THESES OF PH.D. DISSERTATION

THE ROLE OF FDG PET INVESTIGATIONS IN THE DIAGNOSTICS OF MEDULLARY THYROID CARCINOMA

by

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I. INTRODUCTION

1. Positron Emission Tomography

Today, positron emission tomography (PET) is one of the most modern non-invasive biomedical imaging methods, which effectively helps us study the physiological or pathological conditions of different organs or tissues, determine biological-biochemical parameters of the metabolic processes and localize them anatomically.

Briefly, biologically active molecules labeled with positron emitting isotopes produced in cyclotron are injected into the human body or inhaled by the patient. The equilibrium distribution, which is characteristic of the tracer, has important diagnostic information in practice.

The most frequently used tracer in PET studies with oncological indication is a glucose analogue, the [^{18}F]-fluoro-2-deoxi-D-glucose (FDG). FDG, similarly to glucose, is taken up by the cells and is phosphorylated by hexokinase, but never enters the next steps of glycolysis, because the presence of an O atom at C2 position is necessary for further breakdown. Except in the liver, the activity of glucose-6-phosphatase is very low in human cells, therefore the FDG-6-phosphate accumulates in the cells. Furthermore, this molecule is of highly polar nature, therefore its diffusion through the cell membrane is very slow, thus it gets trapped in the cells. It follows from the above that the intracellular concentration of FDG shows a close relationship with the glucose consumption of the tissue.

Although high FDG uptake may refer to tumorous disease, it is by no means considered a specific sign of tumorous diseases. Inflammatory processes also show increased FDG uptake, which results in false positive findings. There are several so called “benign” processes, such as tuberculosis, sarcoidosis, fungal infections, non-specific granulomas, pancreatitis, abscessus, fractures or acute changes in the tissues following irradiation or surgery.

Over the past decade, PET has become a most valuable and cost-effective method in several oncological indications supported by the fact that there are 8 oncological indications among the PET examinations financed by Medicare in the USA.

Indication / clinical condition	Financing
Solitary Pulmonary Nodules	Characterization
Non-Small Cell Lung Cancer	Diagnosis, staging and restaging
Esophageal Cancer	Diagnosis, staging and restaging
Colorectal Cancer	Diagnosis, staging and restaging
Lymphomas	Diagnosis, staging and restaging
Melanoma	Diagnosis, staging and restaging Non-covered for evaluating regional nodes
Breast Cancer	Diagnosis, staging and restaging, follow-up of therapy
Head and Neck Cancers (excluding central nervous system and thyroid)	Diagnosis, staging and restaging
Myocardial Viability	Covered after inconclusive SPECT result
Refractory Seizures	Covered for pre-surgical evaluation

2. Medullary Thyroid Cancer

Medullary thyroid carcinoma (MTC) originating from the parafollicular cells (C cells) of the thyroid gland is responsible for 5%-12% of all malignant thyroid tumors. Most of the MTC (70-75%) are sporadic. The remainder 25-30% has autosomal dominant inheritance and includes 3 well-defined syndromes: familial MTC (FMTC) and multiple endocrine neoplasia types 2A and 2B (MEN 2A [MTC; phaeochromocytoma; parathyroid hyperplasia or adenoma] and MEN 2B [MTC; phaeochromocytoma and typical stigmata: ganglioneuromatosis in the gastrointestinal tract, marfanoid habit, mucosal neurinomas, colon dysfunction, thickening of the corneal nerve, tooth and bone anomalies]).

Similarly to C-cells, the tumor cells also secrete calcitonin, whose measurement is useful in primary and follow-up diagnostics. In addition, secretion

of other neurohormones (e.g. ACTH hormone, somatostatin, histamine, serotonin, etc.) is also observed.

MTC generally develops in one of the lobes of the thyroid gland at the upper-middle third. In the course of growth, the tumor easily infiltrates the tissue, and, having broken through the first anatomic barrier, the capsule, it spreads to the surrounding tissues. At the same time, similarly to papillary cancers, intraglandular metastases may develop through the rich lymphatic drainage of the thyroid gland. Multifocality can also be caused by the polyclonality of the familial forms.

The regional lymph nodes (LNs) of the thyroid gland are cervical and upper mediastinal ones. The first and most frequently involved region of lymphatic spreading is the central cervical compartment. From here the tumor disseminates to the base of the skull through the lateral cervical compartment on the one hand, and to the upper mediastinum through the pretracheal-paratracheal-paraphryngeal lymphatic chain on the other hand. Lymphatic disseminations are rarely observed in LNs of the submental region, along the accessory nerve or the mammary artery in the mediastinum.

The liver, lung and bones are also involved in the disease due to the hematogenic spread of the tumor cells. In the literature, depending on the form of the disease (familial or sporadic, type of inheritance, early or advanced disease), distant metastases are reported to be 2-33% of the cases at the time of primary staging, while this value is higher through the follow-up, at 45%.

Surgery is a treatment of choice for MTC. Routine lymphadenectomy of the cervico-central compartment as part of thyroidectomy is recommended and widely accepted. It is also accepted that compartments which obviously contain LN metastases should be dissected. LN dissection may be omitted in patients identified with genetic screening, when C-cell hyperplasia is proved histologically from a frozen section of the operation. If reoperation is indicated after the primary care it should at least consist of completion of thyroidectomy and cervico-central lymphadenectomy if not performed previously.

Among non-surgical therapies, treatments performed with different radionuclides (^{90}Y labeled octreotide or radioiodinated anti-CEA monoclonal antibody) or external irradiation by individual consideration may be considered.

^{99m}Tc-pertechnetate thyroid scintigraphy and US of the neck/thyroid gland play a role in the presurgical check-up of MTC. Similarly to other thyroid tumors, MTC is depicted as a cold nodule in one of the lobes on the scintigraphic images. Ultrasonographically a hypo-echogenic solid lesion can be seen in the gland. In contrast with scintigraphy, US investigations inform about the state of the cervical LNs. Additional useful information may be obtained with cervical, chest and abdominal CT or MRI during the staging procedures.

After primary care, elevated serum tumor marker (calcitonin and CEA) levels suggest residual or recurrent tumorous tissue. Furthermore, paraneoplastic symptoms (diarrhea, flush) may occur in 20% of the cases mainly accompanying the marker level elevation or rarely by themselves. It is always a challenge for clinicians to search for tumorous foci. Investigations based on morphology (US, CT, MRI) are usually limited to depicting the shape and structure of the organs. Estimation of LN involvement is also delimited, since LNs of >1 cm in short diameter are considered to be pathologic. However, this differentiation may be deficient, because the dimension of the pathologic LN may be below this size. Beside the structural methods many techniques of nuclear medicine play a role in the detection of metastases, but the relatively bad resolution of the method and the varying tracer accumulations can lead to false negative results. The efficiency of detection of metastases using different radiopharmaceuticals varies generally with low sensitivity.

FDG PET investigations have been used successfully in the follow-up of patients with differentiated thyroid cancer. FDG PET examinations were reported to be a sensitive and specific method in the detection of metastases of papillary, follicular and Hürtle-cell carcinoma of the thyroid in cases with elevated serum thyroglobulin level and negative whole body iodine scintigraphy. There have been

a few studies about PET examinations in MTC patients, all with promising results. According to the low incidence of MTC, the number of patients published was below 20 except for a single study. The authors agreed that PET has a higher sensitivity in the detection of tumorous tissue.

However, there is no single sensitive diagnostic imaging modality for the localization of all metastases in patients with MTC.

II. AIMS OF THE PRESENT STUDY

1. There are few publications about the role of PET in MTC diagnostics. The first studies gave promising results, however only small numbers of patients were included. In our study, results of PET are compared to conventional imaging methods (US, CT, MRI, ^{131}I-metaiodobenzylguanidine [MIBG] whole body scintigraphy) in a large proportion of patients. Based on our results, the relation between elevated tumor marker levels and PET positive findings is also studied.
2. The presence and localization of LN metastases are important prognostic factors. There are macroscopic metastases in the cervical and mediastinal LNs in approximately half of the cases at the time of the primary diagnosis. Since the surgical removal of metastases is the only curative therapy, initial staging is important in drawing up the plan of treatment. The efficiency of PET in preoperative diagnostics is investigated, and the results are compared to those of other imaging methods.
3. We deduce the principles of lymphatic spreading of MTC on the results of PET studies and the patients' history.

III. PATIENTS AND METHODS

1. Patients

88 patients (37 females, 51 males) were included in the study and were divided into 2 groups depending on whether the diagnostic imaging procedures were performed before or after primary care.

Group A (preoperative diagnostics). 17 patients (2 females; 15 males; aged between 12-70 years; mean age ± SD, 34.8 ± 18.3 years) were included in this group, 5 with sporadic and 12 with one kind of hereditary (8 MEN2A, 4 FMTC) form of MTC. Based on genetic screening, now also available in Hungary, 11 of the latter patients were certainly mutant gene carriers. After the diagnostic procedures all but two patients underwent total (n=14) or near-total (n=1) thyreoidectomy with cervico-central lymphadenectomy. Further cervical LN dissection was performed on the left side in 2 patients, on the right side in 1 patient and on both sides in 1 patient. Genetically screened patients underwent prophylactic thyroidectomy to prevent developing MTC and metastatic spreading. The disease was considered inoperable in two cases, only biopsies were performed for histological analysis.

Group B (postoperative diagnostics). After primary care, 71 patients (35 females, 36 males; age at the time of diagnosing MTC ranging between 8-73 years; mean age ± SD, 43.7 ± 14 years) with a history of MTC were analyzed. Among the patients 37 had sporadic diseases, 4 FMTC and 21 MEN 2 (16 MEN 2A and 5 MEN 2B) syndrome. In 2 cases the type of inheritance was not settled. Typization was not done in 7 patients owing to lack of sufficient data. Patients with postoperatively elevated or rising tumor marker levels were included. If these levels were normal in normal range, positive finding of some imaging method (radiology first) or persisting general tumor symptoms were the inclusion criterion. All but 5 patients in group B had undergone total, near-total, or subtotal thyroidectomy, and 45 had undergone LN removal. Sternotomy because of the

atypical localization of the primary tumor in the mediastinum and left or right lobectomy were performed in the exceptional cases. External irradiation was used as supplementary therapy in 43 patients, 9 received ^{131}I-MIBG radionuclide therapy, and 3 had chemotherapy.

2. Tumor Marker Determination

Basal plasma calcitonin level (reference level, <10 pg/ml) was measured by human calcitonin enzyme-linked immunosorbent assay (CIS Bio International, Gif sur Yvette, France) with 2 monoclonal antibodies, and CEA (reference level, <6 ng/ml) was determined by luminometry. The marker levels were assessed postoperatively after 2 months and at 6-month intervals thereafter.

3. Imaging

All diagnostic imaging examinations of the same patient were performed at least 3 months after any therapy. Written consent was obtained from all patients before the start of the procedures.

PET investigations. FDG PET studies were performed with a 4096 Plus scanner (General Electric, Uppsala, Sweden) providing fifteen 2-dimensional sections over an axial field of view of 10 cm. The in-plane resolution was 5.5 mm (full width at half maximum), and the axial resolution was 6 mm. In order to reduce the hindrance of FDG uptake due to physiologic glucose the patients were not allowed to eat or drink food containing carbohydrate for at least 4 hours before the examinations with oncological indication. The patients were also reminded to abstain from major physical activity for 48 hours before the study and to drink enough water hours prior to the examination. Whole body examinations begun 40-60 min after receiving 5.55 MBq/kg (0.15 mCi/kg) FDG in intravenous injection and took 70-90 min from the pelvis to the base of the skull in 7-9 steps of bed movement. The patients were also requested to rest in the 40-60 min period after the injection. The acquired data were reconstructed using in part filtered

backprojection with a Hanning filter and an iterative method. We did not correct for tissue attenuation to spare patients from the extra inconvenience of a lengthy transmission scan.

Radiology. US of the neck was done using an apparatus with high frequency transducers. Native and contrast-enhanced helical CT scanning was performed with a Somatom HR (Siemens, Erlangen, Germany) scanner, with a slice thickness of 5 mm from the base of the skull to the apex of the lung and a slice thickness of 10 mm for the rest of the body. Axial and coronal unenhanced T1-, T2-, and protonweighted images of the neck, chest, and abdomen were obtained with a 1.5-T MRI unit (Magnetom; Siemens) for all patients, excluding 5 individuals with claustrophobia. The T1 axial sequences were repeated after the administration of contrast material.

Isotope diagnostics. In both groups of patients, overlapping multiple planar images of the whole body were obtained for all patients, 48–72 h after the injection of 40 MBq ^{131}I-MIBG. Additional SPECT scans were obtained for some patients. Bone scintigraphy with ^{99m}Tc-MDP carried out routinely or because of suspected bone metastases to supply the diagnostic check-up.

Investigations performed (number of patients) in both group are displayed in the following table.

Imaging	Preoperative staging	Postoperative staging
US	17	60
CT	17	67
MRI	16	47
MIBG	16	65
Bone scintigraphy	3	51
FDG-PET	17	71

4. Interpretation

FDG accumulation with a sharp contour was regarded as pathologic, if physiologic uptake of some organ was ruled out and the accumulation of the lesion

was twice as high as that of the surrounding (background) tissue. LNs of >1 cm in short diameter that were detected by radiological methods were likewise considered to be pathologic. Diffuse or focal tracer uptake different from the physiologic distribution on the isotope diagnostic images was also regarded as pathologic. To determine LN involvement, 9 lymphatic regions were defined: central, left and right cervical regions, left and right supralavicular regions, left and right axillary regions and the mediastinum. The pulmonary hili were bilaterally included in the mediastinum. Less lymphatic regions were taken into account in US and MIBG examinations, 5 (neck and supraclavicular) and 8 (except the central cervical region), respectively. Arrangement of LN abnormalities observed in each investigation was based on this classification.

Frequencies of the affected lymphatic regions were determined on the basis of the data of 58 patients with hypercalcitoninemia during the follow up. Results of PET were taken into account as well as the documentation of primary staging (preoperative investigations, description of surgery and result of histology) in the available documentation of the patients. Based on these findings, involvement-frequencies were calculated for each lymphatic region, which were classified in each region affected or unaffected. Involvement-frequency maps of tumors developing in the left and right lobe of the thyroid were also determined. Involvement of lymphatic regions up to and including primary care and the full history of the patient were studied separately.

IV. RESULTS

1. Preoperative Diagnostics

In the preoperative period of 17 patients, calcitonin levels were in the normal range in 2 cases (2.8 and 4.6 pg/ml) and elevated in 15 cases (range,14-1587 pg/ml; mean: 409,4 pg/ml). US revealed the most foci of MTC in the thyroid

gland; various echogenic foci were observed in 10 patients. CT and MRI identified the primary tumor with ≥5 mm in diameter in 3 and 4 patients, respectively. MIBG scintigraphy yielded diffuse tracer accumulation extended to the whole thyroid gland in 3 cases, 2 of whom had C-cell hyperplasia on histology after the operation. There were also 3 cases with high FDG uptake at the site of the thyroid.

US indicated LNs with suspected metastases in 5 cases, CT in 7 and MRI in 10 patients, which means 8, 18 and 20 lymphatic region involvement, respectively by these methods. Whole body PET scans presumed LN metastases in 9 cases with the sum of 25 regions and excluded tumor spreading in 8 cases. Metastatic origin of the LN accumulation was ruled out by the preceding respiratory viral infection and on the basis of the known natural history of MTC. This was proven by the postoperative negative pathological finding from the cervico-central compartment and the 30-month eventless clinical course with a normal serum calcitonin level. Additionally, LN metastases reported by PET were also precluded by histology in two patients. MIBG scintigraphy was positive in only one case in the mediastinum.

Based on pathological evidence and the follow-up data after the diagnostic check-up, it was US that revealed the location of primary tumor of MTC most accurately (diagnostic accuracy 82%), on the other hand PET detected the LN involvement most correctly (diagnostic accuracy 91%).

Only one patient died (but not in consequence of MTC) during the mean follow-up time of 18 months (range, 6–30 months) in patient group A. All but one patient still alive are free of the disease.

2. Results of Postoperative Check-up

Elevated calcitonin levels (range, 13.6–5,260 pg/ml; mean, 933 pg/ml) were detected in 59 patients, 34 of whom had a CEA level (range, 6.3–1715 ng/ml; mean, 184.5 ng/ml) above the reference range. In the normocalcitoninemic patients (n=12) the CEA level was also normal. Various numbers of involved LNs and other metastases were visualized through the different imaging modalities. Scans

of 62 patients were conclusive with PET, 30 with US, 44 with CT, 40 with MRI and 3 with MIBG. Bone scintigraphy revealed osseous lesions in 8 cases. Involvement of at least one of the lymphatic regions was probable in all PET positive cases, and, in addition, metastases were suspected by high FDG uptake in 9 patients in the liver, 3 cases in the lung and 9 cases in the bone. In the same localization CT and MRI were positive in 38, 13, 10, 2, and 36, 8, 3, 2 cases respectively. All positive US examinations showed lesions in the neck or supraclavicular region. ^{131}I-MIBG planar scintigraphy findings were positive in 3 patients only. The results with this method (2 cervical, 1 mediastinal, and 1 bone lesion) did not add any information to the pieces provided by the other diagnostic examinations.

When PET was compared with anatomic tomographic imaging methods, the differences were clear: PET detected more foci in the neck (56 patients) and the mediastinum (46 patients) than the others did. At the same time, CT provided more positive findings in the organs of hematogenic spreading except for the bones. All the three methods (CT, MRI and PET) detected a breast metastasis. Despite the elevated calcitonin level, PET and the other cross-sectional imaging examinations failed to localize any metastases for 6 patients. Two of them had pathologic foci in the neck with US.

Aspiration cytology or surgical intervention assisted in the verification of PET findings in 17 patients. It should also be noted that not all PET-detected lesions were proven pathologically. Subsequent noninvasive radiological examinations verified the PET results in 20 patients. The objective evidence is still missing in 25 patients; only the persistent elevated tumor marker levels and/or general tumorous symptoms indicate the existence of metastases. Negative PET findings of 3 normocalcitoninemic patients proved to be true during the follow up. Lesion detection with PET is independent of the tumor marker levels.

The data obtained during the follow-up from the initial diagnosis clearly show the relatively benign clinical course of MTC: Only 1 patient died during a mean follow-up of 90 months (range, 12–403 months) in group B.

The lymphatic regions with decreasing involvement-frequency were as follows: any of the cervical regions, mediastinum, supraclavicular regions, axillary and finally abdominal lymphatic region.

V. DISCUSSION

1. PET in Primary Diagnostics

There have been a limited number of studies about PET in preoperative staging. High serum calcitonin concentration and diagnostic imaging may be helpful in assessing the development of MTC and LN metastases.

The primary tumor can be found in the thyroid gland in almost all cases. Physical examination, nuclear medicine techniques and US investigations play a role in its detection. In our series of investigations, US proved to be the most effective technique in localizing the primary tumor (diagnostic accuracy 82%).

It is generally problematic to identify LN metastases. Numerous diagnostic methods were tested but they did not turn out to be applicable because of their low sensitivity. Although selective venous catheterization may correctly identify the highest number of tumorous foci but it is an invasive method and its implementation into primary diagnostic check up is not justified. PET had the best results in determining LN involvement (diagnostic accuracy 91%). FDG PET investigations may help in locating resectable tumor tissue in the neck and mediastinum, and identifying such cases by proving distant metastases when radical surgery is not indicated for the patient. Compartment-oriented microdissection was developed to improve the prognosis of MTC. Some authors suggest both cervico-central and cervico-lateral lymphadenectomy in patients

positive for LN metastases, and they also recommend trans-sternal mediastinal extension of the intervention in cases with cervico-mediastinal involvement. Preoperative staging may render significant help in the operative plan. PET may reveal/confirm or rule out LN involvement in the neck and mediastinum. Detecting distant metastases may reduce the radicality of surgery.

LN staging with FDG PET presents a major problem, i.e. false positivity. Since FDG is a non-specific tumor seeking tracer, its increased accumulation in many non-malignant processes (e.g. inflammation, infection, granulomas, posttherapeutic state, etc.) is observable. The distinction of such conditions from tumors is difficult using simple diagnostic protocols; FDG results turned out to be false positive in 3 cases. In one case massive viral pneumonia induced high tracer accumulation. In the other 2 patients histology ruled out PET findings. Considering the probable spreading of MTC and the case history clarified prior to the examination, most of the questions with false positivity can be answered in many cases.

2. PET in the Follow Up

Postoperative elevated or rising calcitonin and CEA levels often prompt the search for residual or recurrent MTC tissue. Conventional imaging methods (CT, MRI, and MIBG scintigraphy) frequently fail to reveal these tumorous lesions, because each modality has its own limitations. In this study, we compared the findings of conventional diagnostic imaging with those of FDG PET in the investigation and restaging of MTC. Although morphologic investigations detected a higher percentage of pulmonary and hepatic metastases than did FDG PET, FDG PET was superior in detecting LN involvement. We succeeded in identifying metastatic LNs in 59 but 6 investigated MTC patients with elevated plasma tumor marker levels, and the number of detected lesions was higher than that found with any of the other conventional methods. The differences were clear in the cervical, supraclavicular and mediastinal metastases since PET detected 191, 36, 148

lesions, CT detected 54, 6, 52 lesions, while MRI detected 85, 6, 50 lesions in such localization, respectively.

LNs in the cervical and mediastinal regions represent the first lymphatic levels of thyroid cancer. The number of involved cervical LNs identified postsurgically seems surprisingly high, indicating the predominantly incomplete nature of the cervical dissections in the investigated group. It is reported that the incidence of LN metastasis in hypercalcitoninemic patients after primary therapy is 94%. We came to similar results in our study, 87% (62/71) of the patients displayed foci with a high tracer accumulation in at least one of the lymphatic regions.

Generally small pulmonary metastases (<1 cm) detected by CT (and MRI) were not visualized by FDG PET. Data in the literature indicate a low sensitivity of FDG PET for small pulmonary metastases.

A previous study brought up that FDG accumulation is only visualized in cases with rapidly elevating or increased CEA levels. The observation was not supported by our results since each method detected metastases-like lesions independent of CEA levels beside hypercalcitoninaemia in 56 patients in whom all of the diagnostic procedures (PET and structural imaging) were performed. In spite of elevated calcitonin levels no metastases were detected in 6 patients and there were rather small numbers of identified lesions in many cases despite high tumor marker levels.

Many publications report that the plasma calcitonin concentration roughly reflects the tumor burden in MTC patients. However, the frequent discrepancy between the relatively low tumor mass detected and the high tumor marker level in many MTC patients also has long been known. The explanation of this mismatch may lie in the heterogeneity of the tumor cell population and in the decrease in tumor marker expression during dedifferentiation of MTC but it may also be explained by undiscovered small metastases. Medullary thyroid carcinoma belongs in the group of neuroendocrine tumors. It is well documented that the natural

history of these tumors includes pronounced early lymphatic spreading and hepatic dissemination of typical hypervascular lesions supplied by the branches of the a. hepatica propria. Thus, in MTC too, hepatic involvement is expected to be a highly probable phenomenon.

Clearing up the difference between the number of lesions detected and the tumor marker levels/general symptoms indicative of the total tumor mass, other non-invasive procedures (dynamic CT and MRI) were applied. These investigations had higher sensitivity than the conventional methods in detecting liver metastases but the results were still not conclusive in two thirds of the cases. Trying an invasive method, liver angiography, mainly small (2-8 mm) hypervascular foci were identified in 89% of the cases. The incidence rates of LN and liver metastases (94% and 89%, respectively) are surprisingly similar in this cohort. As the incidence of the pathologic involvement of LNs relates to the size of the primary tumor, hepatic dissemination may be predicted by the latter.

With ^{131}I-MIBG scintigraphy, only 3 of the 65 patients investigated had positive scan findings. The limited uptake of this tracer indicated questionable diagnostic value of this method for the detection of recurrent MTC.

The results of this study led us to recommend FDG PET examinations of MTC patients with postoperative elevated plasma tumor marker levels to select patients for secondary surgical intervention. If many LNs are involved, a conservative approach (e.g., external irradiation, radionuclide therapy) may be chosen as the appropriate treatment. Meticulous dissection is recommended in cases of limited dissemination or if some of the LN localizations are unfavorable.

3. Lymphatic Spreading

Lymphatic spread follows the established routes of regional lymphatic drainage that are arranged in distinct compartments. The ipsilateral cervico-central and cervico-lateral compartments were most commonly involved followed by the contralateral cervico-central, mediastinal and contralateral cervico-lateral

compartments in an order of decreasing frequency. Data from the primary staging have led to similar results with the exception of the cervico-central compartment. The explanation for this mismatch may be that central LN removal was not performed in the majority of the cases. In addition, supraclavicular LN metastases are located only on the same side of the primary tumor. Axillary involvement is highly unlikely at the early stages of the disease. Mediastinal involvement comes to the front in advanced disease independent of the primary tumor localization and the difference between lateral compartments is reduced.

Therapists must keep an eye on the lymphatic spreading of MTC when choosing therapy during the follow up, since there is no reason for applying local curative therapy (e.g., repeated LN dissections, external irradiation) presuming an extensive development of LN metastasis. Lymphatic spreading is analogous to the already familiar lymphatic dissemination of Hodgkin's disease. This observation is particularly interesting because two malignancies with different histological type and biological behavior act the same way in lymphatic spreading.

VI. SUMMARY

PET investigations play an important role in the diagnostic check up of many tumors. In the present study, PET was analyzed in detecting metastases from medullary thyroid carcinoma, in preoperative staging and in the follow up. Our results were compared to those of conventional imaging methods.

Fitting PET into the primary diagnostic algorithm, we tried to demonstrate that FDG PET investigations may have an important role in identifying regional LN metastases. Feasibility and efficacy of PET in localizing primary tumor are limited.

After primary care, elevated or rising calcitonin and CEA levels and/or general symptoms of tumor refer to residual or recurrent MTC tissue. PET investigations performed during the follow up detected more tumorous foci than the conventional imaging methods did. The difference was particularly obvious in the cervical, supraclavicular and mediastinal lymphatic regions. No close relationship was observed between measured tumor marker levels and metastases detectable with PET. We established that PET detected only a very small proportion of lung and liver metastases.

Analyzing the involvement-frequencies of the lymphatic regions we pointed out that lymphatic spread followed the established routes of regional lymphatic drainage, which must be considered in both diagnostic examinations and therapy planning.

VII. PUBLICATIONS

1. Publications which the theses were based on

1. **Szakáll S Jr**, Ésik O, Bajzik G, Repa I, Dabasi G, Sinkovics I, Ágoston P, Trón L. 18F-FDG PET Detection of lymph node metastases in medullary thyroid carcinoma. J Nucl Med. 2002;43:66-71 **IF: 4,587**
2. **Szakáll Sz Jr**, Bajzik G, Repa I, Miklovicz T, Dabasi G, Sinkovics I, Ésik O. Recidív medulláris pajzsmirigydaganat metastasisainak FDG-PET-vizsgálata. Orv Hetil. 2002;143(Suppl 3):1280-1283
3. Ésik O, Szavcsur P, **Szakáll S Jr**, Bajzik G, Repa I, Dabasi G, Füzy M, Szentirmay Z, Perner F, Kásler M, Lengyel Z, Trón L. Angiography effectively supports the diagnosis of hepatic metastases in medullary thyroid carcinoma. Cancer. 2001;91:2084–2095 **IF: 3,941**
4. Boér A., **Szakáll S Jr**, Klein I, Kásler M, Vincze B, Trón L. Gődény M, Herzog H, Péter I, Ésik O. FDG PET imaging in hereditary thyroid cancer. Eur J Surg Oncol. 2003:000-000 *(in press)* **IF: 1,392**

2. Abstracts, presentations and posters related with the theses

1. **Szakáll S jr**, Ésik O, Balkay L, Lehel S, Füzy M, Berényi E, Trón L (1998) Role of FDG PET in detection of lymph node metastases of recurrent or residual medullary thyroid cancer. A Magyar Radiológusok Tásaságának XIX. Kongresszus, Pécs, 1998. június 4-6.
2. **Szakáll S jr**, Ésik O, Balkay L, Lehel S, Füzy M, Berényi E, Trón L (1998) Role of FDG PET in detection of lymph node (LN) metastases in residual or recurrent medullary thyroid carcinoma. Joint Congress of the European Assiciation of Nuclear Medicine and the World Federation of Nuclear Medicine and Biology, Berlin, 30 August - 4 September 1998. Eur J Nucl Med. 1998;25:1023
3. Füzy M, Környei J, Vincze B, **Szakáll S jr**. Ésik O. 131-I-MIBG therapy of residual and/or recurrent medullary thyroid carcinoma (MTC). 17th Annual ESTRO Meeting, Edinburgh, 20-24 September 1998. Radiother Oncol. 1998;48(Suppl l):S42
4. **Szakáll S jr**, Trón L, Lehel S, Füzy M, Berényi E, Ésik O. Role of FDG PET in detection of lymph node (LN) metastases of residual or recurrent medullary thyroid carcinoma (MTC). 17th Annual ESTRO Meeting, Edinburgh, 20-24 September 1998. Radiother Oncol. 1998;48(Suppl l):S131
5. **Szakáll Sz jr**, Trón L, Balkay L, Lehel Sz, Füzy M, Berényi E, Ésik O. A PET szerepe a pajzsmirigy medulláris carcinomája (MC) regionális

nyirokcsomó-áttéteinek kimutatásában. A Magyar Belgyógyász Társaság 37. Nagygyűlése, Budapest, 1998. november 19-21. Magyar Belorvosi Archivum 1998;51(Suppl 3):304

6. Füzy M, Vincze B, **Szakáll Sz jr**, Ésik O. 131-I-MIBG therapy of residual and/or recurrent medullary thyroid carcinoma (MTC). Magyar Sugárterápiás Társaság 4. Kongresszusa, Szombathely, 1999. május 15-16.
7. **Szakáll Sz jr**, Repa I, Dabasi G, Füzy M, Ésik O, Trón L. Recidív medulláris pajzsmirigydaganat metasztázisainak FDG-PET vizsgálata. „Ötéves a Magyar PET Program", Debrecen, 1999. szeptember 22.
8. Bajzik G, Repa I, Szavcsúr P, **Szakáll Sz Jr**, Trón L, Ésik O (2000) Dinamikus CT és MR vizsgálatok pajzsmirigy medullaris carcinomás betegek májáttéteinek kimutatásában. Első Magyar Pajzsmirigyrák Konszenzus Konferencia, Budapest, 2000. március 16-17.
9. **Szakáll Sz Jr** (2000) PET. Első Magyar Pajzsmirigyrák Konszenzus Konferencia, Budapest, 2000. március 16-17.
10. **Szakáll Sz jr**, Bajzik G, Dabasi G, Füzy M, Mikecz P, Kálvin B, Trón L, Ésik O. Pozitron emissziós tomográfia (PET) a medullaris pajzsmirigyrák áttéteinek kimutatásban. A Magyar Endokrinológiai és Anyagcsere Társaság XVIII. Kongresszusa, Lillafüred, 2000. június 8-10. Orvosi Hetil. 2000;141:1267-1268
11. **Szakáll Sz jr**, Bajzik G, Dabasi G, Füzy M, Emri M, Balkay L, Trón L, Ésik O. A medulláris pajzsmirigyrák áttéteinek kimutatása pozitron emissziós tomográfiával. XX. Magyar Radiológus Kongresszus, Debrecen, 2000. augusztus 31 - szeptember 2. Magyar Radiológia. 2000;74(Suppl 1):20
12. Bajzik G, Repa I, Szavcsur P, **Szakáll Sz jr**, Trón L, Ésik O. Dinamikus CT- és MR-vizsgálat medullaris pajzsmirigyrákos betegek májáttéteinek kimutatására. XX. Magyar Radiológus Kongresszus, Debrecen, 2000. augusztus 31 - szeptember 2. Magyar Radiológia. 2000;74(Suppl 1):109
13. Szavcsur P, Bajzik G, Repa I, **Szakáll Sz jr**, Trón L, Ésik O. Májangiográfia: egyetlen érzékeny módszer a medullaris pajzsmirigyrákos betegek májáttéteinek kimutatására? XX. Magyar Radiológus Kongresszus, Debrecen, 2000. augusztus 31 - szeptember 2. Magyar Radiológia. 2000;74(Suppl 1):110
14. **Szakáll Sz jr**, Márián T, Lengyel Z, Kálvin B, Trón L, Ésik O. The lymphatic spreading of medullary thyroid carcinoma follows a strong cervico-mediastinal orientation. 19th Annual ESTRO Meeting, Istanbul, 19-23 September 2000. Radiother Oncol. 2000;56(Suppl 1):S161
15. Bajzik G, Repa I, Szavcsur P, **Szakáll Sz jr**, Trón L, Ésik O. Dinamikus CT- és MR-vizsgálatok pajzsmirigy medullaris carcinomás betegek májáttéteinek kimutatásában. A Magyar Belgyógyász Társaság XXXVIII. Nagygyűlése, Budapest, 2000. november 16-18. Magyar Belorvosi Archivum, 2000;53(Suppl 3):59

16. **Szakáll Sz jr**, Bajzik G, Dabasi G, Füzy M, Mikecz P, Trón L, Ésik O. Pozitron emissziós tomográfia (PET) a medullaris pajzsmirigyrák áttéteinek kimutatására. A Magyar Belgyógyász Társaság XXXVIII. Nagygyűlése, Budapest, 2000. november 16-18. Magyar Belorvosi Archivum. 2000;53:(Suppl 3)144
17. **Szakáll Sz jr**, Bajzik G, Dabasi G, Sinkovics I, Mikecz P, Kálvin B, Balkay L, Ésik O, Trón L. Medullaris pajzsmirigyrák áttéteinek kimutatása pozitronemissziós tomográfiával. A Magyar Orvostudományi Nukleáris Társaság XII. Kongresszusa, Gyula, 2001. április 18-20. Magyar Radiológia. 2001;75(Suppl):11
18. **Szakáll Sz jr**, Galuska L, Trón L, Ésik O. Medullaris pajzsmirigyrákban a lymphatikus disszemináció a Hodgkin-kórra jellemző terjedés útvonalát mutatja. A Magyar Sugárterápiás Társaság 5. Kongresszusa Nyíregyháza, 2001. június 15-16.
19. **Szakáll Sz jr**, Galuska L, Trón L, Ésik O. A medullaris pajzsmirigy (thyroid) carcinoma (MTC) és a Hodgkin-kór lymphogen terjedése analóg. Magyar Onkológusok Társaságának XXIV. Kongresszusa, Budapest, 2001. november 22-24. Magyar Onkológia. 2001;45:304

3. Other publications

1. Trón L, Ésik O, Borbély K, Clemens B, Csernay L, Csépány T, Csiba L, Degrell I, Halász P, Holló A, Illés Á, Kollár J, Kőszegi Z, Németh Gy, Novák L, Nyáry I, Pávics L, Sikula J, **Szakáll Sz**, Gulyás B és a PET Munkacsoport tagjai. Első hazai tapasztalatok pozitron emissziós tomográfiás (PET) vizsgálatokkal. Orv Hetil. 1997;138:259-269
2. Kőszegi Zs, **Szakáll Sz**, Trón L, Hegedüs I, Édes I, Péterffy Á. Nagy kockázatú koszorúér bypass műtét eredményességének előrejelzése pozitron emissziós tomográfiával. Orv Hetil. 1997;138:1691-1693
3. Csépány T, Gulyás B, Trón L, **Szakáll Sz**, Kiss E, Kollár J, Sikula J, Szegedi Gy, Csiba L. Agyi pozitron emissziós tomográfiai vizsgálatok systemás lupus erythematosusban. Orv Hetil. 1997;138:1947-1952
4. Trón L, Ésik O, Kovács Z, Sarkadi É, Galuska L, Balkay L, Emri M, Molnár T, **Szakáll Sz jr**, Tóth E, Márián T. ^{11}C-metionin: hatékony radiofarmakon az alacsony proliferatív kapacitású daganatok PET-vizsgálatához. Orv Hetil. 1997;138:2107-2112
5. **Szakáll S**, Boros I, Balkay L, Emri M, Fekete I, Kerényi L, Lehel S, Márián T, Molnár T, Varga J, Galuska L, Trón L, Bereczki D, Csiba L, Gulyás B. Cerebral effects of a single dose of intravenous vinpocetine in chronic stroke patients: a PET study. J Neuroimaging. 1998;8:197-204 **IF: 0,935**

6. Galuska L, Felszeghy E, **Szakáll Sz**, Garai I, Trón L. Spongioblastoma kimutatása különböző nukleáris medicinai módszerekkel. Pediáter. 1998;7:7-9
7. Ambrus E, Kuncz Á, Jánoki Gy, Vörös E, **Szakáll Sz**, Balkay L, Emri M, Trón L, Bodosi M, Csernay L, Pávics L. Agydaganatok természetének vizsgálata nukleáris medicinai módszerekkel. Orv Hetil. 1999;140:1979-1983
8. Ésik O, Bodrogi I, Dóczi T, Fekete S, Galuska L, Kálvin B, Kásler M, Kubinyi K, Lengyel Z, Losonczy H, Nyáry I, Rácz K, Rosta A, **Szakáll Sz jr**, Szentirmay Z, Sziklai I, Vitéz Á, Trón L. A pozitronemissziós tomográfia a korszerű onkológiai ellátás hatékony eszköze. Orv Hetil. 1999;140:2555-2562
9. Liptai Z, Barsi P, **Szakáll Sz**, Krivácsy P. Meningitis basilaris. Pediáter. 2000;9:49-51
10. Udvaros I, **Szakáll S**, Oberna F, Pólus K, Ésik O, Trón L, Kásler M. Pozitronemissziós tomográfia a fej-nyaki tumorok diagnosztikájában. Magyar Onkológia. 2001;45:169-172
11. Gulyás B, Bönöczk P, Vas Á, Csiba L, Bereczki D, Boros I, **Szakáll Sz**, Balkay L, Emri M, Fekete I, Galuska L, Kerényi L, Lehel Sz, Márián T, Molnár T, Varga J, Trón L. Egyszeri vinpocetin-infúzió agyi anyagcserére gyakorolt hatásának vizsgálata territoriális típusú ischaemiás stroke-ot szenvedett betegeken. Orv Hetil. 2001;142:443-449
12. Papós M, Takács T, Trón L, Farkas G, Ambrus E, **Szakáll S**, Lonovics J, Csernay L, Pávics L. The possible role of F-18 FDG positron emission tomography in the differential diagnosis of focal pancreatic lesions. Clin Nucl Med. 2002;27:197-201 **IF: 0,502**
13. Kálvin B, Fekésházy A, Lengyel Zs, **Szakáll Sz jr**, Ágoston P, Lengyel E, Székely J, Galuska L, Trón L, Ésik O. Költség-hatékony onkológiai PET-vizsgálatok. Magyar onkológia 2002;46:203-223
14. Kőszegi Zs, Galuska L, **Szakáll Sz jr**, Lehel Sz, Fülöp T, Édes I, Balkay L. A metabolikus PET-vizsgálatok helye a kardiológiai képalkotó eljárások között. Orv Hetil. 2002;143(Suppl 3):1314-1316
15. Halász P, Neuwirth M, Mikecz P, **Szakáll Sz jr**, Emri M, Zelei Zs, Trón L. (2002) A PET helye az epilepsziás agyi működészavar meghatározásában. Orv Hetil. 143(Suppl 3):1298-1301
16. Hunyadi J, **Szakáll Sz jr**, Gilde K, Bégány, Ágnes, Ésik O, Trón L, Galuska L, Ócsai Henriette, Török L. A PET jelentősége a melanoma malignum diagnosztikájában. Orv Hetil. 2002;143(Suppl 3):1272-1275
17. Degrell I, Berecz R, Glaub T, Lengyel Zs, Égerházi Anikó, **Szakáll Sz jr**, Trón L. A pozitronemissziós tomográfia pszichiátriai alkalmazása. Orv Hetil. 2002;143(Suppl 3):1311-1314
18. Papós M, Takács T, Pávics L, Farkas Gy, Ambrus E, **Szakáll Sz jr**, Lonovics J, Csernay L, Trón L. Az FDG-PET-vizsgálat értéke a pancreascarcinoma diagnosztikájában. Orv Hetil. 2002;143(Suppl 3):1283-1286

19. Udvaros I, **Szakáll Sz jr**, Mikecz P, Oberna F, Pólus K, Ésik O, Kásler M, Trón L. Fej-nyaki tumorok daganatkiújulásának megítélése pozitronemissziós tomográfia alkalmazásával. Orv Hetil. 2002;143(Suppl 3):1278-1280
20. Kálvin B, Fekésházy A, Lengyel Zs, **Szakáll Sz jr**, Ágoston P, Lengyel E, Székely J, Várady E, Galuska L, Trón L, Ésik O. Költséghatékony onkológiai PET-vizsgálatok. Orv Hetil. 2002;143(Suppl 3):1255-1261
21. Galuska L, **Szakáll Sz jr**, Emri M, Oláh R, Varga J, Garai I, Kollár J, Pataki I, Trón L. PET- és SPECT-vizsgálatok autista gyermekeken. Orv Hetil. 2002;143(Suppl 3):1302-1304
22. Kálvin B, Márián T, Galuska L, **Szakáll Sz jr**, Géczi L, Ésik O, Trón L, Bodrogi I. Pozitronemissziós tomográfia a malignus heredaganatok vizsgálatában. Orv Hetil. 2002;143(Suppl 3):1286-1289
23. Lengyel Zs, Fekésházy A, Kálvin B, Galuska L, **Szakáll Sz jr**. Standard PET-vizsgálati protokollok. Orv Hetil. 2002;143(Suppl 3):1243-1248