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Limitations and pitfalls of ^{99m}Tc-EDDA/ /HYNIC-TOC (Tektrotyd) scintigraphy

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Abstract

Tektrotyd kit was developed by Polatom company for ^{99m}Tc labeling to make an alternative tracer of somatostatin receptor scintigraphy available. Since 2005, ^{99m}Tc-EDDA/HYNIC-Tyr^3-Octreotide has been used in clinical imaging and achieved high impact in management of patients with neuroendocrine tumors. Knowing the limitations and pitfalls is essential to provide accurate diagnosis. Therefore, the potential pitfalls associated with the use of ^{99m}Tc-EDDA/HYNIC-TOC are reviewed on the basis of own experience.

Data were analyzed of 310 patients who underwent somatostatin receptor scintigraphy with ^{99m}Tc-Tektrotyd. Pitfalls during radiolabeling process or acquisition can worsen the sensitivity of SRS (somatostatin receptor scintigraphy). Recognizing physiological and clinical pitfalls, the diagnostic accuracy will improve.

KEY words: somatostatin receptor scintigraphy, ^{99m}Tc-EDDA/HYNIC-Tyr^3-octreotide, pitfalls

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Introduction

Diagnosed incidence of neuroendocrine tumors (NETs) is predicted to continuously rise at a faster rate than other malignant neoplasms [1]. NETs are heterogeneous groups of tumors originating from different organs including lungs, pancreas, gastrointestinal tract etc. The common characteristic of these tumors is the ability to produce peptides. The primary diagnosis of NET is difficult and late because of general symptoms, tumor heterogeneity and a wide range of origin of the tumor. The cornerstone of the diagnosis of NET was the development of various radiolabeled somatostatin analogs and the introduction of SPECT/CT in clinical work. Fortunately the radiolabeled somatostatin analogs generate the possibility of targeted biological therapy, which offers these patients improved progression-free survival and often better quality of life. Somatostatin receptor scintigraphy is the best option for detection of well differentiated NETs, and classifies the patients based on their somatostatin receptor density. Many radiolabeled somatostatin analogs are available for human use. These radiopharmaceutical scans differ in radionuclides, chelators and the affinity to different subtypes of somatostatin receptors (SSTR). Therefore sensitivity and specificity may differ. The most frequently used radiotracers are ^{111}In- and ^{99m}Tc labeled pharmaceuticals for SPECT imaging. Since 2013, ^{99m}TcEDDA/HYNIC-Tyr^3-Octreotide (Tektrotyd, Polatom) has been used at our Institute for somatostatin receptor scintigraphy. In this study we summarized our experience based on more than 300 patients' examinations focusing on limitation and potential pitfalls in the use of ^{99m}Tc-EDDA/HYNIC-Tyr^3-Octreotide in routine clinical practice.

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Material and methods

Since 2013, we have performed 310 patients' examinations with ^{99m}Tc-EDDA/HYNIC-Tyr^3-Octreotide (Tektrotyd, Polatom) to assess somatostatin receptor expression in neuroendocrine tumors. The majority of the patients' neuroendocrine tumor diagnosis was proven by histology, but in some cases we tried to find the origin of the primary tumor. The main clinical question was to select candidates for therapy with somatostatin analogs or to evaluate its effectiveness. Well-hydrated condition, light food intake and mild laxatives are recommended before the examination, especially when the abdomen is the area of interest. If the patient is on somatostatin analog therapy, it is required to discontinue taking medication for six weeks. In our practice 500–600 MBq^{99m}TcEDDA/ /HYNIC-Tyr^3-Octreotide was injected intravenously. Radiolabeling is easy to perform, but the preparation of the radiopharmaceutical should begin one hour before the time of planned injection.

Acquisition protocol

Early (1 hour after injection) and late (4 hours after injection) whole body scans were performed with two headed large field of view gamma camera equipped with LEHR (low energy high resolution) collimator (AnyscanSC, Mediso) based on the following acquisition protocol: Whole body scan was done in the anterior and

posterior projections (256 x 1024 matrix, 13 cm/min). After 4 hours, whole body scan SPECT/CT was made about the questionable region with the following parameters: 360° noncircular orbit (body contour mode) step and shoot mode, at 30 s per view. The acquired data were collected in a 128 x 128 image matrix, reconstructed using filtered back projections with a Butterworth filter (cut-off 0.6 cycles/pixel, order 5).

Radiolabeling

In our daily routine production we get radiochemical yields (RCY) between 96.5 and 98.9% which is far above the 90% limit. To achieve these results we have to keep the exact orders during the production steps otherwise the specific activity and the RCY can significantly decrease. Several circumstances could affect the labeling procedure but there is only one which requires more attention.

The reaction temperature must be at 80°C for 20 min incubation to reach the efficient RCY. It is important to maintain the temperature at the optimum. Nevertheless, keeping the rule of radiolabeling process the efficacy of radiolabeling and *in vitro* stability of this tracer supports comfortable use in daily practice [2].

Technical considerations and improved diagnostic accuracy

The ^{111}In labeled somatostatin analog ^{111}In-DTPA-D-Phe^{1}-Octreotide has been most frequently used worldwide so far. Development of ^{99m}Tc-labeled somatostatin compounds was a real appreciation of necessity, because of better physical characteristics of ^{99m}Tc. ^{99m}Tc is more suitable for gamma camera imaging, providing higher resolution and better image quality with lower radiation dose. ^{99m}Tc-EDDA/HYNIC-Tyr^{3}-Octreotide results in higher tumor/background ratios than the ^{111}In tracers, especially in relation to heart and muscle. Significantly more lesions could be detected in ^{99m}Tc images [3]. Tomographic images are required especially about the region of interest to improve sensitivity and detection. Furthermore, hybrid technology (SPECT/CT) is also desirable providing anatomical information to precisely localize pathological uptake. The higher resolution of ^{99m}TcEDDA/HYNIC-Tyr^{3}-Octreotide images results in better registration on SPECT/CT increasing better lesion localization in contrast to^{111}In octreotide. Attenuation correction should be considered especially in overweight patients to improve sensitivity resulting in higher diagnostic accuracy. Furthermore, CT scan provides the possibility of quantitative analysis due to advanced level of reconstruction methods (Figure 1).

Physiological distribution of ^{99m}Tc-EDDA/HYNIC-Tyr^{3}-Octreotide and physiological pitfalls

Physiologic distribution of Tektrotyd reflects the specific and non-specific binding and excretion pattern. ^{99m}Tc-Tektrotyd is excreted mainly by the kidneys with a small contribution of hepatic excretion. Cumulative urine excretion within 24h falls in the range of 24–64% of the administered dose. However, kidney uptake of ^{99m}Tc-EDDA/HYNIC-Tyr^{3}-Octreotide is more complex due to the fact that specific and high-affinity SSTR have also been identified in the human kidney. In the cortex, these receptors are located in the proximal tubules and in the medulla in the medullary vasa recta based on autoradiographic results. These receptors probably belong to SSR2 subtypes causing high specific binding on octreotide scans besides excretion. Accordingly, the kidneys are the most jeopardized organs for radiation and radiation protection during targeted radionuclide therapy and diagnostic procedure is important.

Because of hepatic excretion, physiological gallbladder uptake is rarely seen especially on late images under fasting condition. Faint to moderate bowel activity is also visible especially on late scans too (Figure 2).

Uptake in salivary glands, thyroid, pituitary gland, and spleen is mediated by the expression of SSTR with different densities of receptor subtypes. Endocrine organs, gastrointestinal tract and the human lymphatic tissue represent some of the important sites of SSTR expression in the human body observed with in vitro receptor autoradiography [4]. Several lymphatic tissues contain SSTR including thymus, spleen and gut associated lymphatic tissue consisting mainly of activated lymphocytes. The majority of the SSTR in the lymphatic organs belongs to the SSTR2 subtype, as they can bind radiolabeled somatostatin analogs with high affinity. Recognizing these patterns is essential to differentiate normal variants from pathological ones. The most frequently occurring physiological variants were focal accumulation in the head of the pancreas (1–2%),

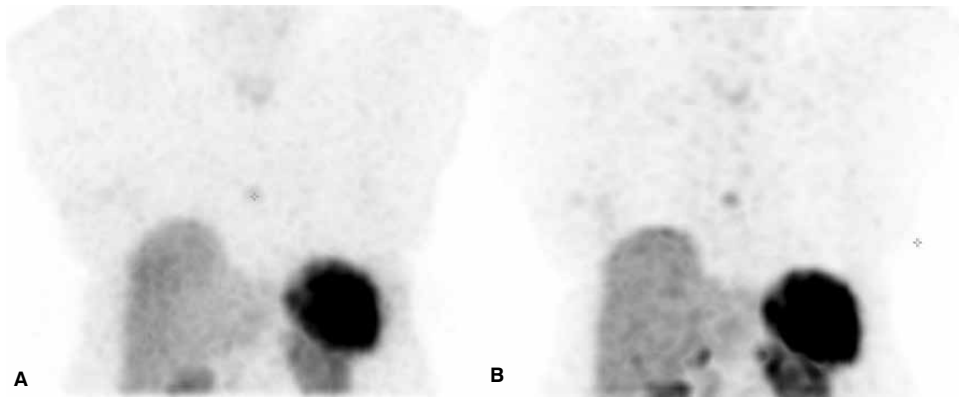

Figure 1. A 67-year-old female patient with a history of histologically proved small-cell lung cancer expressing somatostatin receptors. On NAC (non-attenuation correction) MIP (maximal intensity projection) image (**A**) slight, uncertain uptake was revealed in the mediastinum, but on AC (attenuation correction) MIP image (**B**) intense uptake was found in that area resulting in higher target signal to noise ratio. After removal of this pathologic lymph node the histological analysis proved the diagnosis of somatostatin receptor positive metastasis

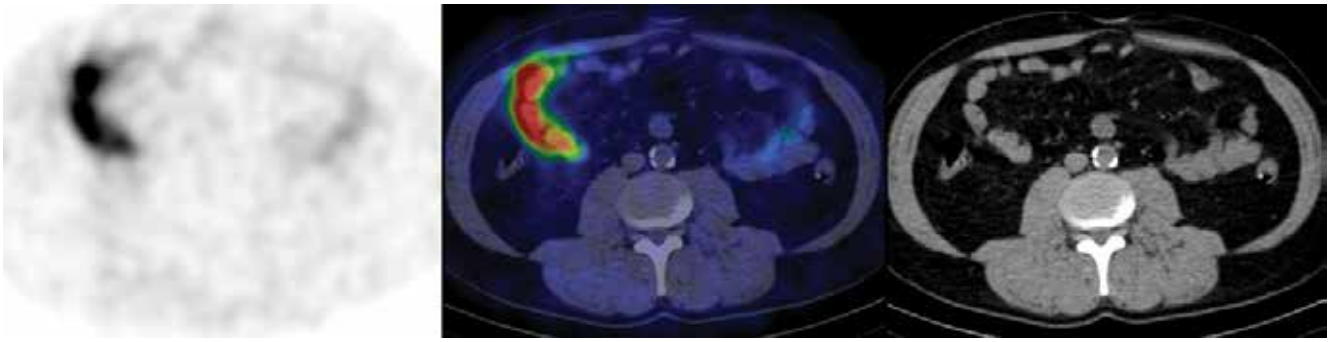

Figure 2. Intense physiological tracer uptake was seen in the bowel on ^{99m}Tc-Tektrotyd SPECT/CT

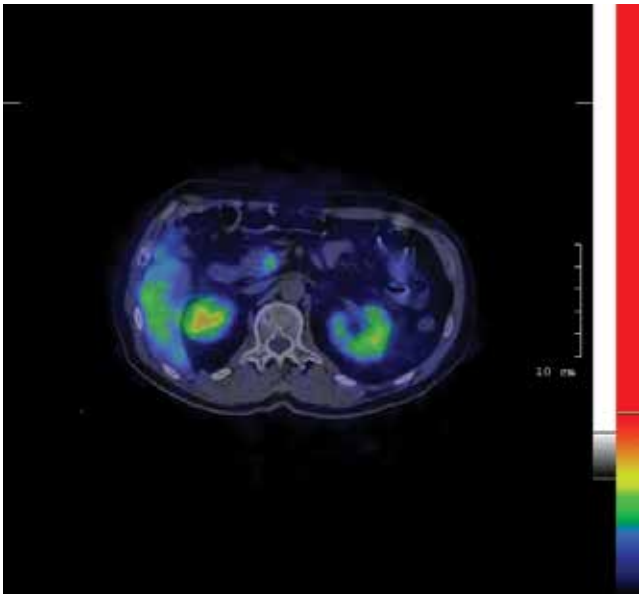

Figure 3. Focal intense uptake was seen in pancreatic head, without morphological abnormality, due to physiologic accumulation of pancreatic uncinate process

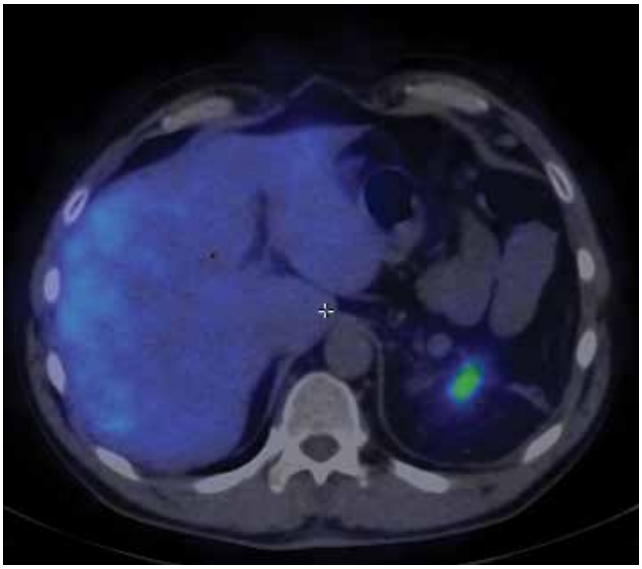

Figure 4. A 58-year-old patient with a history of pancreatic neuroendocrine tumor. The splenectomy was performed and in the splenic bed a small soft tissue mass showed increased uptake of ^{99m}Tc-Tektrotyd, which represents a remnant spleen tissue

associated spleen or splenosis (< 2%) and focal pulmonary uptake without morphological pattern (2.5%) in our cases.

Prominent pancreatic uncinate process accumulation is visible in few percent of patients. Without additional morphology, it is difficult to differentiate from malignant pancreatic process. SPECT/CT can help us to assess normal anatomy in the background of the accumulation. Because of the poor tissue resolution of low dose CT without contrast, further examination — multiphase CT or MRI — sometimes is required for accurate diagnosis (Figure 3).

Splenectomy is often carried out in patients with pancreatic tail NET tumors and splenosis is a common finding in these cases. Focal or multiple, round-like or sometimes irregular soft tissue activity is visible on SPECT/CT in the splenic bed. Diagnosis can be mistaken for mesenteric metastasis. In uncertain cases, spleen scintigraphy with radiolabeled colloids or denatured red blood cells can help in diagnosis (Figure 4).

Nevertheless in patients with normal spleens, an accessory spleen is visible on the scan, but the activity of this tissue is comparable with the normal splenic activity and rarely causes differential diagnostic problem.

An interesting finding on somatostatin receptor scintigraphy was a solitaire or multiple focal intense uptake in the lungs without any morphological abnormality. There was a case of a young man with a history of neuroendocrine tumor who was operated because of findings of focal intense uptake in his lung, but histological analysis could not prove the malignancy. Only bronchiectasia, macrophages and lymphocytes were found in the sample (Figure 5). We suppose that focal bronchitis or bronchiolitis can cause such a sign. Activated lymphocytes and macrophages can express SSTR2 with higher density and Varecza et al. proved in their experimental studies that SSTR4 expression is higher both in subacute and chronic inflammatory reactions in the lungs including smoking subjects as well. They found a large number of SSTR-positive activated macrophages and some lymphocytes in alveoli of chronic inflamed lungs. However, ^{99m}Tc-HYNIC-Tyr^3-Octreotide binds with high affinity to SSTR2 and with low affinity to SSTR3 and SSTR5. This sign is likely the result of complex pathophysiology [5, 6]. Increased radiopharmaceutical uptake is frequently seen in lungs after radiotherapy, but in that case fibrotic-infiltrative changes are also visible on SPECT/CT.

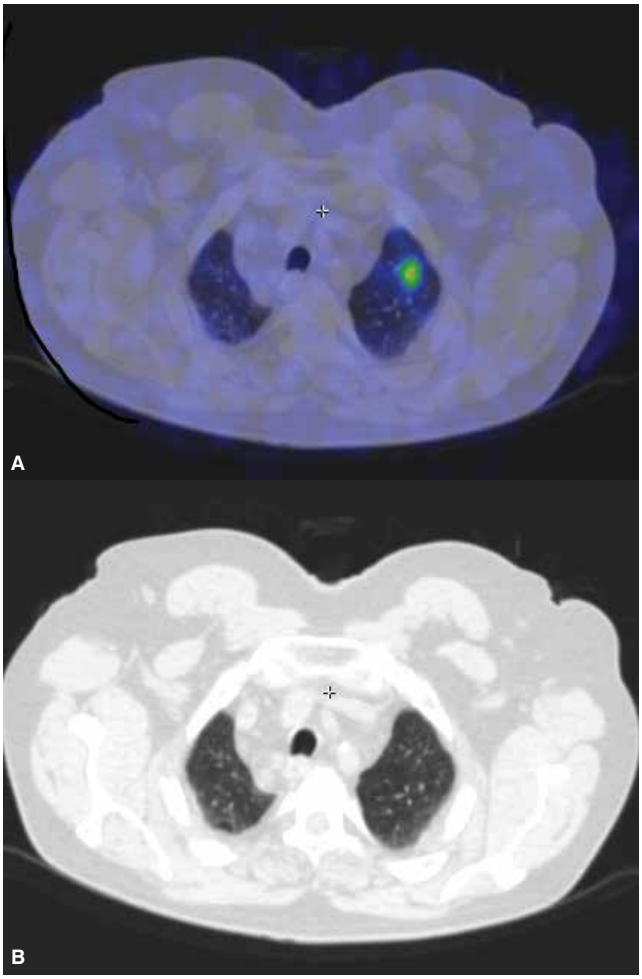

Figure 5. Intense focal accumulation in the upper lobe of right lung on SPECT/CT (**A**) without morphologic abnormality on CT (**B**)

Clinical pitfalls

^{99m}Tc-EDDA/HYNIC-Tyr^{3}-Octreotide demonstrated rapid tissue uptake within the first hour after injection and without significant clearance from normal or tumor tissue up to 20h p.i. In contrast, continuous clearance is detected from normal tissues as well as renal and hepatobiliary excretion using ^{111}In-DTPA-Octreotide [7]. SSTR-positive lesions showed intense tracer accumulation because of high in vivo stability and quick background clearance of ^{99m}Tc-EDDA/HYNIC-Tyr^{3}-Octreotide. However, somatostatin receptor scintigraphy has lower sensitivity for lesions that are present in organs having physiological tracer concentration such as the liver. The detection rate can be improved by SPECT/CT (Figure 6). Furthermore, receptor density can change due to dedifferentiation of tumor or after therapy causing inhomogeneous appearance of the tumor on SRS.

Increased uptake of ^{99m}Tc-EDDA/HYNIC-Tyr^{3}-Octreotide sometimes appears in benign lesions representing higher expression of somatostatin receptors. Osteoblasts express SSTR2 and thus degenerative bone disease, fractures, and epiphyseal growth plates in children can show increased activity on SRS (Figure 7) [8]. Furthermore, parathyroid adenoma and inflammatory processes in different organs, such as colitis, prostatitis, and thyroiditis, also accumulate radiolabeled somatostatin analogs causing false positive results [9].

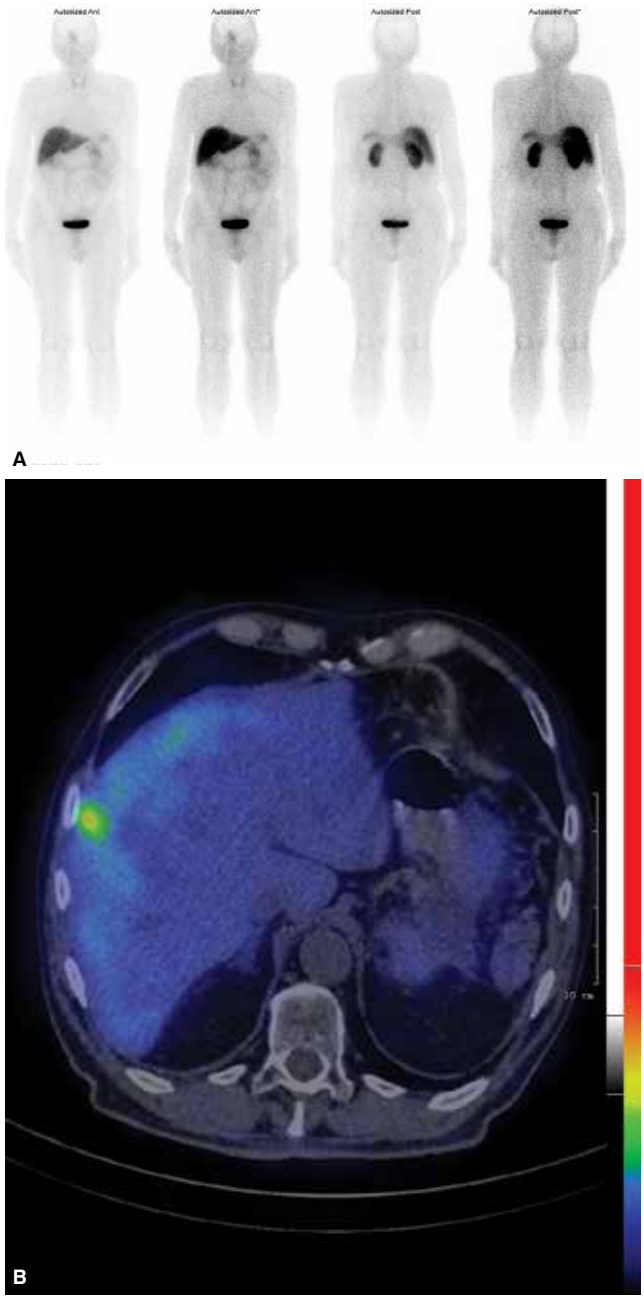

Figure 6. On whole-body scan the tracer distribution of liver seemed homogenous (**A**), but on SPECT/CT, a focal intense ^{99m}Tc-Tektrotyd uptake confirmed the recurrence of metastatic carcinoid tumor in the liver (**B**)

Sometimes the incidental uptake on SRS was found unlikely to the neuroendocrine origin. We have to take into consideration that not only neuroendocrine tumors express somatostatin receptors with high density. Other tumors like meningioma, breast cancer, lymphoma, and prostatic cancer can express SSTR resulting in increased uptake on SRS (Figures 8 and 9) [10].

Conclusion

Somatostatin receptors (SSTR) were identified in various normal human tissues, as well as in several types of human tumors,

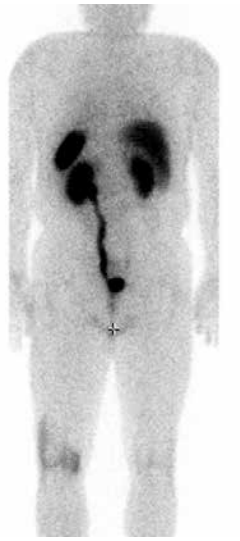

Figure 7. A 56-year-old man with a history of neuroendocrine tumor. On whole-body scan diffuse increased activity was seen in the left knee, because of degenerative disease

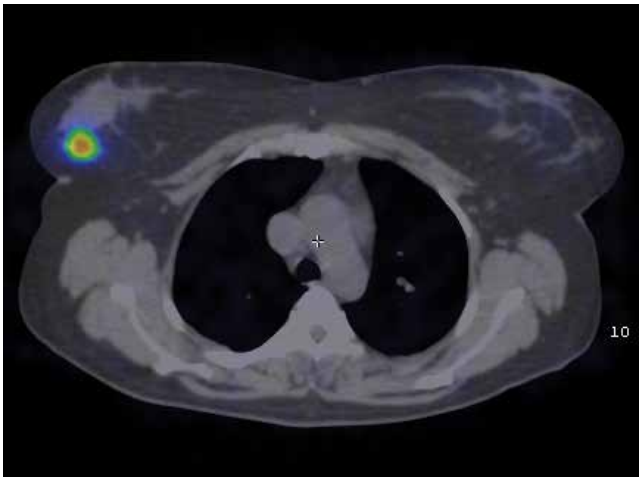

Figure 9. Middle-aged female patient with a history of renal cancer and neuroendocrine tumor. On SRS SPECT/CT an intense focal uptake was found in the right breast. After removal of the tumor the histology confirmed the renal cancer metastasis. (Misalignment is also visible on SPECT/CT because of movement)

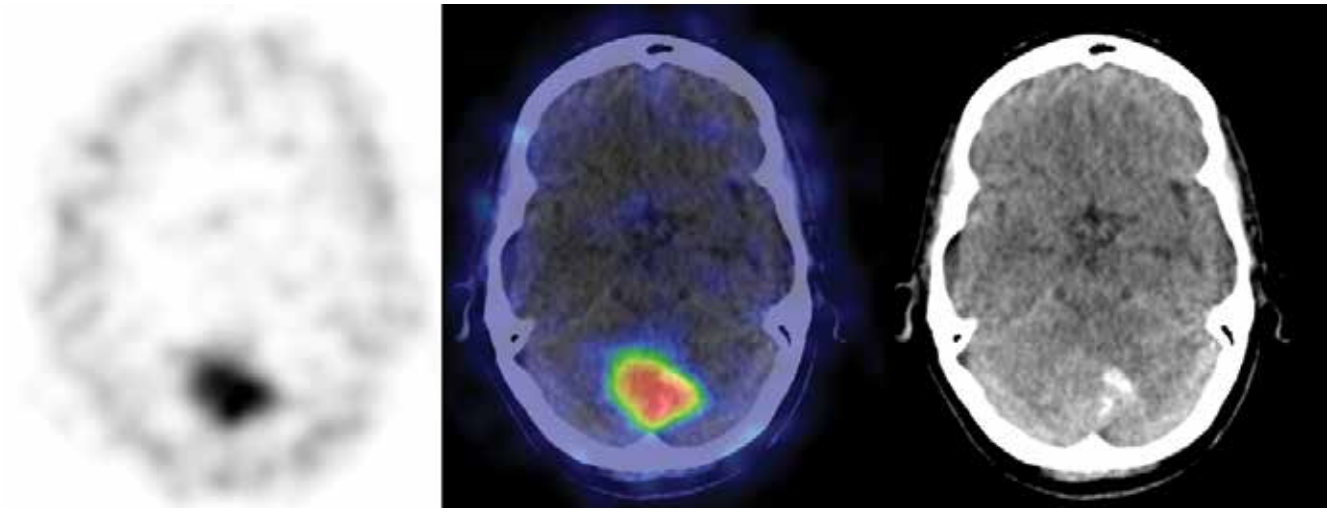

Figure 8. Incidental intense focal tracer uptake was revealed on SRS SPECT/CT in the posterior part in the brain. The final diagnosis was meningioma in the occipital lobe

especially neuroendocrine ones. SRS imaging in neuroendocrine tumors is useful for the primary diagnosis, staging of the disease, selecting patients for targeted therapy, and monitoring its efficacy [11].

Recognizing potential pitfalls and limitations using radiolabeled somatostatin analogs can improve our diagnostic confidence. ^{111}In labeled somatostatin analog is the commonly used tracer and majority of the published literature have been done using this tracer. In studies, the sensitivity of SRS varies for different subtypes of NETs to be between 50 and 95% [12]. Because ^{111}In has longer half-life, and higher energy of emitted gamma rays, ^{99m}Tc labeled agent for somatostatin receptor imaging has gained ground for SPECT imaging. The pharmacokinetic properties of ^{99m}Tc-EDDA/HYNIC TOC were found to be better than those of ^{111}In-Octreotide. Higher target-to-non-target ratios and higher absolute tumor uptake values were observed for ^{99m}Tc-EDDA/HYNIC TOC and the optimal acquisition time for imaging was identified as 4 hours after injection. The potential competitors of ^{99m}Tc radiolabeled somatostatin analogs are ^{68}Ga labeled compounds providing higher resolution using PET imaging [13]. Nevertheless, ^{99m}Tc labeled somatostatin analogs still remain a sensitive and cost effective method in imaging of neuroendocrine tumors.

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