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^{99m}Tc-EDDA/HYNIC-TOC in management of patients with head and neck somatostatin receptor positive tumors

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Abstract

BACKGROUND: Aim of this study was to determine the value of technetium-99m-hydrazinonicotinyl-Tyr3-octreotide (^{99m}Tc-EDDA/HYNIC-TOC) in patients with somatostatin receptor (SSR) positive tumors of head and neck region.

MATERIAL AND METHODS: A total number of 16 patients were enrolled in this study. Planar whole body (WB) and single photon emission computed tomography (SPECT) images were acquired at 2 and 4 hours after the injection of approximately 670 MBq of ^{99m}Tc-EDDA/HYNIC-TOC. Additional single photon emission computed tomography/computed tomography (SPECT/CT) images of the head and neck region were acquired at 4h post tracer injection. Clinical and imaging follow up were taken as the reference standard.

RESULTS: There were 10 female and 6 male patients of age 57.7 ± 12.9 years (58.5; 32–78) years. ^{99m}Tc-EDDA/HYNIC-TOC somatostatin receptor scintigraphy (SRS) was TP in 13 patients, TN in two and FP in one. Follow up period for SRS was 31.1 ± 19.4 (29; 2–63) months. ^{99m}Tc-EDDA/HYNIC-TOC scintigraphy provided additional information in 50% of patients, with impact on patient management in the same percentage of patients. Distant metastases were found in nine out of 16 patients (56%). ^{99m}Tc-EDDA/HYNIC-TOC SRS had sensitivity of 100% (75.3–100%), specificity of 66.7% (9.4–99.2%), accuracy of 93.7%, positive predictive value of 92.9% (66.1–99.8%), and negative predictive value of 100% (15.8–100%).

CONCLUSION: Somatostatin receptor scintigraphy using ^{99m}Tc-EDDA/HYNIC-TOC is very useful imaging method in the evaluation of patients with SSR positive tumors of head and neck region.

KEY words: neuroendocrine tumors, receptors, somatostatin, tomography, emission-computed, single-photon, technetium 99m EDDA-HYNIC-Tyr (3)-octreotide

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Background

Somatostatin receptor scintigraphy (SRS) is considered as an imaging modality of choice for many neuroendocrine tumors (NETs). NETs of head and neck are rare group of neoplasms. NETs originate from neural crest cells and have both neural and endocrine cell features [1]. Head and neck NETs can be divided in two groups: epithelial derived tumors (typical carcinoid, atypical carcinoid and small cell carcinoma) and neurally derived tumors (paraganglioma, olfactory neuroblastoma) [2]. Rarely, NETs from other sites can also metastasize to the head and neck region [3]. Some other types of head and neck tumors; medullary thyroid carcinoma (MTC), meningioma, Hurthle cell carcinoma, also showed somatostatin receptors (SSRs) on the cell membrane surface [4].

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SRS is indicated in the staging of SSR overexpressing tumors, restaging, detection of eligibility for "cold" somatostatin analogues (SSAs) or somatostatin receptors directed radionuclide therapy (peptide radionuclide receptor therapy — PRRT). SRS is useful in monitoring response to "cold" SSAs and in detection of primary SSR positive tumors [5, 6].

The radiopharmaceutical ^{111}Indium-octreotide (OctreoScan™, Mallinckrodt, Petten, Netherlands) has been considered as the gold standard for the management of NET patients [7–9]. Technetium-99m (^{99m}Tc) labeled hydrazinonicotinyl-Tyr3-octreotide (EDDA/HYNIC-TOC, Tektrotyd) has advantages of short half-life, lower radiation burden; so higher dosage can be administered producing better image quality. Physical characteristics of ^{99m}Tc are more suited for gamma cameras and single photon emission computed tomography (SPECT) imaging [10–12]. ^{99m}Tc labeled EDDA/HYNIC-TOC is also a good alternative to Gallium-68 radiotracers (labeled peptides: DOTA-TOC, DOTA-NOC, DOTA-TATE) where PET/CT or Gallium-68 generators are not available.

MTC is a rare malignancy and in comparison with other types of thyroid carcinoma, MTC is more demanding and more difficult

to treat with higher rates of recurrence and mortality. Different radiopharmaceuticals are used for detection of occult metastatic disease and SRS with ^{99m}Tc-EDDA/HYNIC-TOC is the promising method [13–15].

The aim of this study was to determine the value of ^{99m}Tc EDDA/HYNIC-TOC in patients with neuroendocrine and other SSR positive tumors of head and neck region in terms of sensitivity, specificity, diagnostic accuracy. Impact on patient management was also evaluated.

Material and methods

Patients, radiopharmaceutical and imaging

All patients gave their written informed consent for the study. This is a retrospective study of 16 patients who referred to our Department for a routine examination between February 2011 and March 2016. ^{99m}Tc-EDDA/HYNIC-TOC was prepared from a commercially available kit (Tektrotyd, Polatom, Otwock, Poland) following the manufacturer's instructions. Patients were intravenously injected with an average activity of 670 MBq of the tracer. Imaging was performed at 2 and 4 hours with a double-headed gamma camera (Symbia T; Siemens Medical Solutions, Erlangen, Germany). Planar whole body (WB) and single photon emission computed tomography (SPECT) images were acquired at 2 and 4 h. Single photon emission computed tomography/computed tomography (SPECT/CT) images of the head and neck region, or other region of interest, were acquired at 4 h. SPECT image data were reconstructed using FLASH-3D iterative reconstruction with 8 iterations and 8 subsets [16]. All images were reconstructed using syngoMI workstation (SynogMI VA60B; Siemens Medical Solution, Erlangen, Germany).

Any focal tracer accumulation exceeding normal regional tracer uptake was rated as a pathologic tumor uptake. Image analysis was done visually by experienced nuclear medicine physician who performed more than 200 ^{99m}Tc-EDDA/HYNIC-TOC SPECT/CT studies in the past four years.

Quantitative data are presented as their mean ± standard deviation (median; range), if not otherwise stated. Findings on SRS images were classified as true-positive (TP), true-negative (TN), false-positive (FP), or false-negative (FN), as compared to the reference standard (conventional imaging methods, clinical and biochemical follow up).

Results

Patient characteristics are detailed in Table 1. There were 10 female and 6 male patients of age 57.7 ± 12.9 years, (58.5; 32–78) years. Details of the findings of ^{99m}Tc-EDDA/HYNIC-TOC images are presented in Table 2. ^{99m}Tc-EDDA/HYNIC-TOC images were interpreted as positive in 14 patients and as negative in two patients. Follow up period for SRS was 31.1 ± 19.4 (29; 2–63) months. ^{99m}Tc-EDDA/HYNIC-TOC SPECT/CT was TP in 13 patients, TN in two and FP in one. Representative cases are shown in Figures 1–6.

In cases number 1, 2, 6 and 16 SRS was performed for staging of the disease. In cases number 2 and 16, as both patients had NEC of unknown primary (CUP), location of primary tumor was in main focus together with correct staging of the disease. In all other cases (3–5, 7–15) SRS was performed for restaging of the disease.

Cases number 13 and 15, both MTC, were TN with fairly long follow up period of 45 and 53 months, respectively. During this follow up numerous imaging techniques were performed in both patients including whole body PET/CT, MSCT (of the neck, thorax and abdomen region) and once per year US examination of the neck. Once in a year during follow up period patients were admitted to the hospital and on each occasion one of mentioned imaging modality (PET/CT or MSCT) was performed together with US of the neck region.

Table 1. Patient and tumor characteristics

Patient Number	Sex	Age (years)	Follow up (months)	Primary tumor site	Pathohistology	WHO Classification
1	M	52	29	Pharynx	NEC	G3
2	F	43	2	CUP	NEC	G3
3	F	78	38	Lacrimal gland	NET	G2
4	F	65	28	Thyroid	MTC	n/a
5	M	61	4	Pharynx	NEC	G3
6	F	42	12	Lacrimal gland	NET	G2
7	M	69	63	Larynx	NEC	G3
8	F	32	41	Meninges	Meningioma	G3
9	F	73	28	Thyroid	Hurthle cell	n/a
10	F	67	6	Thyroid	MTC	n/a
11	M	71	15	Thyroid	MTC	n/a
12	F	53	45	Thyroid	MTC	n/a
13	F	52	45	Thyroid	MTC	n/a
14	F	56	59	Thyroid	MTC	n/a
15	M	45	53	Thyroid	MTC	n/a
16	M	64	29	CUP	NEC	G3

M — male; F — female; CUP — cancer of unknown primary; NEC — neuroendocrine cancer; NET — neuroendocrine tumor; MTC — medullary thyroid cancer; G2 — grade 2; G3 — grade 3; n/a — not applicable

In five patients (cases 4, 7, 10, 11 and 14) distant spread of disease to skeletal system was found. In these cases ^{99m}Tc-EDDA/HYNIC-TOC findings upstaged disease to stage IV (distant metastasis). This changed initial staging done by conventional imaging methods. In all this cases "cold" SSAs were introduced. In two additional patients (cases 2 and 16) "cold" SSAs were also introduced after positive scintigraphy. Treatment of one patient (case 14) was changed to PRRT after positive scintigraphy scan. In overall, on a clinical basis ^{99m}Tc-EDDA/HYNIC-TOC scintigraphy provided additional information in 50% of patients, with impact on patient management in the same percentage of patients. Distant metastases were found in 56% of patients (9/16). Metastatic bone disease was the most common site of distant metastases in 31% of patients (5/16). Other sites were lymph nodes in 25% (4/16), lungs in 12% (2/16), brain in 6% (1/16) and liver in also 6% (1/16). In one patient (case 3) direct extension of tumor from eyelid and orbital cavity to sphenoid bone was seen. In this patient FP result (in terms of NET spread) was seen in both parotid glands due to chronic inflammatory changes of salivary glands (Sjogren's syndrome, Figure 4).

Table 2. Results of visual image analysis

Patient Number	99mTc-EDDA/ /HYNIC-TOC Positive scan	Lesions locations	Distant metastasis
1	Yes	Nasopharynx, Base of skull, NLN (M)	No
2	Yes	Brain (M), ALN (M)	Yes
3	Yes	Orbital cavity, Bone (Sphenoid)	No
4	Yes	Bone (sacrum)	Yes
5	Yes	Laryngopharynx, NLN (M)	No
6	Yes	Orbital cavity	No
7	Yes	Bone (M)	Yes
8	Yes	Brain	No
9	Yes	Lungs (M)	Yes
10	Yes	Bone (M)	Yes
11	Yes	Bone (humerus), Lungs (M)	Yes
12	Yes	Liver	Yes
13	No	0	No
14	Yes	Bone (M)	Yes
15	No	0	No
16	Yes	NLN(M)	Yes

M — multiple lesions; 0 — no lesions; NLN — neck lymph nodes; ALN — abdominal lymph nodes

In group of patients with NEC (patients 1, 2, 5, 7 and 16) PET/CT and US were used in all patients as reference imaging modality for follow up, while in patients 1, 2 and 5 (because of the neck or head and neck involvement) additional MRI of the head and/or neck was performed. No difference between imaging modalities (^{99m}Tc EDDA/HYNIC-TOC vs. ^{18}F-FDG PET/CT or MRI) was noted. In group of NEC distant metastasis were found in 60% of the patients (3/5).

The comparison between ^{99m}Tc-EDDA/HYNIC-TOC SRS and reference standard (conventional imaging methods, clinical and biochemical follow up) showed that SRS had sensitivity of 100% (75.3%–100%), specificity of 66.7% (9.4%–99.2%), accuracy of 93.7%, positive predictive value of 92.9% (66.1%–99.8%), and negative predictive value of 100% (15.8%–100%).

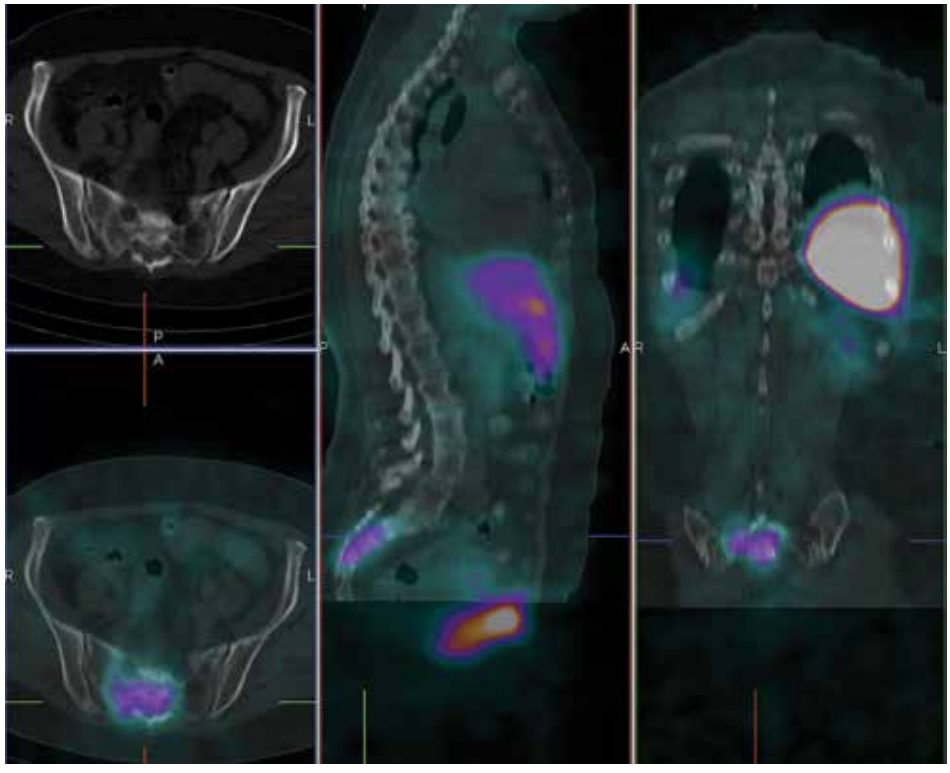

Figure 1. A 65-year-old female with medullary thyroid carcinoma (case number 4). ^{99m}Tc-EDDA/HYNIC-TOC SPECT/CT revealed distant metastasis in sacrum. SPECT/CT, single photon emission computed tomography/computed tomography

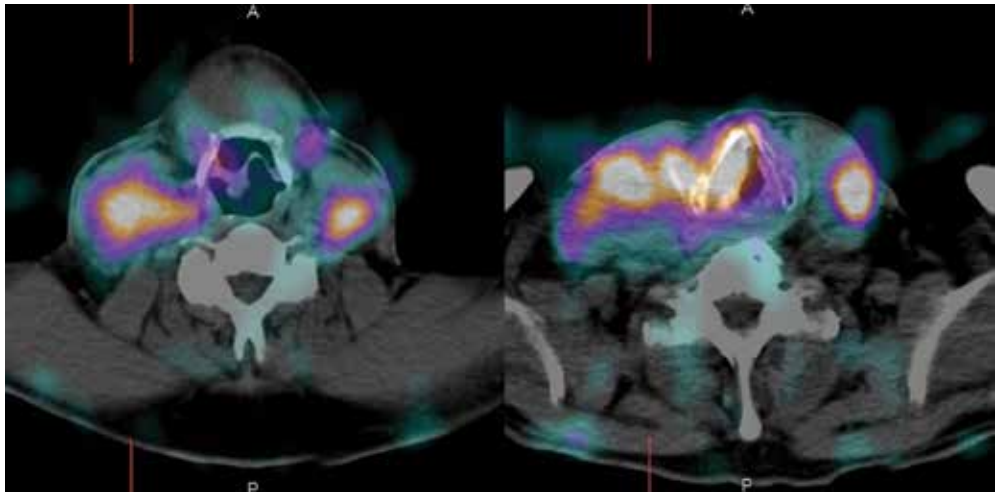

Figure 2. A 61-year-old male with NEC of laryngopharynx (case number 5). ^{99m}Tc-EDDA/HYNIC-TOC SPECT/CT showed intensive uptake in neck lymph nodes (bilateral) and in primary tumor of laryngopharynx. NEC, neuroendocrine carcinoma; SPECT/CT, single photon emission computed tomography/computed tomography

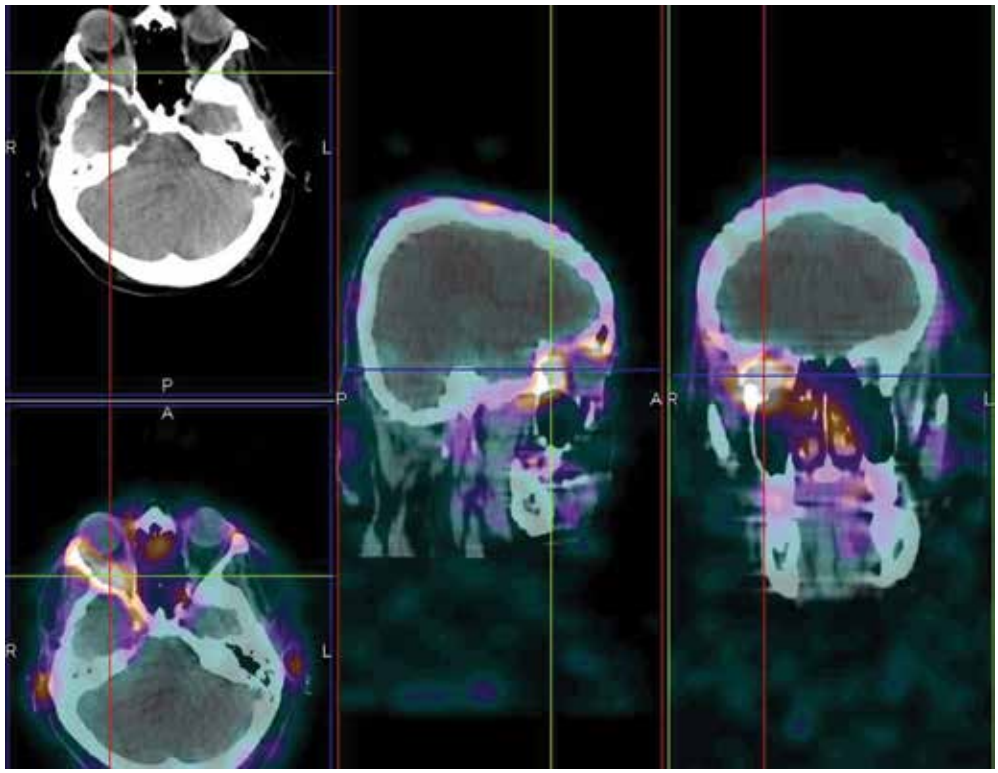

Figure 3. A 42-year-old female with NET G2 (Ki67 8%) of lacrimal gland (case number 6). ^{99m}Tc-EDDA/HYNIC-TOC SPECT/CT was done as preoperative staging. SPECT/CT (axial, sagittal and coronal view) showed increased radiopharmaceutical uptake in the right orbital cavity. NET G2, neuroendocrine tumor grade 2; SPECT/CT, single photon emission computed tomography/computed tomography

Discussion

Precise diagnosis and staging are of incremental value in directing therapy for tumors of head and neck region. Surgical resection is still first choice treatment for a patients with head and neck malignancies, including NET, MTC and other types of SSR positive tumors. In a metastatic disease multiple options are available. In patients with positive finding on SRS one of these options are "cold" SSAs. SSAs are used to control hormone related symptoms. Patients using SSA showed symptomatic and biochemical improvement. SSA anti-tumor effects are still under investigation, they have direct impact on proliferative signaling pathways, on activation of apoptosis, on angiogenesis and on tumor stabilization [17, 18].

In a subgroup of MTC, ^{99m}Tc-EDDA/HYNIC-TOC SRS showed incremental value in identifying additional metastatic lesions, especially distant metastatic lesions in skeletal system, providing more

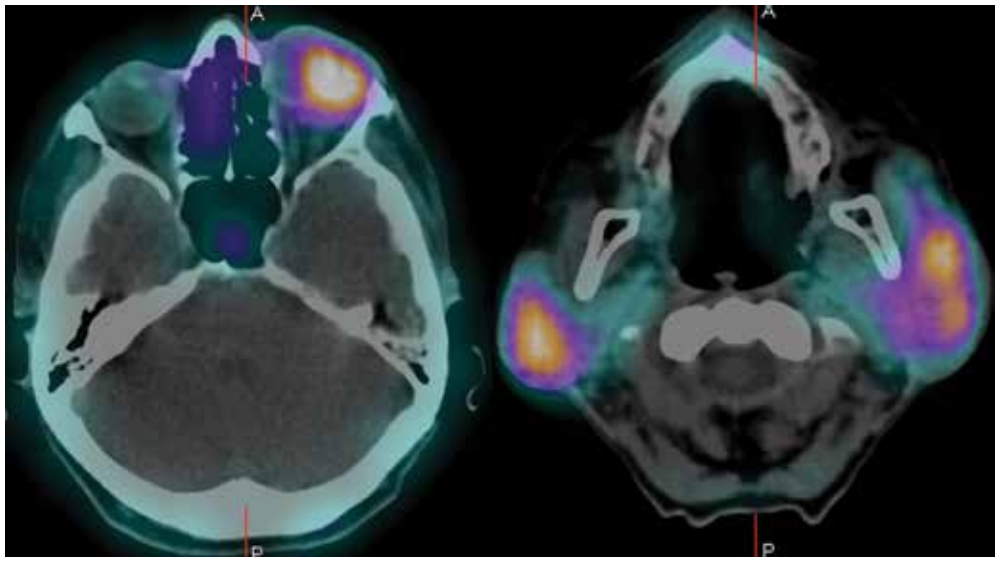

Figure 4. A 78-year-old female with NET G2 of lacrimal gland (case number 3). ^{99m}Tc-EDDA/HYNIC-TOC SPECT/CT was done as restaging. SPECT/CT images (axial view) revealed intensive uptake in left orbital cavity. SPECT/CT showed as well intensive uptake of the radiopharmaceutical in both parotid glands — Sjogren's syndrome. NET G2, neuroendocrine tumor grade 2; SPECT/CT, single photon emission computed tomography/computed tomography

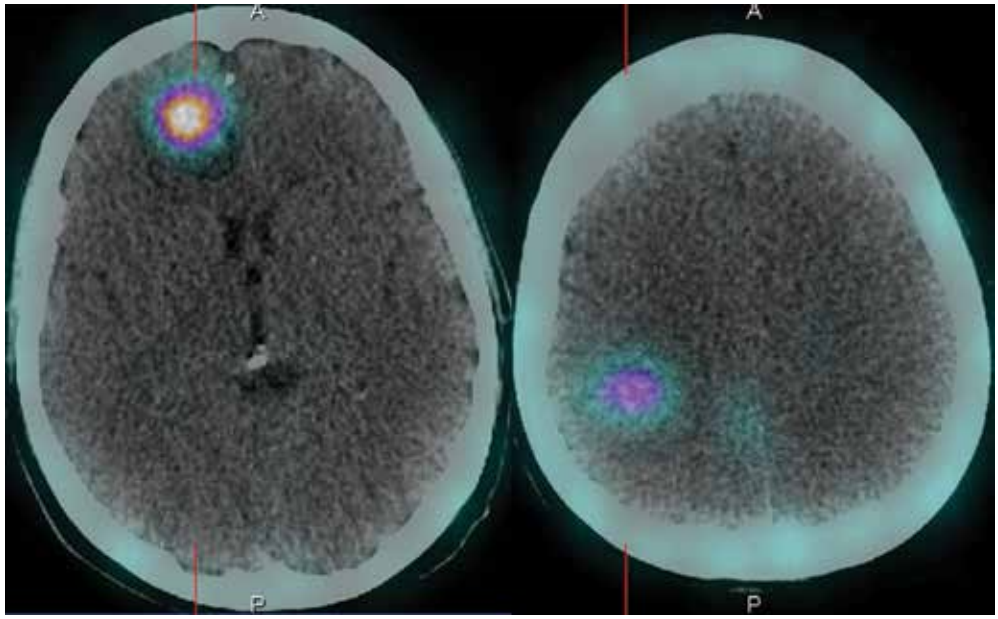

Figure 5. A 43-year-old female with neuroendocrine carcinoma of unknown primary site (case number 2). ^{99m}Tc-EDDA/HYNIC-TOC SPECT/CT didn't reveal primary tumor site. SPECT/CT (axial view) showed increased radiopharmaceutical uptake in frontal and parietal lobe. SPECT/CT, single photon emission computed tomography/computed tomography

accurate staging in these patients. In our group 31% (5/16) of patients were upstaged by SRS, four of them were MTC. Czepczynski et al. showed clinical usefulness of ^{99m}Tc-EDDA/HYNIC-TOC in follow up of patients with medullary thyroid carcinoma. ^{99m}Tc-EDDA/HYNIC-TOC had sensitivity of 79.5%, specificity of 83.3% and diagnostic accuracy of 80% [15].

Although Hurthle cell carcinomas do not belong to the traditional group of NETs, positive SSR in these tumors could provide, especially in negative radioiodine cases, new treatment option like PRRT [4, 19, 20].

Somatostatin scintigraphy of receptors type 2 with radiolabeled octreotide has been shown to be very useful in the meningioma diagnosis [21–23]. In their published study Wang et al. showed that ^{99m}Tc-HYNIC-octreotide SPECT/CT SRS is a sensitive method for detecting meningioma [24]. Several authors investigated this topic using ^{68}Ga-DOTA-peptides PET/CT [25]. We had only one patient with meningioma and ^{99m}Tc-EDDA/HYNIC-TOC SPECT/CT in this case provided additional information concerning tumor recurrence and extension. Planned radiotherapy target volume was slightly modified based on SPECT/CT data. Improved treatment planning

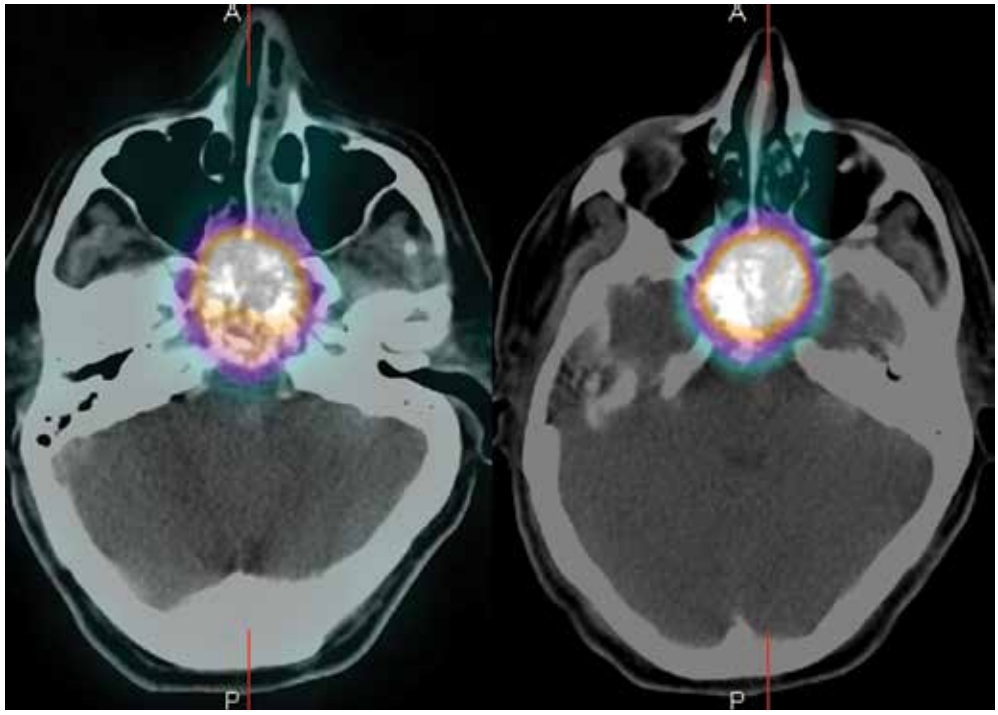

Figure 6. A 52-year-old male with neuroendocrine carcinoma of nasopharynx (case number 1). ^{99m}Tc-EDDA/HYNIC-TOC SPECT/CT was done as preoperative staging. On SPECT/CT images (axial view) is shown increased radiopharmaceutical uptake in the primary tumor with intensive bone destruction at the base of skull. SPECT/CT, single photon emission computed tomography/computed tomography

for meningioma using ^{68}Ga-DOTATOC PET/CT is more and more available method [26–28]. Usefulness of ^{99m}Tc-EDDA/HYNIC-TOC SPECT/CT in this indication is still to be investigated.

"Cold" SSAs were introduced in cases number 2, 4, 7, 10, 11, 14 and 16. In cases number 2 (CUP NEC) and 16 (CUP NEC) "cold" SSAs were introduced to reduce the number of flushing episodes and to improve general clinical condition of patients. Good clinical response to the treatment with reduced number of flushing episodes was noticed after introduction of long-acting SSA.

In five other cases (four MTC and one NEC of larynx), based on positive expression of somatostatin receptors, "cold" SSAs were introduced as antineoplastic treatment but no beneficial effect and no significant improvement in the natural course of the tumor was noted. More evident was an improvement in clinical symptoms as general weakness and weight loss in all the patients. Currently, randomized control studies referring on antitumor effect in patients with MTC, do not exist and only case series or studies of limited value are published, which were not able to demonstrate any consistent antitumor somatostatin effect [29–32].

According to Clarinet study (Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors), usage of long-acting SSA was associated with significantly prolonged progression-free survival among patients with metastatic enteropancreatic neuroendocrine tumors of grade 1 or 2 (Ki-67 < 10%) [33, 34]. This positive antineoplastic result was not seen in our very small group of patients with MTC and NEC (n = 7) that received "cold" SSA.

There are a number of limitations in this study; retrospective design, sample size was small, group consisted of patients with heterogeneous population of different SSR positive primary tumors (NET, MTC, meningioma, Hurthle cell carcinoma and unknown primary NET tumor with metastases in head and neck region in two patients). In our subgroup of NETs only grade 2 and grade 3 NETs were present, we didn't have well-differentiated (low grade) NETs and this could have significantly impact study results. Studies investigating larger and more homogeneous populations are needed.

Conclusion

^{99m}Tc-EDDA/HYNIC-TOC SRS shows high accuracy in detecting SSR positive tumors. SRS is an excellent imaging modality and reliable tool in the evaluation and treatment planning of patients with SSR positive tumors of head and neck region.

Conflicts of interest

There are no conflicts of interest.

Written informed consent was obtained from all patients.

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