PhD thesis

The importance of hybrid imaging methods in the qualitative and quantitative evaluation of brain receptor scintigraphy

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1. Introduction

The increasing incidence of neurodegenerative diseases causes an importance differential diagnostic challenge to neurologist. The damage of the extrapyramidal system leads to motor dysfunctions often manifesting in tremor, bradykinesia and rigidity. Diseases sharing the characteristic of the presynaptic dopaminergic system of basal ganglia and the consequently appearing motor symptoms combined is called Parkinson's syndrome. This group of diseases includes Multi System Atrophy (MSA), a Progressive Supranuclear Palsy (PSP), a Corticobasal Degeneration (CBD) and the Lewy Body Dementia (LBD).

Certain types of Parkinsonism, however also include pathological conditions, which are not characterised a nigrostriatal degeneration. This condition may develop because of drug-induced, vascular or toxic damages and Parkinsonism caused by psychogenic disease.

In patients with nigrostriatal degeneration, dopaminergic therapy may be effective while in diseases with postsynaptic and non-degenerative etiology it is not effective [**1**].

The therapeutic protocols of conditions described above are different, it is easy to understand the importance of earliest possible accurate diagnoses which has an effect on the whole course of the disease. The diagnoses of Parkinson's disease may be established based on post-mortem histological examinations (the presence of Lewy bodies /inclusions) in the dopaminergic neurons) can be established. The establishing of the diagnosis is based on clinical symptoms which are evaluated on the basis of the Unified Parkinson's Disease Rating Scale (UPDRS) of the Motion Disorder Society and Hoehn-Yahr stages, while in evaluating the cognitive status neuropsychological test (e.g. Mattis Dementia Rating Scale (MDRS); Addenbrooke's Cognitive Examination (ACE) are used.

In Parkinson's syndromes besides motor symptoms, the presence of other specific symptoms may help with differentiating while the importance of traditional imaging techniques in this cases is questionable. At the present no conversional imaging procedure is known, which itself could be used for differentiating these diseases.

The conventional MRI examination is less sensitive; especially in the initial state of the disease, however functional imaging techniques (nuclear medicine techniques) are suitable for differentiating „real" Parkinson's syndrome from essential tremor and from drug-induced vascular Parkinsonism.

Of functional imaging techniques SPECT-imaging is more frequently used in Europe than PET [**1**].

The reason most probably is that SPECT radiopharmaceuticals are more readily available (less expensive), and the half-life is longer (^{123}I T1/2: ~13 h, ^{99m}Tc T1/2 : ~6 h), which provides a longer interval for performing the imaging. In the case of PET radiopharmaceuticals the production of most of the isotopes requires cyclotron (the pharmaceutical is most commonly labelled ^{18}F), where it is not available transportations cost need to be calculated and the imaging is more complicated because of the significantly shorter half-time (^{18}F T1/2 : ~120 minutes).

1.1. General characteristics of ^{123}I-Ioflupane

The ^{123}I-FP-CIT dopamine transporter SPECT imaging is a sensitive method for assessing the function of striatal dopaminergic nerve endings. The ^{123}I-FP-CIT is one of the most deeply studied and widely used radiopharmaceuticals in clinical settings. Permission for its application is provided by the European Medicines Agency (EMA) and Food and Drug Administration (FDA) [**2**], [**3**]. The active agent of the ^{123}I-FP-CIT is Ioflupane, which is labelled by gamma radiating ^{123}I isotope. Ioflupane specifically bounds to the presynaptic dopamine transporter (DAT), which renders it capable of detecting the active dopaminergic nerve endings of this striatum, which allows to conclude the degree of the damage of this structures [**4**]. The method has been available in Hungary for several years and in justified cases it can be performed financed by the National Health Insurance Fund Management (NEAK) [**5**].

1.2. Major indications of ^{123}I-FP CIT

The clinical application of ^{123}I-FP-CIT radiopharmaceutical in adults was permitted under the name of DaTSCAN by EMA in 2000, for distinguishing uncertain symptoms or early symptoms of Parkinsonism (PD, MSA, PSP) (it was added in 2013) and also for the differentiation of the essential tremor, and from 2006 on, extending the indications to the differentiation of Lewy-body dementia from Alzheimer disease [**2**].

In the United States clinical application in adults was permitted under the brand name DaTscan by US Food and Drug Administration (FDA) significantly later (in 2011), in which only the differentiation of Parkinsonism and essential tremor is included as indication [**3**].

Based on the publication of the report by EMA (the so called EPAR), the application of DaTSCAN has two major indications in Hungary:

1. The differentiation of clinically uncertain Parkinsonism or Parkinsonism showing early symptoms from essential tremor.
2. The differentiation of Lewy-body dementia from Alzheimer disease.

In addition to the officially permitted indications by EMA, European Association of Nuclear Medicine (EANM) issued a guideline [**4**] which includes two further potential indications (1) the assessment of the severity of Parkinsonism and (2) the differentiation of Parkinsonism showing a presynaptic involvement from the presynaptically not affected Parkinsonism (e.g. drug induced or psychogenic Parkinsonism).

2. Objectives

1. Developing quantificational possibilities ("standardised", „semiautomatic" method and manual delineation procedure specifically applied to patients) based on manual delineation of SPECT/CT images performed with ^{123}I-FP-CIT radiopharmaceuticals.
2. Developing a new automatic MRI-based quantificational procedure for the assessment of DAT SPECT images.
3. Comparing the results of these procedures with each other and with a widely-used four-stage visual classification (validated by Benamer et al.).
4. Determining how different semiquantitative assessment methods can help or modify the visual interpretation of images.
5. Determining the applicability of visual and different quantificational methods in clinical practice, in more accurately determining stages and refining severity grade of the disease.

3. Materials and Methods

3.1. Subjects

Thirty-three patients with Parkinsonian syndrome (PS, 15 men and 18 women; mean age: 60.3±9.7, range: 39-73 years) and 15 essential tremor (ET) patients (8 men and 7 women; mean age: 54.7±16.3, range: 22-78 years) were included in a prospective study. ET patients served as the control group. Only patients who did not take any medication which could significantly influence striatal DAT binding were included in the study.

The diagnosis of PS and ET was confirmed by a movement disorder specialist in accordance with current clinical criteria.

The severity of PS was assessed by Hoehn-Yahr scale, the Hungarian validated version of Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and the documented disease duration. All subjects received detailed information on the investigation and gave written informed consent prior to the examination. The study was approved by the National Ethical Board (36104/2012/EKU). For thyroid blocking, patients received Lugol's solution (30 drops, 3 times a day, for 3 days) before tracer administration.

3.2. Methods

3.2.1. *SPECT imaging*

Three hours after the intravenous administration of 185 MBq of ^{123}I Ioflupane (DaTSCAN, GE Healthcare), brain SPECT examination with low dose computed tomography (CT) was performed. Double head gamma camera (AnyScan, Mediso) with low energy high resolution (LEHR) collimator was used. The imaging parameters were as follows: 128x128 matrix size; 64 frames; 40 sec/frame; angular step 5.6°; zoom 1.45. Transversal, sagittal and coronal slices were created. Images were reconstructed using a Butterworth brain prefilter.

3.2.2. *Magnetic resonance imaging*

Magnetic resonance imaging was performed on a 3T MRI scanner (MAGNETOM Trio a Tim System, Siemens AG, Erlangen, Germany) with a 12-channel head coil. A T1-weighted 3D MPRAGE (TR/TI/TE=2530/1100/3.37ms; Flip Angle=7°; 176 sagittal slices; slice thickness=1mm; FOV=256x256mm^2; matrix size=256x256; receiver bandwidth=200Hz/pixel) sequence was obtained to allow automated MR-based evaluation of dopamine transporter (DAT) binding.

3.2.3. *Visual evaluation*

SPECT images were visually assessed by 2 independent experts blinded to clinical data and uptake measures provided by the automated (or manual) analysis. Striatal DAT binding was classified as normal or abnormal grade I, II and III in accordance with the criteria of Benamer et al. [**6**].

Normal: Tracer uptake bilaterally in putamen and caudate nuclei and largely symmetric.
Abnormal grade I: Asymmetric uptake with normal or almost normal putamen activity in one hemisphere and with a more marked reduction in the contralateral putamen.
Abnormal grade II: Significant bilateral reduction in putamen uptake with activity confined to the caudate nuclei.
Abnormal grade III: Virtually absent uptake bilaterally affecting both putamen and caudate nuclei.

3.2.4. ***Automated evaluation***

Left and right caudate and putamen were automatically segmented on T1-weighted MPRAGE images using FIRST, while occipital cortex was defined by merging the lateral occipital, lingual, cuneus and pericalcarine regions delineated by FreeSurfer 5.3 image analysis suite.
For automated DAT binding quantification, the segmented masks were aligned with each subject's native DAT image, while keeping the original mask resolution of 1x1x1mm^3. The alignment was based on the rigid body (6 degrees-of-freedom) transformation between MR and CT images calculated by FLIRT. Normalized mutual information was used as cost-function.
Mean ^{123}I-FP-CIT uptake values were extracted for each mask by InterView^{TM} FUSION version 2.02.055 (Mediso). Specific to nonspecific uptake ratios were calculated separately for the left and right sides of caudate and putamen using the formula: $(UPT_{striatal} - UPT_{occ})/UPT_{occ}$, where $UPT_{striatal}$ represents the mean uptake in the target region (putamen or caudate) and UPT_{occ} is the mean uptake in the reference region (occipital cortex).
Since, the underlying disease in patients with PS is often asymmetric, the uptake data were defined in terms of the "higher" (less affected) and "lower" specific uptake (more affected) sides, rather than left and right hemispheres. For example, "lower" putamen denotes the lower one from the left and right putaminal specific uptake ratios.

3.2.5. ***Manual evaluation***

Manual ROI delineation included several steps. If ^{123}I-FP-CIT accumulation was apparent bilaterally in the putamen and caudate then manual delineation was performed as follows: left and right caudate and putamen were manually labelled in three axial SPECT slices; the slice showing most intense striatal tracer uptake and the most caudal and cranial slices in which the tracer uptake was still evident for the given brain structure.

Using InterView^{TM} FUSION version 2.02.055 (Mediso), the user-defined two-dimensional (2D) VOIs were automatically extended between these three slices to form a three-dimensional (3D) VOI for each structure. Finally, using the CT images, each 3D VOI was manually corrected according to the anatomical landmarks.

If ^{123}I-FP-CIT accumulation was present only in one hemispheric putamen or caudate, then the 3D VOI around the best preserved putamen or caudate was outlined based on the above. The mirror image of this tracing was used as an initial label for the contralateral side, which was adjusted manually based on the CT image to fit individual anatomy.

If ^{123}I-FP-CIT accumulation was visually absent bilaterally in the caudate or the putamen, the delineation of the 3D VOI covering the corresponding anatomical structure was based on the CT image exclusively.

Three dimensional VOIs of the occipital reference region were drawn in a way to avoid the inclusion of any bone tissue or cerebrospinal fluid.

Similarly to the automated evaluation, specific to nonspecific uptake ratios were calculated separately for the "higher" (less affected) and "lower" specific uptake (more affected) sides of the putamen and caudate. For these calculations, the average of the mean uptake values from left and right occipital VOIs was used as the nonspecific uptake reference (i.e. UPT_{occ}).

3.2.6. ***SPECT/CT based „standardised" delineation***

During this procedure we manually delineated VOIs on the SPECT/CT scan of a normal presynaptic DAT-patient. Later the CT images of this normal („standard") DAT-patient registered with the CT images of other patients, we applied VOIs delineated in the "standardised" patient in order to obtain other patient's numeric parameters.

4. Results

Almost perfect agreement was found between the visual scores by the 2 observers (complete agreement in 42/48 cases; only one grade difference was found in 6 cases; κ=0.829). Most of the disagreement happened at higher grades (grades 3 vs. 2 in two occasions, grades 2 vs. 1 in three occasions, grade 1 vs. 0 in one occasion). All of the patients with a clinical diagnosis of PS were visually classified as abnormal (grade $\geq$ I) by both observers.

A ROC analysis revealed that, in „standard" SPECT/CT and automatic MRI-based assessment quantitative values obtained in the case of putamen are suitable for differentiating Parkinson's disease and essential tremor, similarly to the visual technique and the manual SPECT/CT-based assessment.

However, we found that in the differentiation of the two groups the most effective quantitative parameter is the sample count measured in the case of putamens relative to the occipital cortex.

The AUC value (area under the ROC curve) counted on the "more affected" side was the same in the case of „standard" SPECT/CT based assessment and automatic MRI mask procedure (AUC = 0.988), the AUC value counted on the "less affected" side showed a better result (AUC = 0.994) with the „standard" SPECT/CT-based assessment. In all of the three quantitative procedures and in the case of visual assessment, high specificity and high sensitivity value could be observed, but it must be noted, that these values strongly dependes on the actually used benchmark [**7**]. By shifting the benchmark in the positive direction sensitivity can be improved as opposed to specificity and vice versa.

In patients with Parkinson's disease the „standard" SPECT/CT and automatic MRI mask based procedure revealed lower striatal DAT binding in long-term disease similarly to manual and visual assessment.

The uptake quotient value originating from the putamen showing "lower" specific binding is inversely proportional to all clinical parameters, such as Hoehn-Yahr scale, MDS-UPDRS Total, as well as scores of parts II., III., IV., and this is partially true in „standard" SPECT/CT-based assessment (except for parts II-III. of MDS-UPDRS, where is no significant correlation between two methods), which suggest that these procedures can be effective not only in establishing the diagnosis of Parkinson's disease but also in estimating the severity of the disease.

All of the examined uptake measures were moderately correlated ($|\rho|>0.5$; $P<0.001$) with disease duration. Hoehn-Yahr score was also significantly correlated with all uptake measures, except the "higher" putaminal uptake ratio derived from the manual method. Scores on MDS-UPDRS Part I did not correlate with any uptake measures, while the other MDS-UPDRS scores showed trends or even significant correlations with most of the uptake parameters. Correlation coefficients were negative between clinical severity and the uptake ratios and positive between clinical severity and the visual scores.

5. Conclusion

1. We have successfully developed a “standard” (semi-automatic) method and manual delineation procedure specifically applied to patients in order to quantify SPECT/CT images performed with ^{123}I-FP-CIT radiopharmaceuticals.

2. Our team has developed and validated a new automatic MRI-based quantificational procedure for the assessment of DAT SPECT images [**7**].

3. Comparing the results of the three different quantificational procedures with each other and with a widely-used visual classification, we have proved the high diagnostic capability of all of the four procedure in differentiating Parkinson’s disease and essential tremor.

4. In conclusion it can be stated that our different quantitative assessment methods help and refine the visual interpretation of images and can be applied in the clinical practice and facilitates more accurate stage determination.

6. Works cited in the present thesis

1 Booth, TC, Nathan , M, Waldman, AD, and al. The Role of Functional Dopamine-Transporter SPECT Imaging in Parkinsonian Syndromes, Part 1. *AJNR Am J Neuroradiol* (2015), 36:229-235.

2 EUROPEAN MEDICINES AGENCY. *DaTSCAN ioflupane 123I Product Information. Annex I. Summary of Product Characteristics*.

3 GENERAL ELECTRIC COMPANY. *DaTscan (Ioflupane I123 Injection)for Intravenous Use ,CII Initial U.S.* 2011 (Approval).

4 Darcourt, J, Booij, J, Tatsch, K et al. EANM procedure guidelines for brain neurotransmission SPECT using 123I-labelled dopamine transporter ligands, version 2. *Eur J Nucl Med Mol Imag* (2010), 37:443-450.

5 Perlaki, G, Szekeres , S, Janszky, J, and al. A 123I-FP-CIT SPECT dopamin transzporter képalkotás jelentősége a klinikai gyakorlatban. Összefoglaló cikk. *Ideggyógyászati szemle* (november 2019), 72(11-12):381-388.

6 Benamer, HT, Patterson, J, Grosset, DG, and al. Accurate differentiation of parkinsonism and essential tremor using visual assessment of 123I-FP-CIT SPECT imaging: the 123I-FP-CIT study group. *Mov Disord* (2000), 15:503-510.

7 Perlaki, G, Szekeres, S, Orsi, G, and al. Validation of an automated morphological MRI-based 123I-FP-CIT SPECT evaluation method. *Parkinsonism Relat Disord* (2016), 29:24-29.

8 Suha, B. *Dopamin transzporter funkciójának vizsgálata SPECT/CT-vel az extrapiramidális mozgászavarok differenciál diagnosztikájában*. PTE-ÁOK, 2016.

9 Litvan, I, Bhatia, KP, Burn, DJ, and al. Movement Disorders Society Scientific Issues Committee report: SIC Task Force appraisal of clinical diagnostic criteria for Parkinsonian disorders. *Mov Disord* (2003), 18:467-486.

10 Elble, RJ. Diagnostic criteria for essential tremor and differential diagnosis. *Neurology* (2000), 54(suppl4):S2-S6.

11 Hoehn , MM and Yahr, MD. Parkinsonism: onset, progression and mortality. *Neurology* (1967), 17:427-442.

12 Goetz, CG, Tilley, BC, Shaftman, SR, and al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord* (2008), 23:2129-2170.

13 Horvath, K, Aschermann , Z, Acs, P, and al. Validation of the Hungarian MDS-UPDRS: Why do we need a new Parkinson scale? *Ideggyogy Sz* (2014), 67:129-134.

14 Marshall, VL, Reininger, CB, Marquardt, M, and al. Parkinson's disease is overdiagnosed clinically at baseline in diagnostically uncertain cases: a 3-year European multicenter study repeat 123I-FP-CIT SPECT. *Mov Disord* (2009), 24:500-508.

7. Publications

7.1. Publications related to this thesis

Publications

1. Perlaki, G / **Szekeres, S** ;Orsi, G ; Papp, L ; Suha, B ; Nagy, A, ; Dóczi, T ; Janszky, J ; Zámbó, K / Kovács, N
Validation of an automated morphological MRI-based 123I-FP-CIT SPECT evaluation method
PARKINSONISM AND RELATED DISORDERS 29 pp. 24-29. , 6 p. (2016)

Impakt faktor: 4.484

2. Perlaki, G ; **Szekeres, S** ; Janszky, J ; Dezső, D ; Aschermann, Zs ; Zámbó, K ; Kovács, N
The applicability of 123I-FP-CIT SPECT dopamine transporter imaging in clinical practice
IDEGGYOGYASZATI SZEMLE/CLINICAL NEUROSCIENCE 72(11-12):381-388 (2019)

Impakt faktor: 0.113 (2018)

Lectures, posters

1. G, Perlaki ; **S, Szekeres** ; G, Orsi ; L, Papp ; B, Suha ; E, Schmidt ; P, Bogner ; J, Janszky ; K, Zambo ; N, Kovacs
Visual and automatic assessment of striatal 123I-FP-CIT binding
Neuroimaging Workshop, Szeged, Hungary, 17-18.04.2015.

2. **Szekeres, S** ; Kovács, N ; Orsi, G ; Perlaki, G ; Papp, L ; Suha, B ; Schmidt, E ; Zámbó, K
Datscan vizsgálatok vizuális- és kvantitatív kiértékelésének lehetősége
Hevesy György Magyar Orvostudományi Nukleáris Társaság (MONT) XIX. Kongresszusa, Balatonalmádi, 2015. május 17-19.

3. **Szekeres, S** ; Kovács, N ; Aschermann, Zs ; Orsi, G ; Perlaki, G ; Papp, L ; Suha, B ; Schmidt, E ; Zámbó, K
Az agyi dopaminerg rendszer SPECT/CT vizsgálata (2015)
Magyar Tudományos Parkinson Társaság 2015. évi konferenciája, Budapest, 2015. szeptember 11-12.

4. Perlaki, G ; Zámbó, K ; Aschermann, Zs ; Orsi, G ; Papp, L ; Suha, B ; Schmidt, E ; **Szekeres, S** ; Kovács, N
Az agyi dopaminerg rendszer automatikus kvantitatív és kvalitatív analízise (2015)
Magyar Tudományos Parkinson Társaság 2015. évi konferenciája, Budapest, 2015. szeptember 11-12.

5. **S**, **Szekeres;** N, Kovács; G, Perlaki; G, Orsi; L, Papp; B, Suha; E, Schmidt; K, Zámbó
Importance of different modalities (SPECT/CT, MRI) in the quantative assessment of DaTSCAN findings
28th Annual EANM Congress of European Association of Nuclear Medicine 10-14.10.2015., Hamburg, Germany.

6. **Szekeres, S** ; Kovács, N ; Perlaki, G ; Orsi, G ; Papp, L ; Suha, B ; Schmidt, E ; Zámbó, K
The importance of the visual and quantitave evaluation of DaTSCAN examination the confirmation of advanced stage patient's with Parkinson's disease before Duodopa treatment (2017)
Hevesy György Magyar Orvostudományi Nukleáris Társaság (MONT) XX. Kongresszusa, Budapest, 2017. május 25-27.

7.2. Publications of the author –not closely related to this thesis

Publications

1. Zámbó, K ; Mezősi, E ; Szabó, Zs ; **Szekeres, S** ; Dérczy, K ; Weninger, Cs ; Schmidt, E
A SPECT/CT képalkotás jelentősége a specifikus nukleáris onkológiai vizsgálatokban
MAGYAR ONKOLÓGIA 55 : Suppl. 1 pp. 78-78. , 1 p. (2011).

2. **Szekeres, S** ; Schmidt, E ; Szabó, Zs ; Lengyel, Zs ; Dérczy, K ; Weninger, Cs ; Zámbó, K
Hybrid imaging method in the differential diagnostics of different bone lesions
IME: INTERDISZCIPLINÁRIS MAGYAR EGÉSZSÉGÜGY/INFORMATIKA ÉS MENEDZSMENT AZ EGÉSZSÉGÜGYBEN 10 : 10 pp. 29-34. , 6 p. (2011).

3. Weninger, Cs ; Dérczy, K ; Schmidt, E ; Szabó, Zs; **Szekeres, S** ; Zámbó, K
Kevéssé ismert hibrid képalkotó diagnosztikai módszer: SPECT/CT
BULLETIN OF MEDICAL SCIENCES / ORVOSTUDOMÁNYI ÉRTESÍTŐ 84 : 1. különszám p. 56 (2011).

4. Zámbó, K ; Mezősi, E ; Szabó, Zs ; **Szekeres, S** ; Dérczy, K ; Weninger, Cs ; Schmidt, E
A SPECT/CT módszer diagnosztikus értéke molekuláris onkológiai vizsgálatokban
MAGYAR RADIOLÓGIA 86 : 1 pp. 60-61. , 2 p. (2012).

5. Zambo, K ; Schmidt, E ; Szabo, Z ; Sarkadi, M ; Derczy, K ; **Szekeres, S**
Újdonságok és új lehetőségek a SPECT/CT klinikai alkalmazásában
MAGYAR ONKOLÓGIA 59 : 1 pp. 17-24. , 8 p. (2015).

6. **Szekeres, S** ; Schmidt, E ; Szabó, Zs ; Bán, Zs ; Zámbó, K
Novelties and new potentials in the clinical application of SPECT/CT imaging
JOURNAL OF NUCLEAR MEDICINE AND RADIATION THERAPY 7 : 5 p. 298 , 6 p. (2016).

7. Szujo, S ; Sira, L ; Bajnok, L ; Bodis, B ; Gyory, F ; Nemes, O ; Rucz, K ; Kenyeres, P ; Valkusz, Z ; Sepp, K, **Szekeres, S**, et al.
The impact of post-radioiodine therapy SPECT/CT on early risk stratification in differentiated thyroid cancer; a bi-institutional study
ONCOTARGET 8 : 45 pp. 79825-79834. , 10 p. (2017).

Impakt faktor: 5.168 (2016)

Lectures, posters

1**. Szekeres, S**. ; Schmidt, E. ; Szabó, Zs. ; Zámbó, K
SPECT/CT examination of aspecific MDP cumulations
Hevesy György Magyar Orvostudományi Nukleáris Társaság (MONT) XVI. Kongresszusa, Debrecen, 2009. július 2-4.

2. **Szekeres, S**; Lengyel, Zs ; Dérczy, K ; Weninger, Cs ; Schmidt, E ; Zámbó, K
Hibrid képalkotó eljárások (SPECT/CT,PET/CT) összehasonlítása a csontelváltozások differenciál diagnosztikájában (2011)
Interdiszciplináris Magyar Egészségügy (IME) VI. Képalkotó Diagnosztikai Konferencia, 2011. március 29.

3. **Szekeres, S**. ; Lengyel, Zs. ; Dérczy, K. ; Weninger, Cs. ; Schmidt, E. ; Szabó, Zs. ; Zámbó, K.
Comparing the differential diagnostic value of hibrid imaging techniques (SPECT/CT, PET/CT) in bone lesions (2011)
Hevesy György Magyar Orvostudományi Nukleáris Társaság (MONT) XVII. Kongresszusa, Budapest, 2011. augusztus 25-27.

4. **Szekeres, S**. ; Dérczy, K. ; Weninger, Cs. ; Schmidt, E. ; Szabó, zs. ; Zámbó, K.
Significance of control SPECT/CT examination in identifying the origin of 99mTc-MDP accumulations of unknown etiology in patients with tumor
Hevesy György Magyar Orvostudományi Nukleáris Társaság (MONT) XVIII. Kongresszusa, Pécs, 2013. június 30-július 2.

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