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Original

^{99m}Tc-EDDA/HYNIC-TOC in the diagnosis of differentiated thyroid carcinoma refractory to radioiodine treatment

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Abstract

BACKGROUND: In majority of cases of differentiated thyroid carcinoma (DTC), the ablative radioiodine treatment shows high efficacy. In a small number of patients, mechanism of selective iodine uptake by the DTC cells is insufficient and alternative methods of diagnosis and treatment are needed. As demonstrated in vitro, DTC cells show expression of somatostatin receptors. Radiolabeled somatostatin analogs are widely used in the diagnosis of neuroendocrine tumors. The aim of the study was to evaluate the utility of peptide receptor scintigraphy with the use of ^{99m}Tc-EDDA/HYNIC-TOC in the diagnosis of DTC in patients with elevated thyroglobulin concentrations (Tg), negative WBS and no effect of the consecutive radioiodine therapies.
MATERIAL AND METHODS: Whole body scintigraphy as well as SPECT of neck and chest were performed 3 and 24 h after i.v. administration of 740 MBq ^{99m}Tc-EDDA/HYNIC-TOC. The obtained images were compared with other radionuclide and radiological imaging methods. Forty-three patients with DTC after surgery and ablative radioiodine treatment with negative WBS and elevated Tg were qualified. Patients' age: 18–83 years (mean 58.0).
RESULTS: SRS showed foci of tracer accumulation in 29 cases (67.4%). Sensitivity was 69.0% specificity 78.6%. SRS correctly identified local recurrence in 8 pts., metastatic lymph nodes in 19 pts., lung metastases in 12 pts. and bone metastases in 5 pts. SRS showed high sensitivity in the detection of metastatic lymph nodes (100%) and bone metastases (83.3%) and lung metastases (63.2%). Positive SRS was found in pts. with higher Tg concentrations (130 ± 144 vs. 30 ± 54 ng/ml).
CONCLUSION: Scintigraphy with the use of the studied technetium-99m-labeled somatostatin analog is useful in the evaluation of patients with advanced DTC. It shows relatively good sensitivity and specificity but not high enough to be recommended as a routine imaging method. The role of somatostatin receptor scintigraphy in DTC is complementary to other imaging modalities.

KEY words: somatostatin analogs, thyroid carcinoma, scintigraphy

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Background

Prognosis in differentiated thyroid carcinoma (DTC) is generally good. In less than 20% of patients local recurrence and cervical lymph node metastases may occur after thyroidectomy and radioiodine therapy (RIT). Distant metastases are found in 5–10% of patients; they are located mainly in lungs (57%) and bones (24%) [1]. About 10–15% of patients with DTC have recurrent disease and 25–50% of patients with locally advanced or metastatic DTC become radioactive iodine (131I) (RAI)-refractory [2, 3].

Treatment efficacy is monitored by the measurement of thyroglobulin concentration (Tg). In case of elevated Tg RIT treatment is performed followed by the whole body scan (WBS) that is aimed at the identification of iodine-avid foci of DTC [4]. In about 30% of cases DTC cells lose the ability to concentrate iodine [3]. It is caused by the dedifferentiation of these cells and mutation of natrium-iodide symporter (NIS) gene that is responsible for the uptake of iodide ions into thyroid cells [5–8]. In the situation of elevated Tg and negative WBS other imaging modalities are warranted to detect the localization of DTC foci and evaluate possibility of other treatment options including surgery.

For many years PET-CT using ^{18}-fluoro-deoxyglucose (^{18}F-FDG) has been successfully used in the detection of non-iodine avid DTC recurrence [9, 10]. Sensitivity of PET-CT in population of DTC patients with elevated Tg and negative WBS is estimated between 69 and 95%, especially when performed in the conditions of TSH stimulation [11–16]. It is especially useful in patients with Tg concentrations above 10 mg/l [17].

Another proposed method to visualize non-iodine avid DTC foci is the somatostatin receptor scintigraphy (SRS). In the first publication on this issue, 4 DTC patients were reported in whom 111-indium labeled octreotide (Octreoscan) was used. The scan

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was positive in three of these cases [18]. In numerous later studies different percentage of positive scans was reported ranging from 30 to 100% [19–24].

Synthesis of new ^{99m}Tc-labeled somatostatin analog that had been carried out at the beginning of this century opened a new era of imaging. ^{99m}Tc-labeled compounds showed better diagnostic parameters associated with the preferable physical properties of 99m-technetium in comparison to 111-indium [25–28]. The somatostatin analog, ^{99m}Tc- EDDA/HYNIC-TOC (Tektrotyd) showed good diagnostic performance in neuroendocrine tumors [29, 30], in medullary thyroid carcinoma [31] and some other tumors that express somatostatin receptors. The aim of our study was to evaluate diagnostic performance of ^{99m}Tc- EDDA/HYNIC-TOC in the diagnosis of DTC refractory to radioiodine therapy.

Material and methods

Material

Patients with suspected dedifferentiation of DTC who presented with elevated Tg and negative WBS were qualified to somatostatin receptor scintigraphy using ^{99m}Tc-EDDA/HYNIC-TOC. All patients had undergone total thyroidectomy and at least three courses of RIT. In concordance with local and European guidelines of DTC management [32, 33], the first RIT activity was 60–90 mCi (2.2–3.3 GBq) depending on the risk factors. As none of the qualified patients achieved complete remission, the courses of RIT were repeated with higher ^{131}I activities, ranging from 90 to 150 mCi (3.3–5.5 GBq). The intervals between subsequent courses of RIT ranged from 6 to 12 months. RIT was performed in the conditions of endogenous TSH stimulation after withdrawal of L-thyroxin for at least 4 weeks. Between the courses of RIT, patients were treated with suppressive doses of L-thyroxin (TSH below 0.3 mU/dl). SRS was performed during L-thyroxin treatment, at least 6 weeks after recent RIT.

The control group consisted of patients after total thyroidectomy due to medullary thyroid carcinoma who had SRS for the detection of recurrent disease but who were eventually classified as complete remission, based on the normal values of calcitonin and negative imaging at 2-years follow-up. The obtained SRS were retrospectively utilized as the "normal" image in subjects after thyroidectomy.

Methods

SRS was performed with the use of ^{99m}Tc- EDDA/HYNIC-TOC (Tektrotyd) manufactured by Polatom (Poland). The labeling with 99mTc obtained from Mo/Tc generator (Amersham Health) was performed on-site in concordance with the manufacturer's recommendations (30 min incubation 80°C). The radiochemical purity was assessed with two methods: reverse-phase chromatography and thin-layer chromatography and it ranged between 94.9 and 98.1%.

Each patient was given an i.v. injection of 20–25 mCi (740–925 MBq) of ^{99m}Tc-EDDA/HYNIC-TOC. No adverse effects was observed after injection, including allergic reactions.

Images were registered twice in each patient: 3 h and 24 h post injection. Image acquisition was performed using one of the dual-head gamma cameras: Varicam (Elscint, Israel) or Infinia Hawkeye 4 (GE Healtchcare, USA), equipped with low energy — all-purpose collimators. Acquisition parameters were equal for both scanners. Each imaging session consisted of planar whole body scans in anterior and posterior projections (bed movement speed 15 cm/min, 256 x 1024 matrix) and SPECT images of the neck and chest (60 projections, acquisition time 20 s per frame). In patients scanned with Infinia Hawkeye 4 gamma camera, computed tomography for anatomical correlation were also acquired.

Images were interpreted by two experienced nuclear medicine specialists. Foci of increased tracer accumulation were reported, especially in the most probable location of DTC recurrence (thyroid bed, cervical lymph nodes, mediastinum, lungs and bones). The obtained images were compared with other imaging methods used for verification of the findings: cervical ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MR) performed not earlier than 3 months before and not later than 3 months after SRS.

WBS used for the qualification of the patients to the study was performed using the same gamma cameras with the use of high-energy collimators. The WBS was registered 7–10 days after RIT with the use of 90–150 mCi (3.3–5.5 GBq). Negative WBS defined as no indication of pathologic iodine uptake attributed to remnant thyroid tissue of DTC recurrence or metastasis was used as a qualifying criterion in this study.

Tg measurement was performed with the use of radioimmune assay Dynotest Tg-S (Brahms Diagnostics Berlin, Germany) under conditions of endogenous TSH stimulation. Tg concentration above 2 ng/ml was regarded as elevated and considered as the second qualifying criterion in the study.

Results

Forty-three (36 female and 7 male) patients were retrospectively analyzed. The diagnosis of DTC was made 3 to 17 years (median 7 years) before SRS and was based on the histopathological evaluation of the resected thyroid tumor. Histopathological types of DTC were distributed as follows: papillary carcinoma in 25 patients (58.1%), including 2 patients with follicular variant of papillary carcinoma, follicular carcinoma in 11 subjects (25.6%), including one patient with insular carcinoma and oxyphilic carcinoma in 7 patients (16.3%).

Patients' age ranged from 18 to 83 years (mean 58.0 ± 15.9, median 60 years).

The T stage in TNM classification at the diagnosis was: T1 in 4 patients (15.3%), T2 in 9 pts. (34.6%), T3 in 2 pts. (7.7%) and T4 in 13 pts. (50.0%).

The N stage was estimated as N0 in 17 pts. (65.4%) and N1 in 9 pts. (34.6%). In the remaining 17 subjects TNM classification was not available, particularly in patients who were operated on before 2000 outside large surgical centers.

Stimulated Tg concentrations ranged from 0.57 to 523.9 ng/ml (median 38 ng/ml). Two patients with Tg below 2 ng/ml were exceptionally qualified to the study due to highly elevated anti-Tg antibodies (aTg) suggesting a persistent disease despite normal Tg level.

Prior to SRS, the patients had undergone from 3 to 9 courses of RIT with the cumulative activity of 300 to 1440 mCi (11.1–53.2 GBq), median 720 mCi (26.6 GBq).

SRS showed pathological foci of ^{99m}Tc- EDDA/HYNIC-TOC accumulation in 29 patients (67.4%). SRS was negative in the remaining 14 patients (32.6%).

Comparison of the subgroups of patients with positive and negative SRS is presented in Table 1. In the subgroup with positive SRS mean Tg was higher than in the subgroup with negative SRS ($p = 0.0164$). In patients with oxyphilic carcinoma, SRS was more

Table 1. Patients characteristics and comparison of selected parameters in the subgroup with positive and negative SRS

	All patients	Patients with positive SRS	Patients with negative SRS	p
n	43	29	14	
Age (years)	58.0 ± 15.9	60.2 ± 16.0	53.9 ± 18.0	0.2078
median	60	61.5	57	
Time from diagnosis (years)	8.1 ± 5.1	8.3 ± 5.1	7.8 ± 7.0	0.7914
median	7	6.5	7	
Cumulative ^{131}I activity [mCi]	653 ± 293	702 ± 274	562 ± 265	0.1203
median	570	690	390	
Tg [ng/dl]	95 ± 127	130 ± 144	30 ± 54	0.0164
median	38	101	8	
Papillary thyroid carcinoma	25	16	9	0.0838
	58.1%	64.0%	36.0%	
Follicular thyroid carcinoma	11	6	5	0.5758
	25.6%	54.5%	45.4%	
Oxyphilic type	7	6	1	0.0001
	16.3%	85.7%	14.3%	

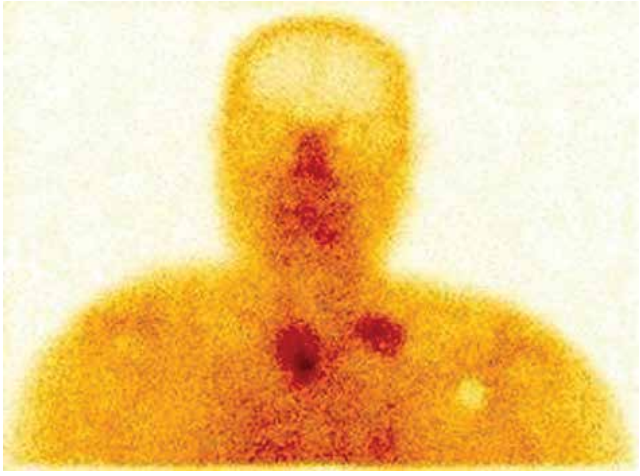

Figure 1. 62-year-old male patient with oxyphilic carcinoma. SRS detected local recurrence and metastatic supraclavicular lymph nodes on the left side

frequently positive than in other histopathological diagnoses. No difference was noted between the subgroups with respect to patients' age, time from diagnosis and RIT cumulative activity.

Local recurrence

Pathologic foci in the neck region were found in 16 pts. (37.2%). In 8 of them (18.6%) the lesion was located in the thyroid bed and was interpreted as local recurrence (Figure 1). In 7 cases local recurrence was confirmed using US and biopsy. The patients were referred to further surgical treatment. In one patient the lesion was not found with US but it disappeared after next two courses of RIT performed despite negative WBS.

Lymph node metastases

In 11 patients (25.6%) pathologic foci in the neck outside thyroid bed were found in SRS: in the submandibular region (3 cases) in the posterior neck triangle (2 cases) and in the supraclavicular region (8 cases). In 10 cases these findings were positively verified using US and/or CT and in 8 cases metastatic character of the lesions was confirmed in fine-needle biopsy. The size of the metastatic lymph nodes varied from 7 to 24 mm.

Focal mediastinal uptake was found in 13 patients (27.9%). In one of them the focus was noted only in SPECT image (not in the planar scan). Contrast-enhanced CT revealed pathologic lymph nodes in the areas indicated at the SRS in 9 of these cases. In 2 patients the focus was verified as hypertrophic thymus. In 2 patients the CT did not disclose any pathologic finding in mediastinum, so the SRS was interpreted as false positive.

Distant metastases

In 13 patients (30.2%) focal uptake in the lungs was found: in 3 cases in form of a solitary focus, in 10 cases as multiple lesions. CT confirmed metastatic character of these findings in 12 patients. In 9 of them the metastases were greater than 10 mm. In the remaining case, the lesion had morphology of primary pulmonary malignancy and was finally diagnosed as pulmonary adenocarcinoma.

In 7 patients without pulmonary lesions at SRS, pulmonary metastases with the diameter of 2–6 mm were visualized at CT. In these cases SRS was interpreted as false negative.

In general, pulmonary metastases were present in 19 patients (44.2%). SRS was true positive in 12 of them (Figure 2). Remaining data is presented in Table 2.

Bone metastases were detected in 6 patients (14.0%). Five of them were positive at SRS. The lesions were found in the skull (2 pts.), spine (3 pts.), ribs (2 pts.) and pelvis (1 patient). All these lesions were confirmed by bone scintigraphy, MR and/or PET-CT. In one case, the metastases were found in bone scintigraphy and MR, but not in SRS (false negative scan) (Figure 3). Follicular carcinoma was predominant diagnosis in patients with bone metastases (4 out of 6 cases).

In one patient a previously unknown cerebellar metastasis was detected by SRS in a patient with multiple pulmonary metastases.

In the statistical analysis of the entire group, the mean age was lower among patients with local recurrence in comparison with lymph node or distant metastases. Patients with bone metastases had significantly higher Tg levels than patients with other DTC locations. Complete data is presented in Table 2.

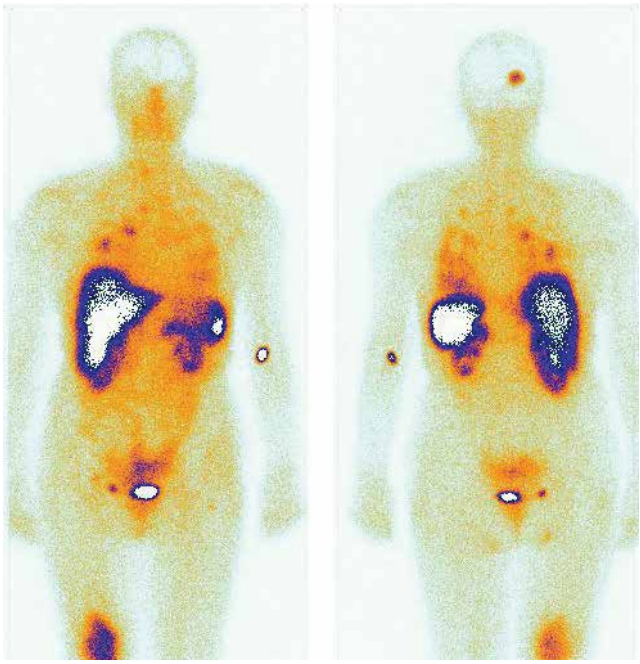

Figure 2. Pulmonary and bone metastases (skull, pubic bone, right femoral bone) in a patient with Tg = 523 ng/ml

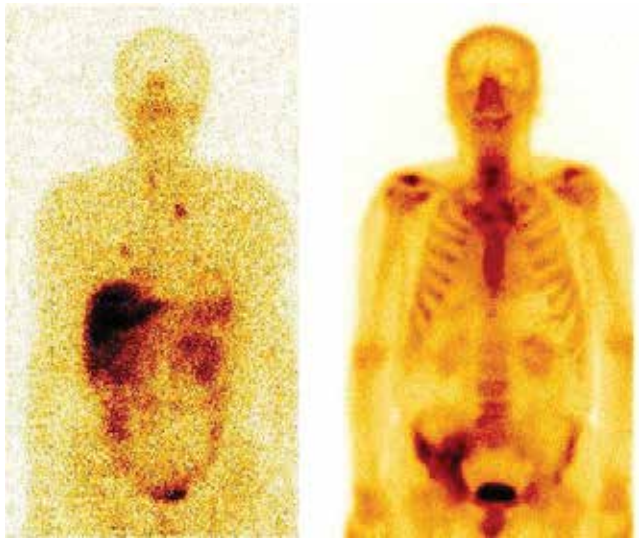

Figure 3. 60-year-old male patient. Mediastinal and hilar lymph node metastases was detected in SRS performed 24 h p.i. (left). The bone scan revealed additionally metastases in the right pelvic bone (right) that were not seen at SRS (false negative finding of bone metastases)

SRS diagnostic performance

Number of positive and negative SRS in general and with respect to different lesion locations is presented in Table 3. For the calculation of diagnostic performance parameters, control group was included in the table.

Based on the presented data, following parameters of the studied SRS with the use of ^{99m}Tc-EDDA/HYNIC-TOC were calculated: sensitivity 69.0%, specificity 78.5%, positive predictive

Table 2. Comparison of different parameters in patients with different findings (mean ± standard deviation and median are presented)

	n	Age (years)	Papillary carcinoma (n, %)	Tg [ng/ml]	Time since diagnosis (years)	Cumulative radioiodine activity [mCi]
All patients	43	58.0 ± 15.9 60	25 58.1%	95 ± 127 38	8.1 ± 5.1 7	653 ± 293 570
Pts. with local recurrence	8	46.4 ± 17.9 47*	5 62.5%	37.4 ± 37.8 19 ♦	7.7± 2.1 7	737 ± 243 630
Pts. with cervical lymph nodes mets	11	63.6 ± 15.4 68*	8 72.7%	86.6 ± 60.6 95 ♦♦	7.3 ± 7.1 7	611 ± 339 450
Pts. with mediastinal lymph node mets	12	68.6 ± 9.42 67**	5 41.7%	132 ± 139 105	7.4 ± 5.7 6	648 ± 258 585
Pts. with pulmonary mets.	20	64.6 ± 15.7 63***	11 55.0%	105 ± 126 78	5.9 ± 3.6 6	699 ± 336 600
Pts. with bone mets	6	68.7 ± 10.1 69****	2 33.3%	227 ± 199 142	6.7 ± 7.3 3	673 ± 260 630

*p = 0.0382; **p = 0.0019; ***p = 0.013; ****p = 0.0184; ♦p = 0.0205; ♦♦p = 0.0439

Table 3. Diagnostic performance of SRS in the studied group

	(1) SRS	(2) Patients with DTC	(3) Control group	(4) Local recurrence	(5) Lymph node metastases	(6) Pulmonary metastases	(7) Bone metastases
n	56	43	13	8	19	19	6
True positive	29	29	0	8	19	12	5
True negative	11	0	11	48	34	36	50
False positive	3	1	2	0	3	1	0
False negative	13	13	0	0	0	7	1

value 90.6%, and negative predictive value 45.8%. With respect to the histopathologic type of the disease, sensitivity and specificity were as follows: in papillary thyroid carcinoma sensitivity — 64.0%, specificity — 78.6%; in follicular carcinoma 54.5% and 84.6%; in oxyphilic carcinoma 85.7% and 84.6% respectively.

Discussion

Somatostatin receptors are expressed in both in normal and malignant cells of the neuroendocrine origin [34]. The somatostatin analog labeled with 99m-technetium, ^{99m}Tc-EDDA/HYNIC-TOC became commercially available in 2003, gradually substituting the 111-indium labeled analog — Octreoscan. The majority of clinical research on ^{99m}Tc-EDDA/HYNIC-TOC was focused on the neuroendocrine tumors. Gabriel et al. reported high sensitivity (88%) and specificity (94%) of this method in a group of 88 patients with neuroendocrine tumors except insulinoma [29]. High diagnostic utility in this clinical setting was confirmed by Chrapko et al. [30]. Similarly high diagnostic accuracy of another analog, ^{99m}Tc-EDDA/HYNIC-TATE was found by authors from Cracow [35]. Some diagnostic utility of ^{99m}Tc-EDDA/HYNIC-TOC scintigraphy was also reported in patients with solitary pulmonary nodule [36].

In our center, more than 1000 SRS using ^{99m}Tc-EDDA/HYNIC-TOC were performed in recent 12 years. Majority of patients were referred for the diagnosis of neuroendocrine tumors. The second group of indications were thyroid tumors. SRS was performed only in highly selected patients with medullary thyroid carcinoma and in DTC in whom standard imaging methods failed to detect foci of the disease. Previously, we documented a relatively high diagnostic utility of ^{99m}Tc-EDDA/HYNIC-TOC in patients with asymptomatic hypercalcitoninemia in course of medullary thyroid carcinoma. The overall sensitivity was 79.5%, specificity 83.3%, positive predictive value 96.9% and negative predictive value 38.5% [31]. In current study, our experiences with this method in patients with DTC recurrence manifested by asymptomatic hyperthyroglobulinemia are summarized. In this group of patients the results were quite similar: sensitivity — 69.0%, specificity — 78.5%, positive predictive value — 90.6%, negative predictive value — 45.8%.

In a similar study performed in Innsbruck, sensitivity of SRS using ^{99m}Tc-EDDA/HYNIC-TOC was similar to that obtained in our study (66%). Comparison with PET with ^{18}F-FDG in the same patient cohort showed its better performance in terms of lesion detection (sensitivity 87%) [16]. In our patient group not all patients were referred for a PET-CT study, so a head-to-head comparison was not possible.

Diagnostic performance of ^{99m}Tc-EDDA/HYNIC-TOC may be also compared to 111-Indium-labeled compound. In earlier years several studies were published with inconsistent results. Sensitivity of ^{111}In-octreotide (Octrescan) in patients with DTC ranged from 20% to 100% [20–23, 37–39]. Such a wide range of results was caused by different classification criteria, wide range of tumor stage, different levels of Tg and in some cases poor statistical quality due to low number of subjects. One of the most similar patient cohort was studies by Giammarile et al. [21]. Among 43 patients with elevated Tg and similar distribution of histopathological diagnosis to our study (20 papillary thyroid carcinoma, 9 — follicular, 8 — oxyphilic) 22 patients showed positive SRS (51%), i.e. less than in our study. Although comparison of two methods in two patient cohorts should not result in clear conclusions, in this case the favorable results obtained with ^{99m}Tc-EDDA/HYNIC-TOC can be easily supported. The main cause of this difference is physical characteristics of gamma radiation emitted by two radionuclides: ^{99m}Tc and ^{111}In. Apart from the image quality (spatial resolution) that is adversely affected by higher energy of ^{111}In, this radionuclide may be safely used in lower doses than ^{99m}Tc due to much longer physical half-life of 67 h versus 6 h and higher dose equivalent [40].

Efficacy of SRS using ^{99m}Tc-EDDA/HYNIC-TOC was not influenced by patients' age, time since diagnosis and cumulative radioiodine activity. There was however clear correlation with the stimulated Tg concentration. Patients with positive SRS had higher Tg values than those with negative SRS. The scan was rarely positive in patients with Tg below 10 ng/ml (11%). This finding can be compared with published results of PET using ^{18}F-FDG. In a study performed on a PET scanner without CT also 11–13% patients with Tg of 10 ng/ml had positive ^{18}F-FDG study [7]. However, in a study performed with the use of a hybrid PET/CT scanner this percentage was much higher — 43–53% [41, 42].

In the presented study, clinical utility of ^{99m}Tc-EDDA/HYNIC-TOC was demonstrated. It must be stressed that these results were obtained on a highly selected group of patients showing signs of dedifferentiation. Treatment options in this patient subgroup is limited. Radioiodine treatment is not effective any more leading to unnecessary radiation burden. Attempts to use chemotherapy did not show sufficient efficacy [43]. Radiation therapy is used sometimes but it is restricted only to localized process. In general, prognosis in patients with dedifferentiation is much worse than in uncomplicated DTC. 5-year survival in patients with pulmonary metastases is ca. 60% if lesions are iodine-avid and only 30% in the absence of iodine uptake [44–46]. Among possible treatment options peptide receptor radionuclide therapy (PRRT) with somatostatin analogs labeled with beta-emitters could be an interesting option. The analogues labeled with beta-emitters (yttrium-90 or lutetium-177) were found to provide encouraging results in patients with disseminated forms of neuroendocrine tumors (NET) [47, 48]. Demonstration of somatostatin receptor expression by the means of SRS is a crucial criterion to qualify to such an experimental treatment. The results of PRRT in DTC in our center have been published elsewhere [49]. PRRT was generally well-tolerated but the outcome was rather poor in majority of cases of radioiodine-refractory DTC.

In summary, SRS using ^{99m}Tc-EDDA/HYNIC-TOC is useful in the detection of disease foci in patients with radioiodine-refractory DTC. The method shows acceptable sensitivity and specificity that is however not sufficient to recommend it as a routine imaging modality. Positive SRS is more likely to occur in patients with highly elevated thyroglobulin concentrations. SRS plays complementary role to other imaging techniques including PET/CT with ^{18}F-FDG.

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