

## Research Article

# SPECT-CT Somatostatin-Receptor Scintigraphy in Medullary Thyroid Cancer (MTC)

Sonya Sergieva<sup>1\*</sup>, Mariana Atanasova<sup>2</sup>, Albena Fakirova<sup>3</sup>, Bozhil Robev<sup>4</sup>, and Anna Saint Georges<sup>1</sup>

<sup>1</sup>Department of Nuclear Medicine, Sofia Cancer Center, Bulgaria

<sup>2</sup>Department of Medical Oncology, Central Hospital, Bulgaria

<sup>3</sup>Department of Pathology, Military Medical Academy, Bulgaria

<sup>4</sup>Department of Medical Oncology, UH"St. Ivan Rilsky", Bulgaria

\*Corresponding author

Sonya Sergieva, Department of Nuclear Medicine, Sofia Cancer Center, Bulgaria, Tel: +359 (2) 875 20 99;

Email: sergieva.sonya@yahoo.com

Submitted: 17 April 2017

Accepted: 02 May 2017

Published: 03 May 2017

Copyright

© 2017 Sergieva et al.

OPEN ACCESS

## Keywords

- Thyroid medullary cancer
- Somatostatin-receptor scintigraphy
- <sup>99m</sup>Tc-Tektrotyd
- SPECT-CT

## Abstract

The medullary thyroid cancer (MTC) is a rare neuroendocrine tumour - made up of 5% to 8% of thyroid neoplasms. It arises from the parafollicular, calcitonin-secreting C-cells. The malignantly transformed thyroid C-cells eminent on the surface somatostatin receptors SSTR, based on their neuroendocrine component. During the last decades, the somatostatin receptor scintigraphy with <sup>99m</sup>Tc-EDDA/HYNIC-TOC (<sup>99m</sup>Tc-Tektrotyd, Polatom) has been introduced for imaging of neuroendocrine tumors.

The purpose of this study was to determine the role of SPECT-CT with <sup>99m</sup>Tc-Tektrotyd in patients with MTC.

Twenty one patients, (14 females/7males) with MTC underwent somatostatin-receptor scintigraphy. Three of them were studied for initial pre-operative N/M-staging whereas 18 out of 21 were follow-up after total thyroidectomy. Plasma calcitonin level was measured as a tumor marker. Twenty-nine 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 <sup>99m</sup>Tc-EDDA/HYNIC-TOC (Tektrotyd, Polatom).

Somatostatin-receptor scintigraphy results were true positive in 16 patients, true negative in 5 patients and false positive in 1 case with high tracer uptake in the benign ovary cyst. False-negative results were obtained in 2 cases with positive cervical lymph node metastases but negative small 1-4 mm pulmonary military lesions. Sensitivity of SPECT-CT somatostatin-receptor scintigraphy with <sup>99m</sup>Tc Tektrotyd in the studied group was 88, 8% (16/18); specificity 83, 3% (5/6) and accuracy 87.5% (21/24).

In conclusion our results showed that the main clinical applications of SPECT-CT somatostatin-receptor scintigraphy in MTC are as follows: 1) for pre-treatment correct N/M staging of MTC. 2) For early determination of recurrence/metastases in cases with clinical and biochemical indices for presence and extent of MTC. 3) To assess SSTR expression in order to predict an individual response to therapy if PRRT is considered.

## INTRODUCTION

The medullary thyroid cancer (MTC) is a rare neuroendocrine tumour - made up of 5% to 8% of thyroid neoplasms [1]. It arises from the parafollicular, calcitonin-secreting C-cells, which are distributed diffusely in the thyroid gland, but with highest concentration in the upper parts of both thyroid lobes. Therefore, most often the tumor develops in the apexes of the thyroid, as a solid modular type [1,2]. The MTC progresses slowly, but can spread fairly quickly in the lymph nodes of the neck and ventral upper mediastinum. Distant metastasis develop in the lungs, liver, bones, adrenal glands, and subcutaneously [1,2].

In 75% of the cases it has to do with a sporadic MTC, and in 25% of the cases it's found to be hereditary. The hereditary MTC is most often bilateral and multifocal. There are three familial types: Familial Medullary, Multiple Endocrine Neoplasia types 2A and 2B [1,2]. These forms are linked to a mutation in RET - the proto-oncogene, where the receptor for tyrosine kinase (RTK) is coded. In about 50-60% of the sporadic medullary carcinoma,

the above mentioned mutation is present, which is the basis of the targeted therapy, carried out in this type of disease [3]. Total thyroidectomy is the main method of treatment of MTC. There is a 50-60% chance of curing with such surgical procedure, in early stage diagnosis. In the case of the hereditary forms, without the presence of distance metastases, curing ranges around 90%. Metastatic infiltration of the loco-regional cervical lymph nodes was found in 20-30% of patients with a tumor less than 1 cm, around 50% in patients with a tumor size 1 cm and 4 cm, and 90% of patients with tumors greater than 4 cm [1,3]. That is why a prophylactic bilateral central lymph dissection is performed, particularly at the C5 and C6 level, in the absence of cervical lymphadenopathy. In the presence of enlarged lymph nodes pre-operatively, lateral cervical dissection is performed at the IIA, III, IV and V levels [1,3].

The parafollicular C-cells do not produce the thyroid hormone and therefore, do not enhance the radioiodine. Due to this reason treatment with <sup>131</sup>I is not applied in the case of MTC. The malignant transformed C-cells produce and secrete different peptides, one

of which is calcitonin, considered as a tumor marker for MTC. Patients with serum calcitonin > 150 pg/ml, must be checked for distant metastasis, especially if a total thyroidectomy has been performed [1,3]. Chemotherapy and radiotherapy are not efficient in MTC. Scientific studies have shown better outcomes with the use of tyrosine kinase inhibitors (TKIs), for example Vandetanib, as a targeting therapy in recidivating /metastatic cases of MTC [1,3].

The malignantly transformed thyroid C-cells eminent on the surface somatostatin receptors SSTR, based on their neuroendocrine component. This allows the enrolment of radio labeled somatostatin analogs, for enabling more specific diagnosis and target metabolic brachytherapy - these are the two main components of theranostics (diagnosis and therapy) - a new theory for a personalized diagnostic and therapeutic manner with the neuroendocrine tumors [3-6]. Peptide receptor radionuclide therapy (PRRT) with marked  $^{177}\text{Lu}/^{90}\text{Y}$  - somatostatin analogs, is another alternative in patients with disseminated and advanced MTC, demonstrating a height presence of SSTR [7,8]. MTC visualization, determination of the stage and the extension of the disease, as well as the individual SSTR status play significant role in considering the right therapeutic approach and effective follow-up of these patients. During the last decades, the somatostatin receptor scintigraphy with  $^{99\text{m}}\text{Tc}$ -EDDA/HYNIC-TOC ( $^{99\text{m}}\text{Tc}$ -Tektrotyd, Polatom) has been introduced for imaging of neuroendocrine tumors [9,10]. This radiopharmaceutical has high affinity to over expressed SSTR2 and lower to SSTR3 and SSTR5. Better physical properties and pharmacokinetic parameters of  $^{99\text{m}}\text{Tc}$ -labelled somatostatin analogs, lower physiological uptake in the liver and bowel, respectively higher tumor/background ratio, lower radiation exposition and one-day imaging protocol are its advantages over the widely used  $^{111}\text{In}$ -pentetreotide [9,10]. One of the most up to date nuclear medicine methods in the last years that came into clinical practice is SPECT-CT somatostatin-receptor scintigraphy in endocrine tumors [11].

The purpose of this study was to determine the role of SPECT-CT with  $^{99\text{m}}\text{Tc}$ -Tektrotyd in patients with MTC.

## MATERIAL AND METHODS

Twenty one patients, (14 females/7males; aged 29-81years, mean 52 year-old) with MTC underwent somatostatin-receptor scintigraphy. Three of them were studied for initial pre-operative N/M-staging whereas 18 out of 21 were follow-up after total thyroidectomy with or without cervical lymph node dissection. Immunohistochemistry with commonly used neuroendocrine marker such as calcitonin was performed in all 21 patients after surgical treatment. Plasma calcitonin level was measured as a tumor marker. Twenty-nine 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  $^{99\text{m}}\text{Tc}$ -EDDA/HYNIC-TOC (Tektrotyd, Polatom). SPECT-CT gamma camera Symbia T2, Siemens, was used for topographic localization and morphological identification on scintigraphy with evidence of abnormal lesions. Double-head SPECT acquisition included 64 projections, 30 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, biochemical and radiological data.

## RESULTS

Somatostatin-receptor scintigraphy results were true positive in 16 patients, true negative in 5 patients and false positive in 1 case. In this case there was a high tracer uptake in the benign ovary cyst. False negative results were obtained in 2 cases with positive cervical lymph node metastases but negative small 1-4 mm pulmonary miliary lesions (Table 1).

Initial pre-operative staging showed high tracer uptake in the primary tumor and secondary infiltrated enlarged cervical and supraclavicular lymph nodes in all 3 cases and false negative imaging of multiple small lung metastases in one of them, visualized only on the CT part of the fusion images (Figure 1,2). These results correlated with the high level of serum calcitonin (Table 1). In the group of patients who underwent SPECT-CT exams after surgery, true negative results were obtained in 5 cases after thyroidectomy: 2 cases with residual thyroid tissue images, corresponding to the very low values of the tumor marker. Somatostatin-receptor scintigraphy was positive for tumor persistence in 1 case with locally advanced MTC (Figure 3). In 11 patients local recurrence in the thyroid bed with paratracheal, (Figure 4) and/or retrotracheal localization, (Figure 5) and enlarged cervical, mediastinal and/or supraclavicular lymph nodes, were seen. In two cases with a conglomerate of metastatic cervical lymph nodes, tracer uptake was imaged only in the periphery of the tumor mass due to necrotic process in the central tissue part. Osteolytic bone metastases were described in 2 patients, lung nodules with size more than 10 mm were positive in one patient (Figure 6,7). SPECT-CT study in the region of abdomen identified hepatic metastases in a patient with high background activity in the liver (Figure 7). Plasma levels of calcitonin vary from 94 to 5496 pg/ml in all 13 patients with local recurrence, tumor persistence and/or loco-regional and distant metastases (Table 1).

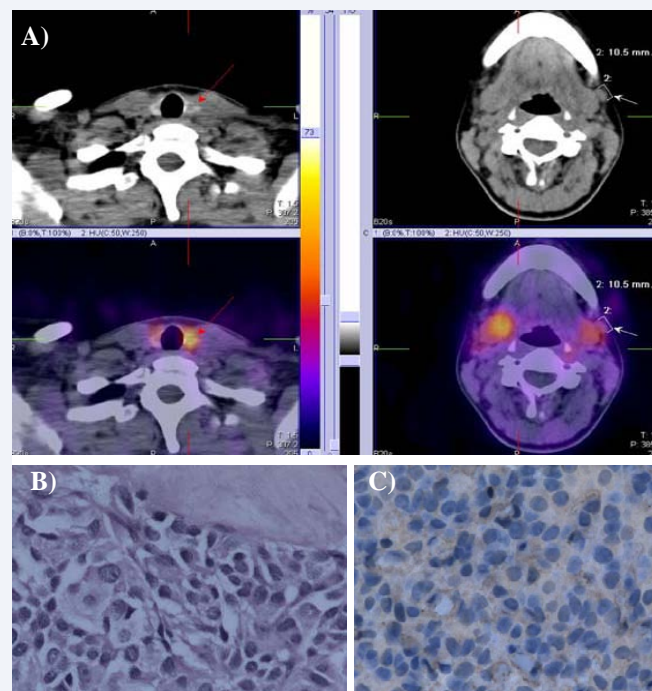
Sensitivity of SPECT-CT somatostatin-receptor scintigraphy with  $^{99\text{m}}\text{Tc}$  Tektrotyd in the studied group was 88, 8% (16/18); specificity 83, 3% (5/6) and accuracy 87.5% (21/24) (Table 2).

## DISCUSSION

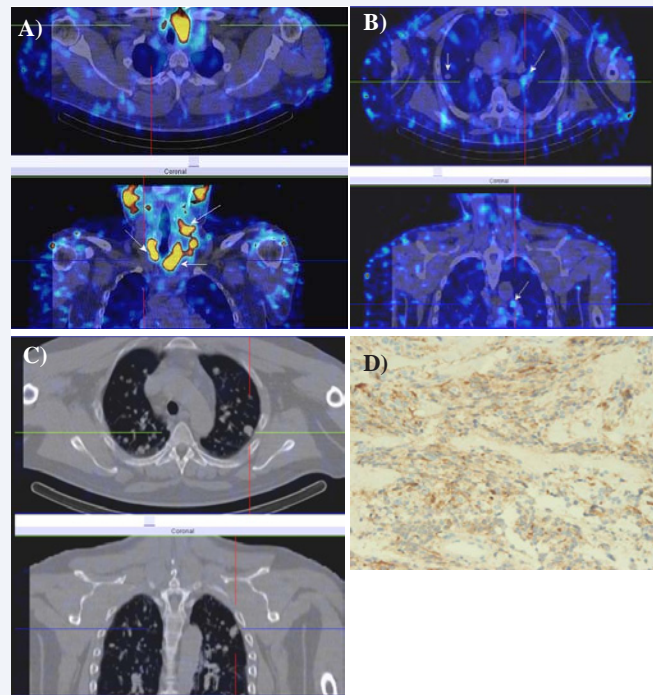
A variety of different radiopharmaceuticals,  $^{99\text{m}}\text{Tc}$ -Sestmibi/Tetrofosmin,  $^{99\text{m}}\text{Tc}$ -DMSA(V),  $^{131}\text{I}/^{123}\text{I}$ -MIBG,  $^{111}\text{In}$ -Octreotide and recently  $^{99\text{m}}\text{Tc}$ -Tektrotyd, have been used in clinical practice, for detection of MTC [3,6,9,10,12]. Czepezyński R. and colleagues have compared the sensitivity, specificity and accuracy of various nuclear medicine techniques to the clinical application of  $^{99\text{m}}\text{Tc}$ -EDDA/HYNIC-TOC [10]. The conclusion of their study was that this  $^{99\text{m}}\text{Tc}$ -labeled somatostatin analogue should be considered the diagnostic method of choice in cases with MTC and increased calcitonin levels in comparison to other useful imaging tracers -  $^{99\text{m}}\text{Tc}$ -DMSA(V),  $^{131}\text{I}$ -MIBG and  $^{111}\text{In}$ -Octreotide, due to the highest established tumor detection rate, respectively sensitivity was 79.5%, specificity 83,3% and accuracy 80.0% [10]. These results were confirmed by Parisella and colleagues [13]. Our data suggested that somatostatin-receptor imaging with  $^{99\text{m}}\text{Tc}$ -EDDA/HYNIC-TOC resulted in correct pre-operative N/M staging of patients with MTC, except in two cases where small military

**Table 1:** Clinical characteristics and imaging results in all 21 patients. Legend: TN- True Negative; TP- True Positive; FP- False Positive; FN-False Negative.

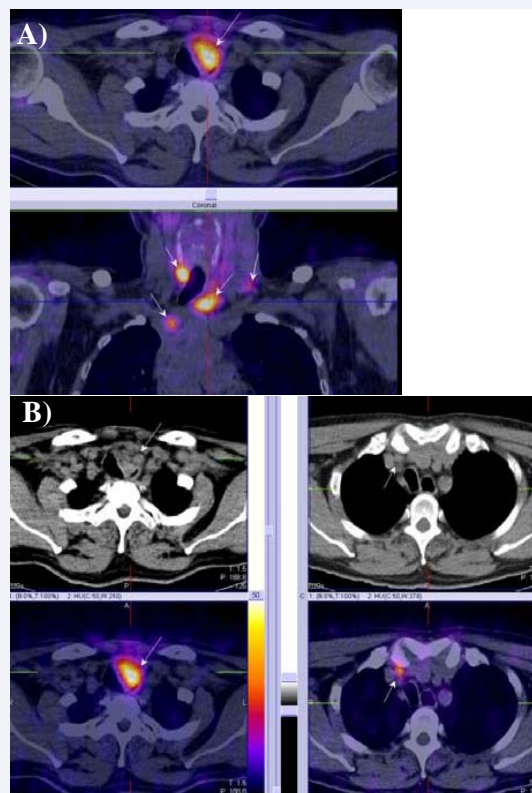
mn- nPPRPa- tient No N	Gander F/M	Age /yr/	Total thyroidectomy	No surgery	Primary/ re- current tumor	Lymph node mets	Bone mets	Lung mets	Liver mets	Calcitonin /pg/ml/
1.	M	71	+	-	TN	TN	-	-	-	0.8
2.	F	55	+	-	TNresidual tissue	TN	-	-	-	1.5
3.	F	64	-	+	TP	TP	-	-	-	308
4.	F	43	+	-	TP	TP	-	-	-	1818
5.	F	47	+	-	TP	TP	-	FN	-	727
6.	F	64	+	-	TN	TN	-	-	-	0.5
7.	M	55	+	-	TNresidual tissue	TN	-	-	-	1.9
8.	F	30	+	-	TP	TP	-	-	-	238
9.	F	33	+	-	TN	TN	-	-	-	2.0
10.	M	50	+	-	TN	TN	-	-	-	1.8
11.	F	54	+	-	TP	TP	-	-	-	94
12.	F	37	-	+	TP	TP	-	FN	-	1174
13.	M	29	-	+	TP	TP	-	-	-	519
14.	M	61	+	-	TP	TP	TP	-	-	1056
15.	F	39	+	-	TP	TN	-	-	-	95
16.	M	72	+	-	TP	TP	TP	TP	TP	5496
17.	F	59	+	-	TP	TP	-	-	-	326
18.	F	45	+	-	TP	TP	-	-	-	213
19.	F	81	+	-	TN	TP	-	-	-	950
20.	M	60	+	-	TP persistence	TP	-	-	-	2012
21.	F	44	+	-	TP	TP	-	-	-	232

**Figure 1** M/29year-old with high level of calcitonin – 519pg/ml. SPECT-CT with  $^{99m}\text{Tc}$ -Tektrotyd was positive for intensive tracer uptake in the tumor formation with mixed solid/cystic structure on the left thyroid lobe with 1 enlarged laterocervical lymph node on the left (A).

Standard H&amp;E histological and immunohistochemical examinations positive for Calcitonin, performed after surgery, confirmed medullary thyroid cancer, x20 (B,C).

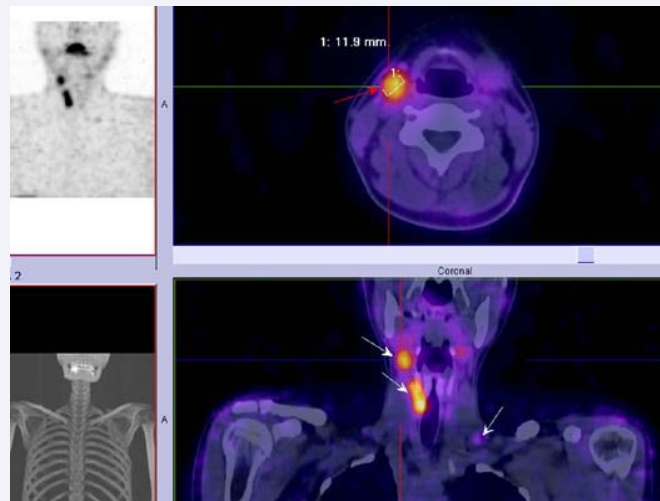


**Figure 2** F/37year-old with high level of calcitonin -874 pg/ml. SPECT-CT with  $^{99m}\text{Tc}$ -Tektrotyd was positive for intensive tracer uptake in the tumor formation of the left thyroid lobe, infiltrated surrounding tissues with laterocervical, supraclavicular and hilar lymphadenopathy (A). SPECT-CT showed a lot of metastatic small miliary lesions in the both lungs without uptake (B,C). Immunohistochemistry confirmed medullary thyroid cancer, positive after surgery for Calcitonin, x20 (D).



**Figure 3** M/60 year-old with MTC after parcial thyroidectomy, cervical lymph node dissection – pT4pN2M0 and increased calcitonin level – 2012pg/ml. SPECT-CT with  $^{99m}\text{Tc}$ -Tektrotyd showed tumor persistence in the region of the left thyroid lobe, trachea deviation to the right and enlarged laterocervical and bilateral supraclavicular lymph nodes with high tracer uptake (A,B).

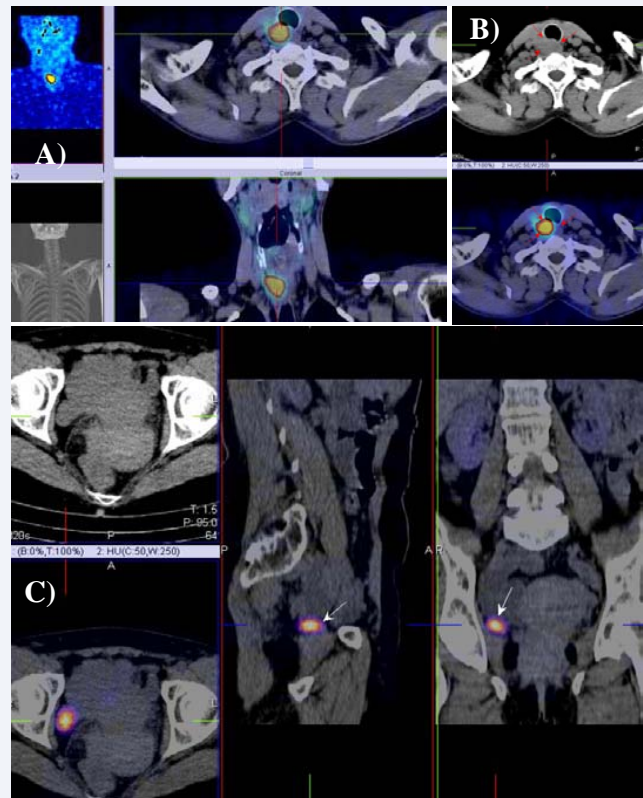




**Figure 4** /54 year-old with MTC after total thyroidectomy with increased calcitonin level – 94pg/ml. SPECT-CT with <sup>99m</sup>Tc-Tektrotyd showed local paratracheal recurrence in the thyroid bed and 1 enlarged laterocervical lymph node on the right and 1 supraclavicular lymph nodes on the left with high tracer uptake (A).

**Table 2:** Diagnostic performance of SPECT-CT somatostatin-receptor scintigraphy (SRS) in the studied group.

SRS Results	Patient No	Primary/ recurrent tumor	Lymph node mets	Bone mets	Lung mets	Liver mets	Ovary mets
True positive	16	14	15	2	1	1	0
True negative	5	0	0	0	0	0	0
False positive	1	0	0	0	0	0	1
False negative	2	0	0	0	2	0	0



**Figure 5** F/39 year-old with MTC after total thyroidectomy with increased calcitonin level – 95pg/ml. SPECT-CT with <sup>99m</sup>Tc-Tektrotyd showed local disease recurrence with intensive tracer uptake and retrotracheal localization (A,B). High activity was imaged in the region of a benign ovary cyst. (C).

lung nodules were detected only on the CT part of SPECT-CT images without tracer uptake. These results were described as false negative, probably due to undetectable size of the lesions and metastatic cell dedifferentiation with insufficiently somatostatin-receptor expression [6,10]. False positive imaging result in one case concerning benign ovary cyst could be explained with moderate somatostatin-receptor expression, described in some benign tumors and inflammation [13,14].

The use of the hybrid SPECT-CT machines in clinical nuclear medicine, optimizes to a great extent the ordinary planar and SPECT somatostatin-receptor imaging. First data from the initial SPECT-CT examinations in patients with thyroid carcinoma - differentiated papillary and medullar types, were published in the Journal of Nuclear Medicine, 1997 by C. Perault and colleagues [15]. The authors have undergone SPECT-CT studies with <sup>131</sup>I and <sup>111</sup>In OctreoScan, respectively in the 2 groups of patients. The main conclusions drawn from this study were that fused CT and SPECT images increased the diagnostic power of each separate imaging modality for detection and localization of thyroid cancer recurrence or metastases and could be of clinical utility in the management and care of the patients [15].

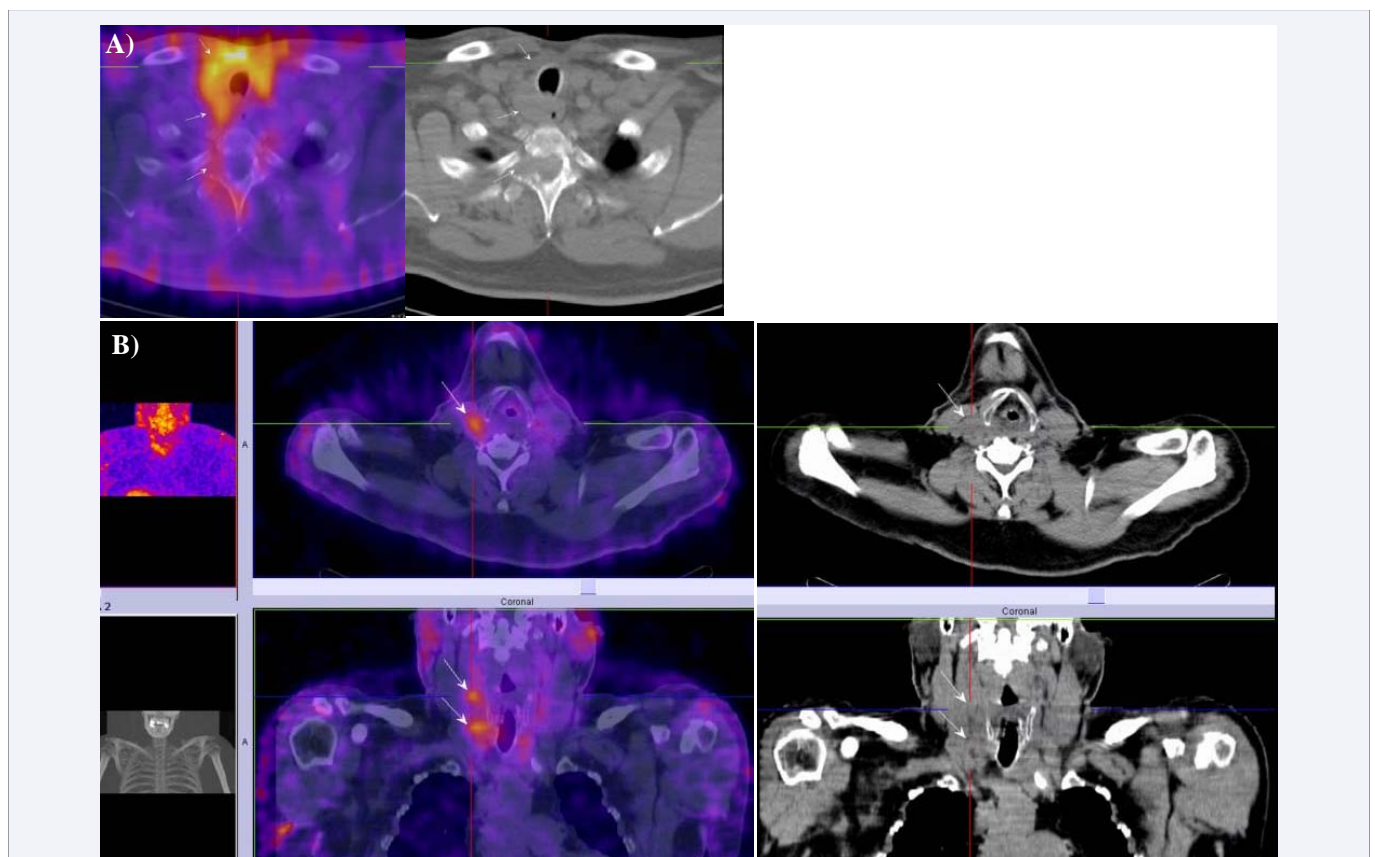
The optimization of the examination quality, due to the imaging attenuation correction, makes the visualization of lesions under 10 mm possible. Fusion SPECT-CT images enable exact topographic localization and morphological

characteristics of the lesions with abnormal enhancement. The precise determination of the physiological activity from pathological tracer uptake improves the diagnostic specificity of the scintigraphic studies. Published data in scientific literature demonstrate that the SPECT-CT imaging technique is more informative and superior in comparison to the planar images 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 [11,12,14].

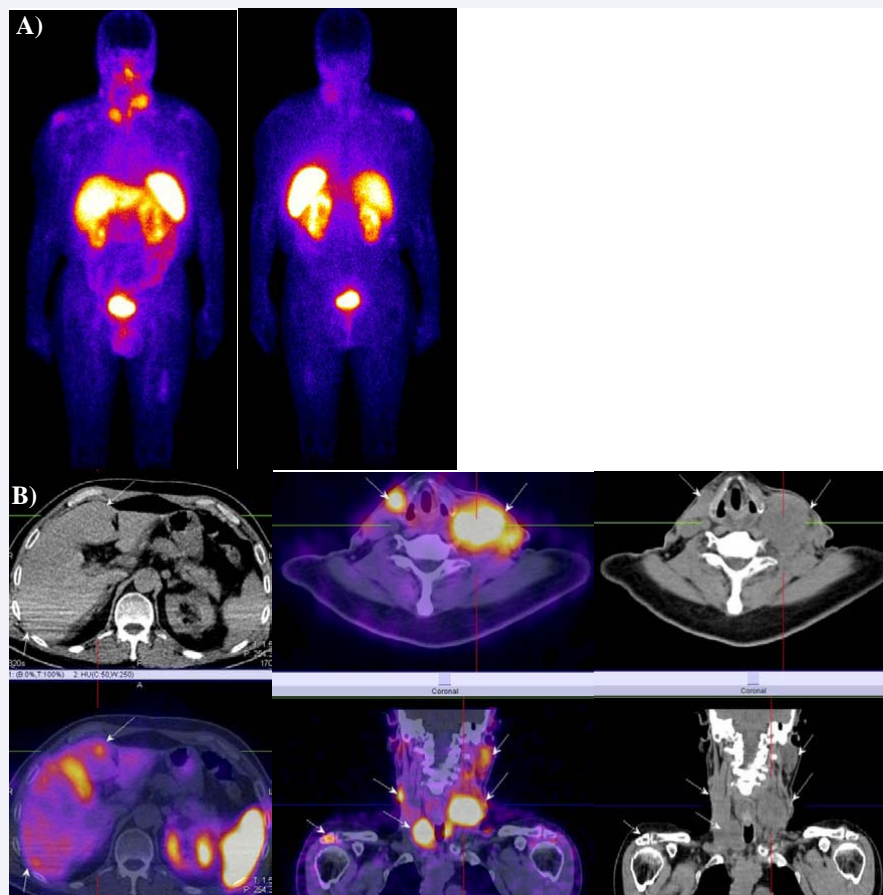
## CONCLUSION

Our results showed that SPECT-CT somatostatin-receptor scintigraphy should be used in the MTC imaging as following:

1. For pre-treatment correct N/M staging of MTC
2. For monitoring of surgical treatment
3. For early determination of recurrence/metastases in cases with clinical and biochemical indices for presence and extent of MTC.
4. For differential diagnosis of proliferative tumor tissue from benign lesions and physiological uptake.
5. For precise topography of metastatic foci in patients with disease extension.



**Figure 6** M/61year-old with MTC after thyroidectomy and increased level of Calcitonin 1056 pg/ml. SPECT-CT with <sup>99m</sup>Tc-Tektrotyd was positive for soft-tissue tumor formation in the thyroid bed with retrotracheal extension(A), significant for local recurrence infiltrated surrounding tissues, laterocervical lymph nodes on the right (B) and secondary osteolytic destruction of Th1 and Th2(A).



**Figure 7** M/72 year-old with MTC after total thyroidectomy and cervical lymph node dissection- pT3pN1aM0 with increased calcitonin level – 5496pg/ml. Whole body scan followed by SPECT-CT with <sup>99m</sup>Tc-Tektrotyd showed exact topographic disease extension in the region of the thyroid bed, bilateral laterocervical, mediastinal and supraclavicular bilateral enlarged lymph nodes, lung secondary lesions, bone metastases in bilateral shoulder joints, left femur, liver metastases with high tracer uptake (A,B)..

6. To assess SSTR expression in order to predict an individual response to therapy if PRRT is considered.

## REFERENCES

- Pacini F, Castagna MG, Brilli L, Pentheroudakis. Thyroid cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2010; 21: v214-219.
- Nikiforov YE, Steward DL, Robinson-Smith TM, Haugen BR, Klopper JP, Zhu Z, et al. Molecular testing for mutations in improving the fine-needle aspiration diagnosis of thyroid nodules. *J Clin Endocrinol Metab.* 2009; 94: 2092-2098.
- Rubello D, Wong KK, Marzola MC, Beheshti M, Ambrosini V, Chondrogiannis S, et al. Evolving paradigms for successful molecular imaging of medullary thyroid carcinoma. *Eur J Nucl Med Mol Imaging.* 2012; 39: 563-568.
- Reubi JC, Caser B. Concomitant expression of several peptide receptors in neuroendocrine tumors: molecular basis for in vivo multireceptor tumour targeting. *Eur J Nucl Med Mol Imaging.* 2003; 30: 781-793.
- Bodei L, Mueller-Brand J, Baum RP, Pavel ME, Hörsch D, O'Dorisio MS, et al. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRT) in neuroendocrine tumours. *Eur J Nucl Med Mol Imaging.* 2013; 40: 800-816.
- Freudenberg L, Eising E, Gorges R, Bockisch A. Somatostatin receptor imaging in recurrent medullary thyroid cancer. *The Internet Journal of Nuclear Medicine.* 2004; 2: 35-42.
- Salavati A, Puranik A, Kulkarni HR, Budiawan H, Baum RP. Peptide Receptor Radionuclide Therapy (PRRT) of medullary and nonmedullary thyroid cancer using radiolabeled somatostatin analogues. *Semin Nucl Med.* 2016; 46: 215-224.
- Makis W, McCann K, McEwan AJ. Medullary thyroid carcinoma (MTC) treated with <sup>177</sup>Lu-DOTATATE PRRT: a report of two cases. *Clin Nucl Med.* 2015; 40: 408-412.
- Decristoforo C, Mather S, Cholewinski W, Donnemiller E, Riccabona G, Moncayo R. <sup>99m</sup>Tc-EDDA/HYNIC-TOC: a new <sup>99m</sup>Tc-labelled radiopharmaceutical for imaging somatostatin receptor-positive tumors: first clinical results and intra-patient comparison with <sup>111</sup>In-labelled octreotide derivatives. *Eur J Nucl Med.* 2000; 27: 1318-1325.
- Czepczyński R, Parisella MG, Kosowicz J, Mikołajczak R, Ziemnicka K, Gryczyńska M, et al. Somatostatin receptor scintigraphy using <sup>99m</sup>Tc-EDDA/HYNIC-TOC in patients with medullary thyroid carcinoma. *Eur J Nucl Med Mol Imaging.* 2007; 34: 1635-1645.
- Bural G, Muthukrishnan A, Oborski M, Mountz J. Improved benefit of SPECT/CT compared to SPECT alone for the accurate localization of endocrine and neuroendocrine tumors. *Mol Imaging Radionucl Ther.* 2012; 21: 91-96.
- De Bonilla-Damia A, Calvo-Moron C, De La Riva-Perez PA, Iglecias-

- Jerez R, Molina-Mora M, Castro-Montano J. Detection by SPECT-CT scan with (99m)Tc-(V) DMSA of bone metastases in patient with medullary thyroid cancer. *Rev Esp Med Nucl.* 2011; 30: 365-367.
13. Parisella MG, Chianelli M, Alessandria CD, Todino V, Mikolajczak R, Papini E, et al. Clinical indications to the use of 99mTc-EDDA/HYNIC-TOC to detect somatostatin receptor-positive neuroendocrine tumors. *Q J Nucl Med Mol Imaging.* 2012; 56: 90-98.
14. Sergieva S, Robev B, Dimcheva M, Fakirova A, Hristoskova R. Clinical application of SPECT-CT with 99mTc-Tektrotyd in bronchial and thymic neuroendocrine tumors (NETs). *Nucl Med Rev Cent East Eur.* 2016; 19: 81-87.
15. Perault C, Schwartz C, Wampach H, Liehn JC, Delisle MJ. Thoracic and abdominal SPECT-CT image fusion without external markers in endocrine carcinomas. The Group of Thyroid Tumoral Pathology of Champagne-Ardenne. *J Nucl Med.* 1997; 38: 1234-1242.

**Cite this article**

Sergieva S, Atanasova M, Fakirova A, Robev B, Georges AS (2017) SPECT-CT Somatostatin-Receptor Scintigraphy in Medullary Thyroid Cancer (MTC). *JSM Thyroid Disord Manag* 2(2): 1011.