-FDG-PET/CT in the detection of myocardial involvement in systemic sclerosis patients.
- To compare results of cardiac ^{18}F-FDG-PET/CT and 2D speckle-tracking echocardiography in systemic sclerosis patients.

3 PATIENTS AND METHODS

3.1 Comparison of FDG-PET/CT and CT tumour volume delineation in head and neck cancer patients

3.1.1 Patients

We enrolled 70 patients undergoing radiation therapy planning for head and neck cancer in the current study. The average age of the patients was 58± 9 years (19–77 years). 20% of the studied patients (14/70) were women and 80% (56/70) were men. Histological distribution was the following: (94.3%; 66/70 patients) squamous cell carcinomas, 3 adenocarcinomas (4.2%), and 1 patient had neurofibrosarcoma (1.5%). Interobserver and intraobserver variance analyses were performed on the ^{18}F-FDG-PET/CT scans of 16 randomly selected patients. In this group,

the average age of patients was 58 years (44–73 years), and the male to female ratio was 16:0. Histology examination confirmed squamous cell carcinoma in all 16 patients.

3.1.2 Imaging

During patient preparation the head and neck region was positioned with four or five-point thermoplastic masks. After treatment planning CT (topo CT) imaging, ^{18}F-FDG-PET/CT scan was performed within 3 weeks in the same patient position using thermoplastic fixation (SIEMENS Biograph 6 HD, Siemens Knoxville TN).

3.1.3 Tumour contouring

GTV was manually delineated in each patient with both modalities. GTV selection for treatment planning was manually performed on both the conventional CT based topometric slides (GTV_{CT}) and the PET/CT registered images (GTV_{PET}) by a skilled radiologist and by a nuclear medicine specialist independently. XIO 3D planning system (Elekta Ltd, Crawly, UK) was used for evaluation. GTV_{CT} contouring on the radiation planning CT was performed according to the guidelines of the Department of Oncotherapy. Available images of former contrast CT or MRI scans were reviewed under the supervision of a radiologist. Tumour volumes were recorded and determined in units of cm^3. For ^{18}F-FDG-PET/CT intraobserver and interobserver variation analyses of manual contouring 20 solid lesions with different size were evaluated on the scan images of 16 randomly selected patients.

3.1.4 Quantitative evaluation

In each case, the GTV volume based on the performed ^{18}F-FDG-PET/CT scan was compared to the GTV provided by the CT scan and their difference was described both in cm^3 and in percentage. For the geometric comparison of each tumour volume of interest (VOI), the Intersection/Union (I/U) ratio was calculated. The total patient population (Group 1.), was

divided into subgroups based on differences in GTV of the two modalities (Group A: $GTV_{PET-CT} > GTV_{CT}$; Group B: $GTV_{PET-CT} \leq GTV_{CT}$). The before mentioned volumetric and geometrical comparisons were repeated in both subgroups.

3.2 Detection of myocardial inflammation by ^{18}F-FDG-PET/CT in patients with systemic sclerosis

3.2.1 Patients

Sixteen consecutive patients affected with SSc (according to the ACR/ EULAR (American College of Rheumatology, European League Against Rheumatism) guidelines for systemic sclerosis classification) but without overt cardiovascular involvement were enrolled in the current prospective study. To avoid unnecessary radiation exposure to healthy subjects, 9 persons (5 male, 4 female; age 46.55±18.05 years) who underwent FDG-PET/CT examination for various other diagnostic reasons were enrolled as control. Control subjects did not have systemic sclerosis, nor had evidence of active inflammatory disease or cardiac disease, and complied otherwise with the general exclusion criteria, and underwent the same FDG-PET/CT image acquisition and analysis protocol as study patients.

3.2.2 Laboratory and clinical assessment

All SSc patients underwent comprehensive rheumatologic and cardiovascular evaluation including but not limited to the assessment of: disease duration, EUSTAR (European Scleroderma Trials and Research group) disease activity score, Framingham score, presence of gastrointestinal involvement, pulmonary involvement, digital ulcers, prior immunosuppressive treatment, cardiovascular risk factors and current medication. General laboratory workup including determination of disease specific auto antibodies and markers of inflammation were performed according to local practice guidelines.

3.2.3 Patient preparation and imaging

To suppress physiological glucose uptake in the myocardium patients were instructed to take low-carbohydrate, high-fat, high-protein diet for 24 hours followed by a minimum of 6 hours fasting before PET/CT scan examinations according to previously published cardiac FDG-PET/CT guidelines (SNMMI/ASNC/SCCT (Society of Nuclear Medicine and Molecular Imaging /American Society of Nuclear Cardiology/ Society of Cardiovascular Computed Tomography)). All scans were performed on an integrated whole-body PET/CT system (GE Discovery ST 4, GE Healthcare, Amersham, UK). Imaging of the cardiac region in 2D and 3D, non-gated mode was carried out 60 minutes after the administration of the radioisotope.

3.2.4 Cardiac ^{18}F-FDG-PET/CT image analysis

FDG-PET images were visually evaluated for the presence of FDG uptake in the heart by consensus reading of two experienced PET/CT specialists. Quantitative evaluation of FDG uptake was performed by PMOD version 3.704 software (PMOD Technologies Zurich) on attenuation corrected 2D PET images. Seventeen segment cardiac model was used according to the scientific statement from the American Heart Association. Body weight standardized uptake value (SUV) in g/ml was calculated. To specify pathophysiological uptake a coefficient of variation as a metric of image heterogenity was also determined. The coefficient of variation (heterogenity index; HI) was calculated as the standard deviation of SUV divided by the average of SUV.

3.2.5 Echocardiography

All patients with SSc underwent comprehensive echocardiography within 24 hours after PET/CT scanning. Echocardiographic examinations were performed in all patients at rest using commercially available ultrasound machine (Vivid S70, GE Medical Systems, Horten, Norway). All measurements were performed according to the recommendations of the

European Association of Cardiovascular Imaging/American Society of Echocardiography. The 2D Speckle Tracking echocardiography (2DSTE) mages were analyzed using dedicated software package (EchoPac PC, Version, GE Vingmed, Horton, Norway).

4 RESULTS

4.1 Comparison of FDG-PET/CT and CT tumour volume delineation in head and neck cancer patients

4.1.1 Inter- and intraobserver variability

Macroscopic tumour volume delineated in Group 2. during the 5 measurements (A1, A2, A3, B, and C) was 13.20 ± 13.43 cm^3 (0.60–54.20 cm^3). During interobserver comparison (A1, B, and C), the average difference in measured volume was 3.08 ± 2.36 cm^3 (0.10–5.56 cm^3), which described a difference of 29.49 ± 18.00% (5–78%). The intraclass correlation coefficient was 0.9724. Higher differences in percentage (46.75 ± 20.25 % vs. 20.19 ± 9.17 %, unpaired two-samples Wilcoxon Rank Sum test $p < 0.05$) were characteristic mostly for tumours of smaller size (<5 cm^3). The geometric intersection union ratio was 0.68 ± 0.12 in overall comparison of the members in the three series. For intraobserver comparison difference in volumes (A1, A2, and A3) was 1.12 ± 1.1 cm^3 that is 12.31 ± 7.4%. The intraclass correlation coefficient was 0.9903.

4.1.2 Comparison of radiation therapy target volumes delineated by ^{18}F-FDG PET/CT and CT

Tumour volumes were identical in 1 out of 70 cases (1%), decreased in size in 57 cases (81%) of the cases, and increased in 12 cases (18 %) of the cases, when the results acquired by the ^{18}F-FDG-PET/CT scan were compared to the results defined by topo-CT scan. Tumour volumes defined by the two different imaging modalities were non-identical in 99% of the cases. In 11 out of 70 cases, the difference in the percentage of volumes was lower than 10%. The difference

in the percentage of volumes was higher than 10% in 59 out of 70 patients (84% of all patients). Tumour volume defined by the ^{18}F-FDG-PET/CT was significantly smaller (paired T test, p <0.0001) than tumour size defined by the topo-CT scan: GTV_{CT}: 52.54 ± 51.11 cm^3 (1.80–208.50 cm^3), GTV_{PET-CT}: 33.16 ± 39.78 cm^3 (1.00–188.40 cm^3). Difference in volume (independent of in which modality was higher or lower) was 22.33 ± 23.33 cm^3 (0.40–116.00 cm^3), which describes a difference of 53.77% ± 40.94% (0.55–213.25%). During geometrical analyses I/U was 0.32 ± 0.19 (0.03–0.77).

4.2 Detection of myocardial inflammation by 18F-FDG-PET/CT in patients with systemic sclerosis

4.2.1 ^{18}F-FDG-PET/CT

According to visual classification of cardiac ^{18}F-FDG-PET images in Ssc patients, 8/16 none, 0/16 diffuse, 6/16 focal, 2/16 focal on diffuse patterns were found. In all of the control subjects, the cardiac FDG-uptake was near or equal to lower than blood pool activity meaning a “none” pattern. In SSc patients, global myocardial SUV was 3.019±0.02 g/ml and blood pool SUV was 2.1±0.56 g/ml. In control patients, the same values were 1.81±0.26 g/ml and 1.85±0.27 g/ml (p < 0.05). After normalization according to blood pool uptake SUV ratio in the patient population was 1.38±0.65 and 0.98±0.03 in the control group (p <0.05). Heterogenity indices of SSc and control patients were 0.095±0.04 and 0.05±0.02 (p <0.05). In contrast, in the 8 visually “PET-negative” SSc patients, normalized SUV ratio and heterogenity index did not differ significantly from control subjects (normalized SUV ratio: 0.98±0.05 versus 0.98±0.03; HI: 0.05±0.01 versus 0.05±0.02). No significant differences were detected between the two groups in regards to clinical characteristics and laboratory parameters. No correlations were found between ^{18}F-FDG-PET/CT derived values and type of SSc, disease activity scores, disease duration and laboratory indices of inflammation or cardiac involvement and echocardiographic parameters.

4.2.2 Echocardiography

There were no significant differences between DcSSc and LcSSc patients based on TTE parameters. There was also no statistically significant difference between PET positive and negative groups in regards to conventional TTE findings and, of special interest, global longitudinal peak strain (17.18±3.49 v. 17.59±3.65). No correlations were found between GLPS values and ^{18}F-FDG-PET/CT derived indices (global SUV, normalized global SUV and HI).

4.2.3 Spatial agreement

Spatial agreement between ^{18}F-FDG-PET/CT and 2DSTE derived segmental longitudinal strain was assessed according to the 17- segment model in a total of 234 left ventricular segments. Overall, 96/234 segments with increased FDG-uptake were found. According to 2DSTE analysis 48/234 segments had pathological low segmental longitudinal strain value. Overall and PET positive patient spatial agreement between the two methods was poor (κ=0.04 and κ=0.021). To avoid possible orientation bias for further analysis, the left ventricular bull's eye was divided into four anatomical regions: apex (13-17 segments), septum (2-3, 8-9 segments), anterior and anterolateral wall (1,6,7,12 segments) and inferior and inferolateral wall (4,5,10,11 segments). Pathological ^{18}F-FDG-PET/CT (20/56) and STE derived segmental longitudinal strain (21/56) regions were determined. Overall and in patients with pathological PET findings, spatial agreement between the two methods remained to be poor (κ=0.12 and κ=0.15).

5 CONCLUSIONS

1. In the first part of the dissertation the specific requirements of patient preparation and image acquisition protocol for cardiac ^{18}F-FDG-PET/CT are discussed and analyzed. Relevant literature of indications in cardiology are reviewed, in cases highlighted by own examinations while placing special emphasis on inflammatory disorders involving the heart. This relatively

newer class of indications includes prosthetic valve endocarditis, cardiac implantable device infection, myocardial inflammation of varying origin such as sarcoidosis. ^{18}F-FDG-PET/CT appears to be particularly useful in differential diagnosis of cases where standard investigation is non-diagnostic or equivocal.

(2-3). Manual tumour contouring of ^{18}F-FDG-PET/CT images provide excellent intra- and interobserver reliability in head and neck cancer patients. Our results proved that CT based tumour volumes differ significantly compared to ^{18}F-FDG-PET/CT based. ^{18}F-FDG-PET/CT imaging with additional metabolic information may allow for better radiation therapy target volume planning and viable tumour mass definition, while lessening organ at risk radiation exposure. In overview a combination of structural (CT) and metabolic information (^{18}F- FDG) is necessary for optimization of radiotherapy planning.

(4-5). Myocardial inflammation, as a potential sign of early cardiac involvement may be detected by ^{18}F-FDG-PET/CT in a considerable percentage of systemic sclerosis patients presenting without cardiac symptoms. No correlations were found between ^{18}F-FDG-derived values and echocardiographic strain parameters. The results capture the dual nature of the disease: pathological glucose uptake representing early immune mediated inflammation and lower strain values representing subtle mechanical changes caused by fibrosis.

6 LIST OF PUBLICATIONS

Full papers directly related to the thesis

1. **Besenyi** Z, Ágoston G, Hemelein R, Bakos S, Nagy FT, Varga A, Kovács L, Pávics L: Detection of myocardial inflammation by 18F-FDG-PET/CT in patients with systemic sclerosis

without cardiac symptoms: a pilot study. Clinical and Experimental Rheumatology 2018 Dec 7. [Epub ahead of print] IF: 3,238

2. **Besenyi** Zsuzsanna, Nagy Ferenc Tamás, Sághy László, Pávics László: 18F-fluoro-dezoxi-glükóz pozitron emissziós tomográfia/komputer tomográfia (18F-FDG-PET/CT) képalkotás a kardiológiában. Orvosi Hetilap; 160: 1015-1024. (2019) IF: 0,564

3. **Besenyi** Zsuzsanna, Hideghéty Katalin, Lengyel Zsolt, Urbán Szabolcs, Bakos Annamária, Farkas István, Sipka Gábor, Séra Teréz, Pávics László: Tumortérfogat meghatározása fej-nyaki daganatokban 18F-FDG-PET/CT vizsgálattal. MAGYAR RADIOLÓGIA ONLINE 8:1-13 p. (2017)

Abstracts directly related to the thesis

1. **Besenyi** Z, Ágoston G, Hemelein R, Bakos A, Kovács L, Varga A, Pávics L: Cardiac FDG-PET/CT in systemic sclerosis. European Journal of Nuclear Medicine and Molecular Imaging 44: Suppl. 2 p. S249 (2017)

2.Agoston G, **Besenyi** Z, Hemelein R, Palinkas A, Kovacs L, Pavics L, Varga A: Detection of myocardial involvement in patients with systemic sclerosis by cardiac 18F-FDG PET/CT and speckle tracking echocardiography. European Heart Journal 38: Suppl. 1 p. P2424 (2017)

3. **Besenyi** Zsuzsanna, Urbán Szabolcs, Hideghéty Katalin, Lengyel Zsolt, Pávics, László: Az FDG-PET/CT szerepe a fej-nyak tumorok térfogat meghatározásában. Magyar Onkológia 59: 1 pp. 7-8., 2 p. (2015)

4. **Besenyi** Z, Urban A, Sera T, Pavics L: Tumor volume determination in head and neck cancer for radiotherapy planning using CT and FDG-PET/CT. Nuklearmedizin-Nuclear Medicine 54: 2 Paper: P59 (2015)

5. **Besenyi** Z, Urban S, Hideghethy K, Sera T, Lengyel Z, Pavics L: Comparison of imaging modalities (CT, FDG-PET/CT) in head and neck cancer patients. European Journal of Nuclear Medicine and Molecular Imaging 41: suppl 1 pp. S321-S322. (2015)