Research Article

Glucagon-Like Peptide-1 Receptor Imaging with [Lys\textsuperscript{40} (Ahx-HYNIC-\textsuperscript{99m}Tc/EDDA)NH\textsubscript{2}]-Exendin-4 for the Diagnosis of Recurrence or Dissemination of Medullary Thyroid Cancer: A Preliminary Report

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Introduction. Epidemiological studies on medullary thyroid cancer (MTC) have shown that neither a change in stage at diagnosis nor improvement in survival has occurred during the past 30 years. In patients with detectable serum calcitonin and no clinically apparent disease, a careful search for local recurrence, and nodal or distant metastases, should be performed. Conventional imaging modalities will not show any disease until basal serum calcitonin is at least 150 pg/mL. The objective of the study was to present the first experience with labelled glucagon-like peptide-1 (GLP-1) analogue [Lys\textsuperscript{40} (Ahx-HYNIC-\textsuperscript{99m}Tc/EDDA)NH\textsubscript{2}]-exendin-4 in the visualisation of MTC in humans. Material and Method. Four patients aged 22–74 years (two with sporadic and two with MEN2 syndrome-related disseminated MTC) were enrolled in the study. In all patients, GLP-1 receptor imaging was performed. Results. High-quality images were obtained in all patients. All previously known MTC lesions have been confirmed in GLP-1 scintigraphy. Moreover, one additional liver lesion was detected in sporadic MTC male patient. Conclusions. GLP-1 receptor imaging with [Lys\textsuperscript{40} (Ahx-HYNIC-\textsuperscript{99m}Tc/EDDA)NH\textsubscript{2}]-exendin-4 is able to detect MTC lesions. GLP-1 scintigraphy can serve as a confirmatory test in MTC patients, in whom other imaging procedures are inconsistent.

1. Introduction

Medullary thyroid cancer (MTC) is a neuroendocrine neoplasm arising from the parafollicular cells, or C cells, of the thyroid. It accounts for nearly 5–10% of thyroid malignancies. In nearly all MTC cases, cancer cells secrete calcitonin, a specific and highly sensitive biomarker—its measurement plays an important role in diagnosis and postoperative followup of patients [1–3]. The majority of MTCs are sporadic, but up to 25% of all cases result from a germ-line activating mutation of the RET protooncogene [4, 5]. Hereditary MTCs occur in the setting of the multiple endocrine neoplasia (MEN) syndrome type 2 (2A or 2B) or as familial MTC (FMTC)—a variant of MEN2A syndrome. The most common form of hereditary MTC is MEN 2A (approximately 80–90% of patients with hereditary MTC). Overall, the prognosis for patients with MTC is good. The 10-year survival rate is 75–85%. Approximately half of the MTC patients present with disease limited to the thyroid gland with a 10-year survival rate of 95.6%. One-third of patients present with locally invasive tumour or clinically apparent spread to the regional lymph nodes. Patients with regional disease have a 5-year overall survival rate of 75.5%. Recurrent disease develops in approximately 50% of patients with MTC [1, 6]. Neck ultrasound should be performed as a part of the initial evaluation of each patient with newly diagnosed MTC. Fine-needle aspiration (FNA) cannot always distinguish MTC based on the appearance of tumor cells alone, so the diagnosis
is typically confirmed by immunostaining or by the measure-
ment of calcitonin level in the washout fluid from FNA.
This latter technique appears to be even more sensitive than
cytology with immunohistochemistry [1].

The primary treatment for MTC is surgical resection.
Total thyroidectomy with complete resection of central
neck, paratracheal, and upper mediastinal lymph nodes is
frequently needed. Currently, surgical excision is the only
effective treatment for MTC. Patients who have clinically
apparent disease are best treated with a minimum of total
thyroidectomy and bilateral central neck dissection [7, 8].
Followup should start 2-3 months postoperatively by obtain-
ing new baseline calcitonin levels. An undetectable basal
serum calcitonin level is a strong predictor of complete
remission. Patients with biochemical remission after initial
treatment have only a 3% risk of recurrence during long-term
followup [1, 2].

Calcitonin and stimulated calcitonin levels are very
sensitive ways for detecting either residual or recurrent
disease. When the postoperative calcitonin level is elevated,
a careful search for metastases has to be performed prior
to surgical exploration. Imaging techniques will not show any
disease until basal serum calcitonin level exceeds 150 pg/mL.
In patients with serum calcitonin lower than 150 pg/mL,
localization of the disease should be focused on careful
examination using neck ultrasound because such calcitonin
levels are usually associated with locoregional disease. The
optimal timing of this followup should be based on calcitonin
and CEA (carcinoembryonic antigen) doubling times (DT),
which are strongly correlated with disease progression [9–12].

There are some MTC patients in whom, despite of the
elevated postoperative calcitonin levels and/or abnormal
results of the pentagastrin test, there is no evidence of the
disease in conventional imaging techniques. Prolonged delay
in disease localization usually results in treatment failure
even if the tumor recurrence/residue is finally detected.
Molecular imaging techniques, based on the development of
tracers which are taken up by MTC cells or are bound to
MTC-specific receptors, could be applied in such group of
patients. Therefore, besides the use of those well-known and
commonly used radiotracers, such as labelled somatostatin
analogues or mIBG, there are still clinical trials performed
to find more specific and sensitive substances. Glucagon-like
peptide 1 (GLP-1) labelled analogues have been considered
as a promising tool for visualization of MTC. Physiologically
GLP-1 (glucagon-like peptide-1) receptors have been found in
organs like pancreas, blood vessels, stomach, or parafollicular
C cells. Their expression is also observed in different types
of neoplasms including MTC [13]. Both 
\[^{111}\text{In} \text{(Ahx-DTPA-^{111}\text{In})NH}_2\times\text{exendin-4}
\] and
\[^{68}\text{Ga}^{99m}\text{Tc} \text{labelled GLP-1 analogue exendin-4 were success-
fully used in patients with insulinoma [14–16].}
\]

The aim of the paper is to present the first experi-
ence of our department with the new radiopharmaceuti-
cal \[\text{[Lys}^4\text{(Ahx-HYNIC-}^{99m}\text{Tc/EDDA})\text{NH}_2\times\text{exendin-4 as}}\)
a diagnostic tool in patients with suspected or confirmed
recurrence or dissemination of MTC and to compare its
performance with conventional imaging methods.

2. Material

Four patients (1 female, 3 males, aged 22–74 years) were
enrolled in the study. In all of them, recurrence or dissem-
ination of MTC was suspected, based on previous imaging
results and elevated calcitonin levels. In all patients, neck
ultrasound was performed with fine-needle aspiration biopsy
of suspected lesions in 3 cases. In two patients, neck and chest
tomography (CT) and in one case abdominal CT
were also performed. All subjects underwent somatostatin
receptor scintigraphy (SRS).

**Patient 1 (J.S.).** Patient with sporadic MTC underwent total
thyroidectomy with complete lymph nodes resection in the
central neck and paratracheal compartment in 2004. In 2009,
based on results of CT and SRS, patient was diagnosed
with liver metastases and qualified to the peptide receptor
radioisotope therapy (PRRT). Patient received 13.32 GBq
(360 mCi) of \[^{90}\text{Y-DOTA-TATE. Treatment led to the sta-
lization of the disease. GLP-1 receptor imaging was per-
fomed to compare results with standard imaging procedures}
(US, CT and SRS).

**Patient 2 (S.S.).** Patient with sporadic medullary cancer
underwent total thyroidectomy with neck lymph nodes
resection in 2003. In 2008, based on elevated calcitonin levels,
neck ultrasound, fine-needle aspiration biopsy, neck and
chest CT, and SRS dissemination to the neck and mediastinal
lymph nodes were confirmed. Patient was disqualified from
the surgery. Patient received 14.8 GBq (400 mCi) \[^{90}\text{Y-
DOTA-TATE in 2008, which resulted in the stabilization of the}
disease. GLP-1 receptor imaging was performed to compare
results with conventional imaging methods (US, CT, and
SRS).
3.2 Preparation of \([\text{Lys}^{40} (\text{Ahx-HYNIC})], \text{EDDA})\text{NH}_2\) Exendin-4. Technetium-99m labelled \([\text{Lys}^{40} (\text{Ahx-HYNIC/EDDA})\text{NH}_2]\)-exendin-4 was obtained from lyophilized kits prepared by the Institute of Atomic Energy, Radioisotope Center POLATOM. Exendin-4 (20 \(\mu\)g) was modified C-terminally with \(\text{Lys}^{40}-\text{NH}_2\), where the lysine side chain was conjugated with Ahx-HYNIC (Ahx is aminohexanoic acid). Tricine and EDDA as coligands for \(99\text{mTc}\) were added. The radiopharmaceutical preparation was carried out in the Nuclear Medicine Unit of the Endocrinology Department, Cracow University Hospital and was performed under aseptic conditions. Two-vial freeze-dried kits were used for radiolabelling with 0.3–1.5 mL pf \(99\text{mMo}/99\text{mTc}\) generator eluate (0.37–1.85 GBq) followed by 20 min incubation at 80 °C. The TLC (thin layer chromatography) method was used for assessing the radiochemical purity of the compound. The mean injected activity was 740 MBq.

3.3 Imaging Technique. GLP-1 receptor imaging with the use of \(\text{Lys}^{40} (\text{Ahx-HYNIC,}99\text{mTc/EDDA})\text{NH}_2\)·exendin-4 was performed at the Nuclear Medicine Unit of the Endocrinology Department in the University Hospital in Cracow. At the beginning, images were acquired with a dual-head, large field of view E.CAM gamma camera with low-energy high-resolution (LEHR) collimators (Siemens Healthcare, 2000). From 2010 all examinations were performed with the use of Symbia TruePoint T16 hybrid system also with LEHR collimators (Siemens Healthcare, 2007).

SPECT studies were performed at 2 time points, between 3-4 h and 5-6 h after the injection of the tracer. The SPECT examinations were done with 128 × 128 matrix, 64 images, 30 sec per image, step and shoot mode, noncircular orbit and dual-energy window for scatter correction. The acquired data were reconstructed using OSEM Flash 3D iterative reconstruction method with 8 subsets and 10 iterations. After the installation of the new hybrid device in the unit, SPECT/CT studies were carried out in all next patients with the same settings for the SPECT part of the study.

In all cases low-dose CT imaging was performed for the attenuation correction and a improved localization of pathological uptake of the tracer.

The obtained images were assessed by the experienced nuclear medicine specialist.

4. Results

The average radiochemical purity of the administered compound, prepared according to manufacturer’s instruction and determined by TLC, was higher than 90%.

The quality of obtained \(\text{Lys}^{40} (\text{Ahx-HYNIC,}99\text{mTc/EDDA})\text{NH}_2\)·exendin-4 images was assessed by the nuclear medicine physician as very good.

### Table 1: Patients clinical data.

| Initial | Age | Sex | Diagnosis | Genetic | CT | SRS | Diff. studies | GLP-1 |
|---------|-----|-----|-----------|---------|----|-----|--------------|--------|
| J.S.    | 74  | M   | Dissem    | Sporadic| +  | +   | US−          | +      |
| S.S.    | 70  | M   | Dissem    | Sporadic| +  | +   | US+          | +      |
| K.G.    | 22  | M   | Recurr    | MEN 2A  | na | −   | US+          | +      |
| Z.P.    | 60  | F   | Dissem    | MEN 2B  | +  | −   | US+          | +      |

*F/M: female/male, −: negative result, +: positive result, na: not available, recur: recurrence, and dissem: dissemination.*
In all patients results of scintigraphy with [Lys$^{40}$ (Ahx-HYNIC-$^{99m}$Tc/EDDA)$\text{NH}_2$]-exendin-4 corresponded to the results of previously performed imaging examinations.

In the first patient (J.S.) $^{99m}$Tc-GLP-1 receptor scintigraphy revealed in homogenous liver uptake and focally increased tracer uptake at the location of previously confirmed liver metastases (Figure 1). Moreover, an additional liver lesion not seen on SRS, was detected. Patient 1 is still available for followup with stable disease after PRRT.

In the second patient (S.S.), $^{99m}$Tc-GLP-1 receptor scintigraphy performed after PRRT revealed small focal uptake in the neck. The image was comparable with SRS findings.

In the patient K.G. (patient 3), $^{99m}$Tc-GLP-1 receptor scintigraphy showed focal tracer uptake at the location of the ultrasonographically detected lesion on the left side of the neck. The patient was further qualified for the surgery.

In the patient Z.P. (patient 4), $^{99m}$Tc-GLP-1 receptor scintigraphy revealed tracer uptake at the location of the neck and chest lesions seen on CT. However, patient was disqualified from surgery due to heart failure.

No adverse reactions were observed after tracer injection.

5. Discussion

MTC is still one of the most challenging endocrine cancers for both physicians and patients. In some MTC patients, despite of the elevated postoperative calcitonin levels and/or abnormal results of the pentagastrin test, there is no evidence of the disease in standard imaging procedures. Therefore searching for new targets for radioisotope diagnostics is warranted. $^{99m}$Tc(V)-dimercaptosuccinic acid (DMSA) was considered by many authors the agent of choice in the postoperative work-up of MTC. Sensitivities ranging from 50% up to 85% have been reported in patients with primary and recurrent MTC using planar scans. SPECT has increased the sensitivity of lesion detection. Shahram reported that $^{99m}$Tc(V)-DMSA had 91% sensitivity and 75% specificity for the detection of lung MTC compared to serum calcitonin as gold standard [21]. Another diagnostic modality is scintigraphy with $^{99m}$Tc-MIBI. Overall sensitivity and specificity of this agent range from 36% to 89% and 89% to 100%, respectively [22]. Üğur et al. have compared the sensitivity of $^{99m}$Tc-MIBI, $^{201}$TI, and $^{99m}$Tc(V)-DMSA and shown them to be 47%, 19%, and 95%, respectively [23]. MIBG labelled with $^{123}$I or $^{131}$I, in spite of its high specificity (>95%), is of little clinical utility with a reported sensitivity of 30% [24]. Results from imaging with monoclonal antibodies including $^{123}$I-, $^{131}$I-, and $^{111}$In labeled CEA, both whole antibody and fragments, and $^{111}$In-anticalcitonin antibody varied, ranging from 0% for anticalcitonin antibody to 78% for $^{131}$I-anti-CEA antibody [25]. Results of somatostatin receptor scintigraphy (SRS) using an octreopeptides labeled with either $^{111}$In-DTPA or $^{99m}$Tc-EDDA/HYNIC in MTC patients reported in the literature have been also extremely variable. The overall sensitivity of $^{111}$In-pentetreotide scintigraphy for the detection of MTC varies between 35 and 70% in different studies. Krenning et al. reported sensitivity of 65% in detecting MTC lesions by octreoan, although the sensitivity was lower for liver metastases as a result of nonspecific hepatic uptake [26]. According to other authors, scintigraphy with $^{111}$In-DTPA-octreotide has shown a sensitivity of 50–75%, that is higher than radiolabelled MIBG [27] and similar or slightly superior to $^{99m}$Tc(V)-DMSA [28]. $^{18}$FDG-PET was more sensitive especially in detecting cervical, supraclavicular, and

![Figure 1: The positive results of GLP-1 receptor imaging in a 74-year-old patient (J.S.) with sporadic MTC; pathological uptake of the tracer in liver metastases is visualized. (a) Axial slices and (b) coronal slices.](image-url)
mediastinal lymph nodes, but failed to detect small lesions in the lungs and liver [29]. However, other studies have shown a lower sensitivity of ¹⁸F-FDG-PET when compared with CT [30]. Data from the study by Ong and coworkers suggested that ¹⁸F-FDG-PET is useful mainly in patients with calcitonin levels exceeding 1000 pg/mL (78% sensitivity), whereas it has limited value in patients with calcitonin levels below 500 pg/mL (20% sensitivity) [31]. Preliminary data suggest that ¹⁸F-L-dihydroxyphenylalanine (L-DOPA) PET may provide a better lesion detection than ¹⁸F-FDG for MTC lesions. Beheshiti et al. observed that ¹⁸F-DOPA correctly visualized 81% of MTC lesions compared to 58% detected with ¹⁸F-FDG [32]. Hoegerle et al. reported an overall sensitivity of 63% for ¹⁸F-DOPA PET in 11 patients with MTC, which was lower than that observed with CT/MRI (it should be stressed that authors used a stand-alone PET system and not a hybrid PET/CT system), but higher than those observed with ¹⁸F-FDG and ¹¹¹In-DTPA-octreotide scan [33].

Above-mentioned diversity of sensitivity and specificity of different imaging modalities used in patients with suspicion of recurrence or dissemination of MTC stresses the necessity of searching for new more accurate diagnostics tools.

To the knowledge of the authors, this paper presents the first clinical experience with Lys⁴⁰(Ahx-HYNIC-⁹⁹mTc/EDDA)NH₂-exendin-4 in the detection of the recurrence or dissemination of MTC. The quality of obtained images was high; however, the image fusion was mandatory for proper diagnosis in all reported cases.

So far, the knowledge on GLP-1 application in MTC has emerged from experimental studies. The GLP-1 receptor protein expression was qualitatively and quantitatively investigated in many nonneoplastic and neoplastic human tissues with autoradiography method by Körner et al. [34]. They found GLP-1 receptor expression in 28% of medullary thyroid carcinomas examined and in 6% of normal human thyroid glands. GLP-1 receptor density of MTC cells was equal to 1,326 ± 264 dpm/mg tissue of receptor-positive cases. According to authors, medullary thyroid carcinomas exhibited a notable, but lower, GLP-1 receptor expression compared with, for example, pheochromocytomas. In recent paper by Gier et al. thyroids obtained from 12 individuals were examined for GLP-1 receptor protein by immunostaining [35]. GLP-1 receptor immunoreactivity was detected in approximately 10–30% of the tumor cells in five of the MTC cases. However, there was clear heterogeneity, with many calcitonin immunoreactive C cells being negative for GLP-1 receptor. The authors stated that these studies are in agreement with the work of Körner et al. [34].

Taking into account the GLP-1 receptor incidence and density in MTC, it seems that GLP-1 receptor imaging should not be used as the first-line diagnostic procedure in this group of patients. Nevertheless in case of patients with unclear or negative results of other imaging methods, but with clinical symptoms of MTC recurrence and/or elevated calcitonin concentration, this method gives the opportunity of localization of cancer tissue. Indeed, in our group of patients, the GLP-1 receptor imaging was carried out in two cases because of the discrepancy between results of performed diagnostic tests and resulted in confirmation MTC spread.

To sum up the GLP-1 receptor-expressing tumors, among others also MTC, are prospective candidates for in vivo targeting with Lys⁴⁰(Ahx-HYNIC-⁹⁹mTc/EDDA)NH₂-exendin-4.

6. Conclusions
Scintigraphy with Lys⁴⁰(Ahx-HYNIC-⁹⁹mTc/EDDA)NH₂-exendin-4 is able to detect the MTC lesions. It offers a new diagnostic tool to assess recurrence and staging of the disease in patients with MTC. GLP-1 receptor imaging should be considered as an alternative choice by clinicians especially in case of MTC patients in whom standard imaging techniques fail. However, further studies on the subject are needed.

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