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Original

Clinical application of SPECT-CT with ^{99m}Tc-Tektrotyd in bronchial and thymic neuroendocrine tumors (NETs)

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Abstract

Neuroendocrine tumors (NETs) of the thorax including bronchial and thymic tumors belong to foregut NETs. Limited loco-regional thoracic NETs can be resected with surgery, but in extensive metastatic disease the treatment is mainly palliative. A high incidence and density of somatostatin receptors (SSTR2, SSTR3, and SSTR5) are found in thoracic NETs. The purpose of this study was to evaluate the role of SPECT-CT somatostatin receptor scintigraphy (SRS) with ^{99m}Tc-Tektrotyd for imaging, staging and follow up of patients with bronchial and thymic neuroendocrine tumors.

Forty-one patients with thoracic tumors with neuroendocrine differentiation were studied. Sixty-eight examinations including SPECT-CT studies of the neck and chest and/or abdomen and pelvis were carried out 2–4 hrs. post i.v. administration of average 740 MBq activity dose of ^{99m}Tc-EDDA/HYNIC-TOC (Tektrotyd, Polatom). In all 41 investigated patients we obtained 81.25% (13/16), 88% (22/25) and 85.36% (35/41) of sensitivity, specificity and accuracy of this diagnostic approach, respectively. Somatostatin-receptor scintigraphy correctly identified all primary NETs located in the lungs and thymus. SPECT-CT studies with ^{99m}Tc-EDDA/HYNIC-TOC resulted in exact pre-surgical and pre-treatment N/M staging of bronchial and thymic NETs, except 2 cases with multiple hepatic metastases and 1 with massive suprarenal metastasis. It can be concluded that SPECT-CT with ^{99m}Tc-EDDA/HYNIC-TOC is a valuable tool for staging and follow-up of patients with thoracic NETs.

KEY words: Thymic neuroendocrine tumors, bronchial neuroendocrine tumors, ^{99m}Tc-EDDA/HYNIC-TOC, SPECT-CT

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Introduction

Neuroendocrine tumors (NETs) of the thorax including bronchial and thymic tumors belong to foregut NETs. Carcinoid bronchial tumors are an uncommon group (2%) of all lung neoplasms and approximately 20–30% of all NETs, developing from neuroendocrine enterochromaffin or Kulchitsky cells, located in the bronchial mucosa [1–3]. Primary neuroendocrine tumors of the thymus account for less than 5% of all anterior mediastinal neoplasms and 2% of thymic lesions [4–6]. Bronchial NETs are classified according to the grade of biological aggressiveness (G1–G3) and the extent of tumor cell differentiation (well-differentiated/ poorly-differentiated). The well-differentiated neoplasms comprise typical (G1) and atypical (G2) carcinoids. Large-cell neuroendocrine carcinomas as well as small-cell carcinomas (G3) are poorly differentiated [1, 2]. Primary neuroendocrine thymic tumors were recognized for the first time in 1972 by Rosai and Higa [7]. Moran and Suster indicated that thymic neuroendocrine carcinomas are closely related neuroendocrine neoplasms that can display a variable spectrum of differentiation. They also highlighted the generally more aggressive nature of these tumors when arising in mediastinal location [8]. These tumors can be divided adequately based on their histopathologic features into well-differentiated, moderately differentiated, and poorly differentiated neoplasms [6, 8].

Limited loco-regional thoracic NETs can be resected with surgery, but extensive metastatic disease is mainly treated palliatively. Patients with carcinoid and/or paraneoplastic syndromes caused by advanced thoracic NETs should be treated individually in order to control hormonal oversecretion and to improve their quality of life [1, 2, 4]. Serum markers such as chromogranin A (CgA) and neuron specific enolase (NSE) are important additional tools for follow up of NETs patients [1, 2]. Except the histological classification, the assessment of other parameters is critical for correct staging according Union for International Cancer Control, UICC, 7th TNM-classification [1, 2, 4]. A high incidence and density of somatostatin receptors (SSTR2, SSTR3, and SSTR5) are found in thoracic NETs [9, 10]. Several somatostatin analogs with high affinity to these receptors have been developed for diagnosis and

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therapy [11–17]. According to the ENETS recommendations 2015, the functional hybrid PET-CT and SPECT-CT imaging modalities with radiolabeled somatostatin analogs has important role in diagnosis, staging and follow up of patients with bronchial and mediastinal NETs, since these methods are more specific than conventional imaging techniques especially for typical and atypical carcinoids [2]; somatostatin-receptor SPECT-CT/PET-CT studies can also predict the response to peptide receptor radionuclide therapy (PRRT) [1, 2]. Recently, the somatostatin receptor scintigraphy (SRS) technique SPECT-CT with ^{99m}Tc-EDDA/HYNIC-TOC (^{99m}Tc-Tektrotyd, Polatom) has been approved in Bulgaria for diagnostics of NETs [18–20]. This tracer has high affinity to SSTR2 and lower to SSTR3 and SSTR5. Optimal physical parameters and biodistribution of ^{99m}Tc-labelled somatostatin analog, lower physiological uptake in the liver and bowel, lower radiation burden and one-day imaging protocol are its advantages over ^{111}In-pentetreotide [19, 20]. Fusion SPECT-CT images improve image quality, anatomical localization, morphological characteristics of scintigraphic "hot" spots and provide differential diagnosis of the most uncertain lesions, reducing false positive and false negative results and thus improving specificity and accuracy of somatostatin-receptor SPECT studies [19, 20].

The purpose of this study was to evaluate the role of SPECT-CT somatostatin-receptor scintigraphy with ^{99m}Tc-^{99m}Tc-EDDA/HYNIC-TOC for imaging, staging and follow up of patients with bronchial and thymic neuroendocrine tumors.

Material and methods

Forty-one patients, (27 males/14 females) with neuroendocrine bronchial and thymic tumor differentiation: 50–100% positive-staining tumor cells were studied during the period June, 2012–June 2016:

— with large-cell neuroendocrine carcinomas;
— with small-cell neuroendocrine carcinomas — SCLC;
— 5 with lung carcinoids (typical and atypical);
— with thymic NETs;
— with metastatic lesions from tumor with unknown primary origin (UPO), expressed neuroendocrine markers, suspected for lung neuroendocrine origin.

Patients were referred to SRS SPECT-CT because of the clinical, radiological and/or biochemical suspicion of thoracic NETs. Plasma chromogranin A (CgA) level was measured. Thirty-six patients underwent somatostatin-receptor scintigraphy for initial staging, whereas 5 patients with metastatic neuroendocrine lesions with UPO were examined in order to visualize location of primary bronchial NET. Immunohistochemistry with commonly used neuroendocrine markers such as chromogranin A, synaptophysin, TTF1 and CD56 was performed in all 41 patients after surgical treatment or bronchoscopy. Proliferation index Ki67 was established for differentiation of low-grade (G1, G2) versus high-grade (G3) NETs. Fifteen patients, in whom the locally advanced and metastatic disease was found, were followed up by control SRS SPECT-CT during therapy with cold somatostatin analogs. During the follow up patients were examined after 4 weeks of withdrawal of "cold" long acting somatostatin analog, if applicable.

Sixty-eight examinations including SPECT-CT studies of the neck and chest and/or abdomen and pelvis were carried out 2–4 hrs. post i.v. administration of average 740 MBq activity dose of ^{99m}Tc-EDDA/HYNIC-TOC (Tektrotyd, Polatom). SPECT-CT gamma camera Symbia T2, Siemens, was used for topographic localization and morphological substratum of "hot" abnormal foci. Double-head SPECT acquisition included 64 projections, 25 s/projection, matrix 256x256. Low dose CT scanning was performed in the helical mode. Acquisition parameters included settings at 130 KeV; 30 mA; 3–5 mm slice thickness. The images were interpreted based on all other clinical and radiological data.

Results

Primary lung neuroendocrine tumors were visualized in 5 patients with UPO, proven histologically. Primary bronchial and thymic NETs were imaged in all other 36 patients showing intensive tracer uptake, sensitivity of SRS was 100% (Figure 1–3). Correct pre-treatment N and M staging according to the UICC 7th TNM-classification was performed in studied patients. Loco-regional supraclavicular, mediastinal and hilar lymphadenopathy were imaged in 16/41 cases (Figure 1–3). Distant liver, pulmonary, bone and/or suprarenal positive metastatic lesions overexpressing somatostatin receptors were visualized in 15/41 cases, showing a good correlation with increased level of Chromogranin-A (Figures 4 and 5). There was no tracer uptake in the liver multiple secondary lesions in 1 patient with large-cell neuroendocrine bronchial tumors and in 1 with atypical carcinoid, visualized on the CT part of hybrid SPECT-CT images, maybe due to metastatic cell dedifferentiation and insufficient expression of somatostatin receptors (Figure 1). Enlarged suprarenal glands in 1 case were negative because of tumor necrosis. Diagnostic performance of SRS in the studied group is summarized in Table 1. Fifteen patients with locally advanced and extended disease were followed-up after the complex treatment. Somatostatin receptor scintigraphy with ^{99m}Tc-EDDA/HYNIC-TOC was very useful to assess SSTR expression in order to predict an individual response to therapy with somatostatin analogs and thus to plan PRRT in individuals with non-operable thoracic NETs. SPECT-CT studies were performed to evaluate the effect of therapy according to revised RECIST guideline, version 1.1. [21]. Functional imaging results were compared with biochemical markers such as CgA.

— complete therapeutic response after surgical treatment was obtained in 2 patients with locally advanced lung NETs: the negative scan of the thorax was obtained with normalization of CgA level;
— partial response — in 4 pts: ≥ 30% decrease in the sum of the longest diameters of 2 target lesions compared with baseline or disappearance of > 50% of hot spots;
— stable disease — in 6 pts: persistence of one or more lesions and/or the maintenance of decreased tumor marker level of CgA above the basic value (Figure 5);
— progressive disease — in 3 pts: appearance of one or more new lesions and/or unequivocal progression of existing lesions. Local relapse after surgery was observed in one patient (Figure 4). Progression of the disease was observed in 1 case with atypical and in another with large-cell neuroendocrine bronchial tumor, but liver metastases were false negative, imaged only on the CT projection of SPECT-CT study — scheme of chemotherapy was changed. In one case the presence of a malignant tumor did not correlate with biochemical findings — level of CgA was < 100 ng/ml, (normal range 1–100 ng/ml).

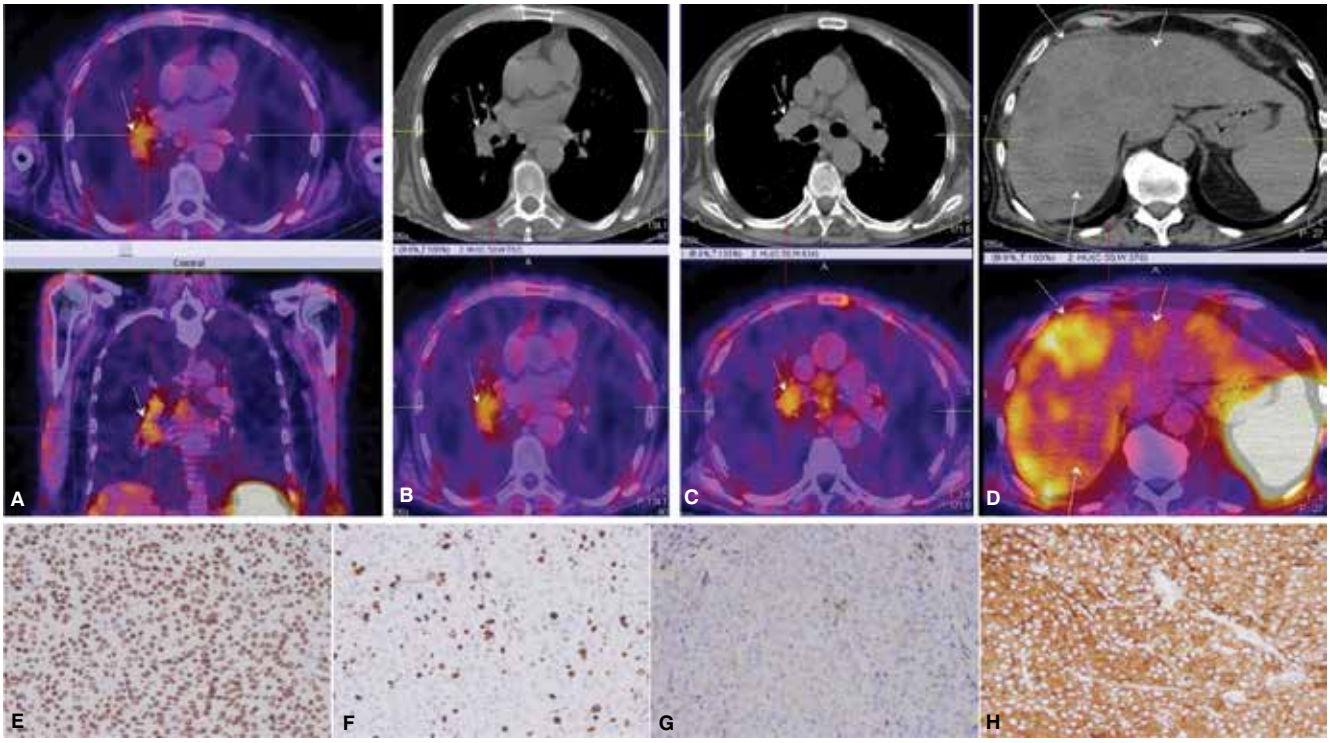


Figure 1. Male (51-year-old), with hepatic meta from NET with UPO. SPECT-CT showed exact topographic location of the primary pulmonary carcinoid in the right lung (**A**) and ipsilateral hilar (**B**) and mediastinal lymphadenopathy (**C**) (N-staging), with intensive tracer uptake, significant of SSTR overexpression. Some of liver mets showed low tracer uptake because of cell dedifferentiation (**D**). Immunohistochemistry confirmed atypical carcinoid (**F**) with synaptophysin (**H**), TTF-1 (**E**) and CD56 (**G**) positive markers

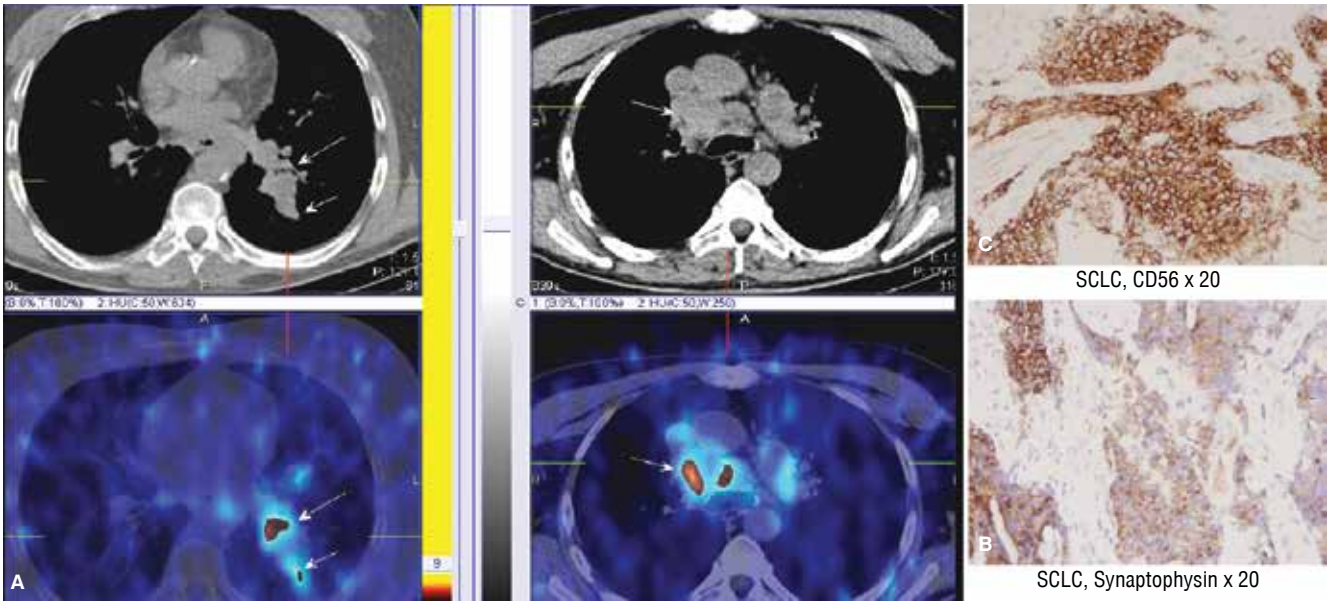
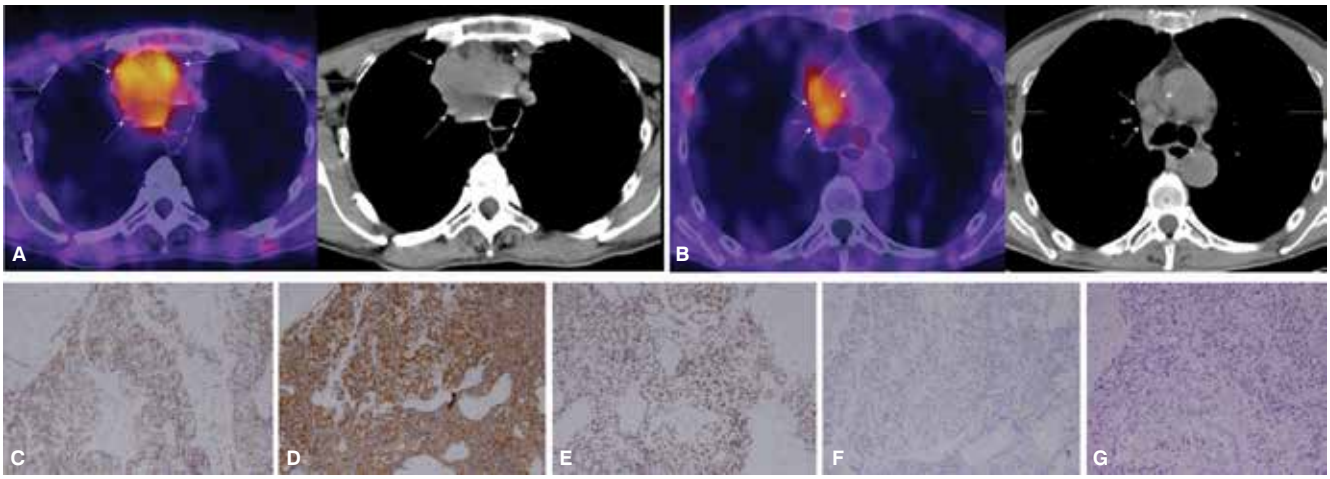


Figure 2. Female (61-year-old). SPECT-CT showed exact topographic location of the primary pulmonary carcinoid in the left lung and bilateral hilar and mediastinal lymphadenopathy (N-staging) with intensive tracer uptake, significant of SSTR overexpression (**A**). Immunohistochemistry confirmed small-cell lung cancer with positive synaptophysin (**B**) and CD56 (**C**) markers

High tracer uptake was observed in 2 benign tumors — in 1 suprarenal adenoma and in 1 thyroid adenoma. In one case positive benign ovary cyst was visualized due to the presence of inflammatory condition (Figure 6). Intensive physiological uptake was shown in the both breasts of 2 young women (< 45-year-old) due to fibrocystic alteration, in 2 pts with accessory spleen and in the region of the pancreatic duct and bowel.



Mediastinal NET, CK7 x 10 | Mediastinal NET, Synaptophysin x 10 | Mediastinal NET, TTF-1 x 10 | Mediastinal NET, CgA x 10 | Mediastinal NET, H&E x 10

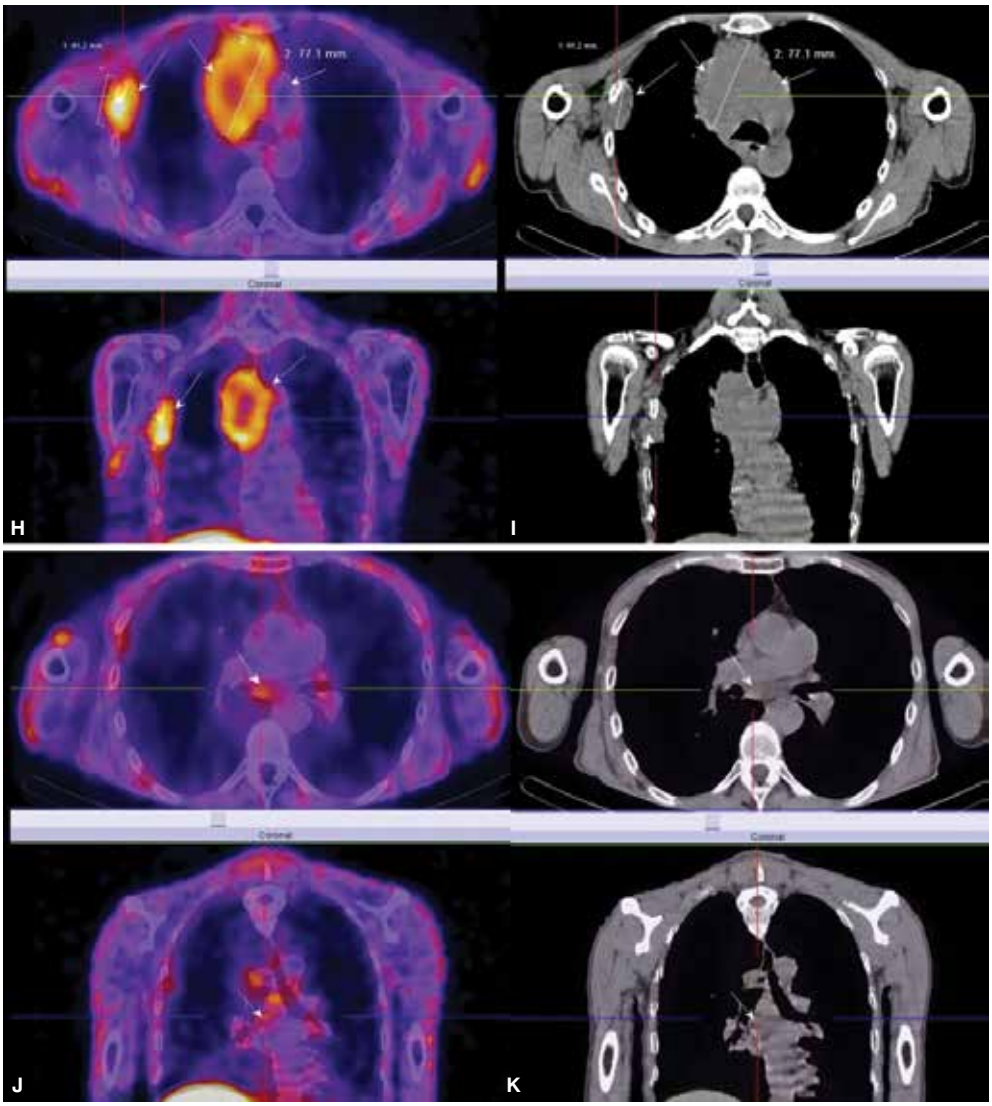


Figure 3. Female (52-year-old), with thymic NET. SPECT-CT showed exact topographic retrosternal location of the primary NET in the anterior mediastinum (**A**) and mediastinal lymphadenopathy (**B**) (N-staging) with intensive tracer uptake, significant of SSTR overexpression. Immunohistochemistry confirmed mediastinal NET, G3 (**G**) with synaptophysin (**D**), TTF-1 (**E**) and CK7 (**C**) positive markers but CgA negative expression (**F**) — typical for low differentiated with high malignancy NETs. 3. Control study 6 month later after chemotherapy in the same patient. SPECT-CT showed enlarged primary thymic tumor with d = 77 mm with central necrotic part without tracer uptake (**H, I**), persistence of mediastinal lymphadenopathy (**J, K**) and new pleural metastatic lesion on the right significant for disease progression

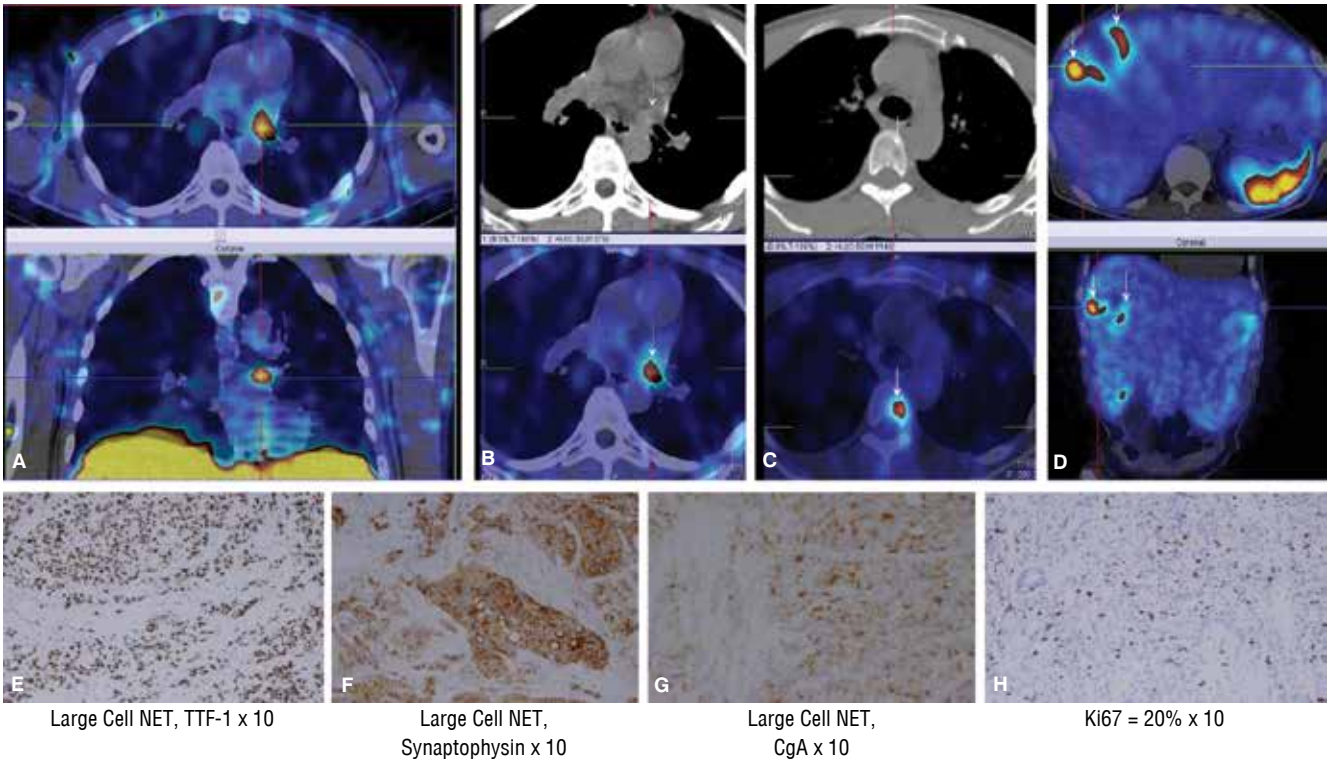


Figure 4. Male (40-year-old), operated due to NET of the left lung with bronchoplasty. In 2013 — hepatic meta from NET proven after biopsy; CgA = 700 ng/ml. SPECT-CT showed relapse in the region of bronchoplasty (**A, B**) with hepatosplenomegaly, 2 lesions in the liver and a lot of bone lesions (**C, D**), overexpressing SSTR. Immunohistochemistry confirmed Large Cell NET with positive TTF-1 (**E**), synaptophysin (**F**) and CgA expression (**G**); Ki67 = 20% (**H**). Chemotherapy and Sandostatin LAR x 30 mg/28 d were considered

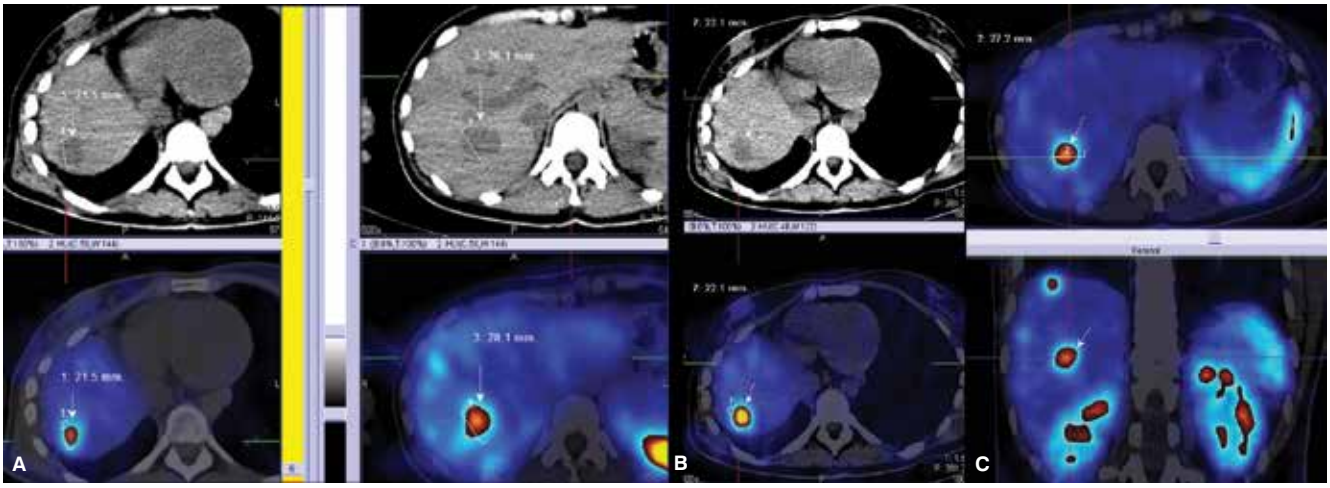


Figure 5. Female (26-year-old), operated due to pulmonary carcinoid; elevated CgA = 177 ng/ml. Control SPECT-CT showed exact topography and size of two secondary hepatic lesions overexpressing SSTR (**A**). Somatostatin-receptor scintigraphy performed after 6 applications of 30 mg/28 d Sandostatin LAR showed the same number, location, size and tracer uptake (**B, C**). CgA = 148 ng/ml — stable disease

In all 41 investigated patients we obtained **81.25% (13/16), 88% (22/25) and 85.36% (35/41) of sensitivity, specificity and accuracy** of this diagnostic approach, respectively.

Discussion

Our data confirmed the published results of other studies that somatostatin receptor scintigraphy correctly identified all primary NETs located in lung and thymus [11, 22]. SPECT-CT studies with ^{99m}Tc-EDDA/HYNIC-TOC resulted in exact pre-surgical and pre-treatment N/M staging of bronchial and thymic NETs, except in one case where total massive bilateral suprarenal metastatic lesions were detected only on the CT part of SPECT-CT images without tracer uptake and in two cases with negative multiple hepatic lesions. These results were described as false negative, probably due to necrotic process and metastatic cell dedifferentiation with

Table 1. Diagnostic performance of SRS in the studied group

SRS Results	Patient No	Lymph node metastases	Liver metastases	Bone metastases	Suprarenal metastases
True positive	13	13	7	6	2
True negative	22	0	0	0	0
False positive	3	3	0	0	0
False negative	3	0	2	0	1

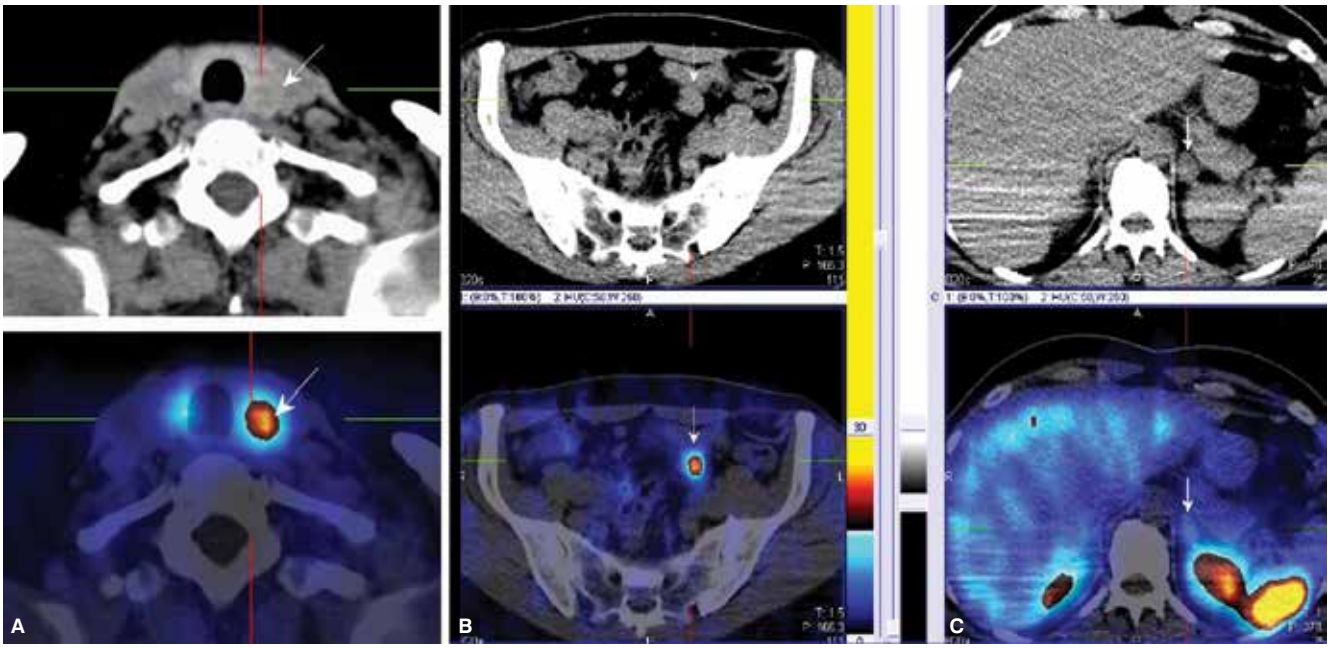


Figure 6. Thyroid adenoma in the left lobe (**A**), positive benign cyst of the left ovary (**B**) and benign adenoma of the left suprarenal gland (**C**) with intensive tracer uptake

absence of somatostatin-receptor expression [10–22]. Positive imaging results concerning benign thyroid adenoma and suprarenal adenoma could be explained with moderate somatostatin-receptor expression, described in some benign tumors and inflammation [10, 22, 23]. Some authors reported that ^{111}In-octreotide scintigraphy failed to identify all liver metastatic lesions maybe because density of somatostatin receptors is much lower in metastatic cells originated from more aggressive histological types of pulmonary NETs such as large-cell neuroendocrine lung cancer [10, 22, 23].

Clinical role of SRS SPECT-CT imaging in patients with NETs can be summarized as follows [1, 19, 20]: (1) Anatomical cross-sectional SPECT-CT data increase specificity and sensitivity of standard somatostatin-receptor scintigraphy because of their excellent spatial resolution and improved imaging quality. (2) SPECT-CT images provide excellent anatomic characterization and localization of the most of unclear scintigraphic "hot" spots in order to differentiate malignant from benign lesions and physiological uptake, and thus improve the diagnostic accuracy of SPECT images with ^{99m}Tc-labeled somatostatin analogs.

In our results, the advantage of SRS SPECT-CT with ^{99m}Tc-^{99m}Tc-EDDA/HYNIC-TOC was to visualize primary bronchial and thymic tumors in case of metastatic lesions from tumor with unknown primary origin and to assess SSTR expression status in order to predict an individual response to therapy with somatostatin analogs and thus effectively plan PRRT in patients with non-operable and metastatic thoracic NETs. However, in the diagnosis of primary NETs the SRS has limited role and might be useful only in selected cases, to depict the most appropriate tumor lesion for correct biopsy in the thorax.

SRS SPECT-CT with ^{99m}Tc-^{99m}Tc-EDDA/HYNIC-TOC was also useful for pre-treatment correct N&M staging of NETs according to the UICC 7th TNM classification, except imaging of liver metastases, and in the follow-up of patients after the treatment: (1) for monitoring of functional and morphological treatment response according to revised RECIST guideline, version 1.1. (Eur J Cancer 2009; 45: 228–247): as complete, partial, stable or progressive disease, (2) for differential diagnosis of malignant lesions from benign tumors and physiological activity especially in the regions below the diaphragm, (3) for early determination of local relapse or recurrence in cases with negative anatomical imaging (CT, MRT) but with clinical and biochemical indications for presence and extent of NETs, (4) for precise topography of metastatic foci in patients with disease extension. However, in patients with negative SRS, PET-CT studies should be performed.

It can be concluded that SPECT-CT with ^{99m}Tc-Tektrotyd is a valuable tool for staging and follow-up of patients with NETs localized in the thorax.

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