



# TeleNEN as a telemedicine model for neuroendocrine neoplasm management in case of Meckel's diverticulum NET

Tele NEN — zastosowanie telemedycyny w postępowaniu w nowotworach neuroendokrynnych na przykładzie NET uchyłka Meckela

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## Abstract

A case of a 25-year-old female with NET deriving from Meckel's diverticulum is described.

The patient had a one-year history of dermatological skin problems. Ultrasound examination of the abdomen, performed because of arterial hypertension, revealed multiple hepatic lesions, which was confirmed in contrast-enhanced CT. The typical contrast-enhanced metastatic lesions in CT and elevated levels of chromogranin A suggested NET of unknown origin. SRS with <sup>99m</sup>Tc-HYNICTOC was performed for primary tumor localisation, revealing liver and paraaortic lymph node metastases but no sign of primary tumour location. As a next step for primary tumour localisation <sup>68</sup>Ga-DOTATATE PET/CT was performed, which revealed a focus of increased uptake in the small intestine, considered to be the primary tumour site. The imaging and clinical history of patient was discussed on TeleNEN (a novel model for the application of telemedicine in management of NEN). Due to the location of the primary tumour in the small intestine with no anatomical changes in CT, laparotomy guided with gamma probe after <sup>68</sup>Ga-DOTATATE injection was performed. During the surgery procedure, the primary tumour was hardly palpable in the tip of Meckel's diverticulum, confirmed by gamma probe. After surgery, tandem peptide receptor radionuclide therapy (PRRT) was started. The patient received four doses of <sup>90</sup>Y/<sup>177</sup>Lu-DOTATATE with total activity of 360 mCi (13.32 GBq). The three-month follow-up <sup>68</sup>Ga-DOTATATE PET/CT showed stable disease in the patient.

The presented case shows the importance of the role of a multidisciplinary team cooperating in patient management. Use of RGS is essential in cases like the one presented, when the tumour cannot be localised only by surgical palpation. (*Endokrynol Pol* 2018; 69 (3): 313–317)

**Key words:** Meckel neuroendocrine tumour, <sup>68</sup>Ga-DOTATATE, <sup>99m</sup>Tc-HYNICTOC, <sup>90</sup>Y/<sup>177</sup>Lu-DOTATATE, tandem PRRT

## Abstrakt

W pracy przedstawiono przypadek 25-letniej kobiety z nowotworem neuroendokrynny (NET) wywodzącym się z uchyłka Meckela. Pacjentka od roku była leczona dermatologicznie ze względu na występujące problemy skórne. Z powodu nadciśnienia tętniczego przeprowadzono badanie ultrasonograficzne, które ukazało liczne zmiany w wątrobie. Wynik ten został potwierdzony w tomografii komputerowej (CT) z kontrastem. Typowe zmiany przerzutowe w obrazie CT oraz podwyższone stężenie chromograniny A sugerowały NET o nieznanym punkcie wyjścia. W celu zlokalizowania punktu wyjścia nowotworu wykonano scyntyografię receptorów somatostatynowych (SRS) z <sup>99m</sup>Tc-HYNICTOC, w której wykryto przerzuty w wątrobie i okołoaortalnych węzłach chłonnych, jednak nie znaleziono punktu wyjścia nowotworu. Kolejnym krokiem w poszukiwaniu punktu wyjścia nowotworu było wykonanie badania <sup>68</sup>Ga-DOTATATE PET/CT, które ukazało ognisko zwiększonego wychwytu w jelicie cienkim, będące prawdopodobnym punktem wyjścia nowotworu. Zwołano ENETS Tumor Board, na którym przedyskutowano wyniki przeprowadzonych badań obrazowych oraz historię choroby pacjentki. Jako że w miejscu lokalizacji guza pierwotnego w jelicie cienkim nie widać było odpowiadającej zmiany anatomicznej w CT, przeprowadzono laparotomię pod kontrolą śródoperacyjnej sondy gamma z wykorzystaniem <sup>68</sup>Ga-DOTATATE. Odnaleziono prawie niewyczuwalny guz pierwotny w końcowej części uchyłka Meckela. Po zabiegu wdrożono celowaną terapię radioizotopową analogami somatostatyn (PRRT). Pacjentka otrzymała 4 dawki <sup>90</sup>Y/<sup>177</sup>Lu-DOTATATE o całkowitej aktywności 360 mCi (13,32 GBq). Po trzech miesiącach wykonano kontrolne badanie <sup>68</sup>Ga-DOTATATE PET/CT, które wykazało stabilny stan zmian chorobowych u pacjentki.

Przypadek ten został zaprezentowany w celu ukazania niezwykle istotnej roli jaką odgrywa współpraca zespołu wielodyscyplinarnego w leczeniu pacjentów. W momencie gdy zlokalizowanie guza niemożliwe jest wyłącznie za pomocą palpacji chirurgicznej, kluczową rolę odgrywa wykorzystanie izotopowej sondy śródoperacyjnej (RGS) podczas zabiegu tak, jak w prezentowanym przypadku. (*Endokrynol Pol* 2018; 69 (3): 313–317)

**Słowa kluczowe:** guz neuroendokrynny uchyłka Meckela, <sup>68</sup>Ga-DOTATATE, <sup>99m</sup>Tc-HYNICTOC, <sup>90</sup>Y/<sup>177</sup>Lu-DOTATATE, tandem PRRT



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## Introduction

Neuroendocrine tumours (NETs) are neoplasms that can synthesise, store, and release bioactive compounds. The most common localisation of NETs is the gastrointestinal tract. They are usually silent, which leads to very late diagnosis, when distant metastases are present. 30% of patients present the signs of carcinoid syndrome [1]. This is characterised most commonly by the abdominal pain (63%), diarrhoea (40%), weight loss (33%), and flushing (13%) [2].

NETs can originate from uncommon sites, which can lead to clinical confusion, delayed diagnosis, and inappropriate treatment. One of the less common localisations is Meckel's diverticulum. A study on a group of 13,715 patients with neuroendocrine tumours reported Meckel's diverticulum as a localisation only in 0.48% of cases overall and in 0.74% if only gastrointestinal tract is concerned [3].

Somatostatin receptor scintigraphy (SRS) is very useful for primary tumour location due to overexpression of somatostatin receptor by the majority of NETs. Previously  $^{111}\text{In}$ -DTPA-pantetreotide ( $^{\circ}$ Octreoscan, Malincrodt) was used with mean sensitivity 80% [4, 5] and  $^{99\text{m}}\text{Tc}$ -HYNICTOC ( $^{\circ}$ Tektrotyd, Polatom) with sensitivity 80–82%, specificity 69–92%, positive predictive value 92–98%, negative predictive value 47%, and accuracy 79–82% [6, 7]. The increasing availability of positron emission tomography (PET) led to the introduction of somatostatin analogues labelled with  $^{68}\text{Ga}$ , which became an indispensable part of the NET diagnosis with mean sensitivity 90.9% and specificity 90.6% in meta-analysis [8].

In the majority of NETs surgical treatment of the primary tumour is very important. Radioguided surgery

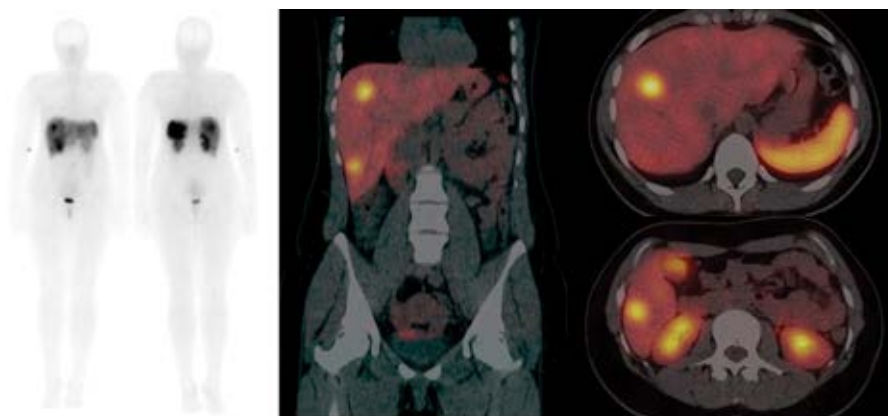
(RGS) uses a radiation detection probe to localise the tumour. According to Kaemmerer et al., RGS with  $^{68}\text{Ga}$ -labeled somatostatin analogues allows detection of nearly two times more of NET lesions comparing with surgical palpation and in 56% of cases leads to a change of surgical procedure [9].

## Case report

A 25-year-old female with a one-year history of dermatological skin problems, like flushing and acne, diarrhoea, eyelid oedema, and lacrimation, was referred to the nuclear medicine department with suspicion of NET of unknown origin.

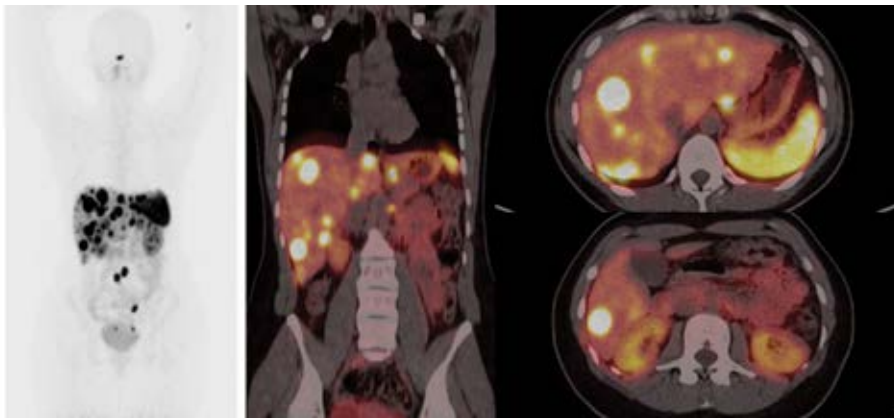
Because of arterial hypertension 200/120 mmHg with tachycardia up to 120/min, the patient was referred for ultrasound (US) examination of the abdomen, which revealed multiple hepatic lesions. The next diagnostic step, abdominal CT examination, showed multiple hepatic lesions previously seen in US, with typical enhancement for NETs in the arterial phase, and several mesenteric lymph nodes, but no characteristic sign of primary tumour location. The typical contrast enhanced metastatic lesions in CT and elevated levels of chromogranin A (163.32 ng/ml; reference range 0–98 ng/ml) suggested NET of unknown origin.

The patient was therefore referred to the nuclear medicine department. SRS with  $^{99\text{m}}\text{Tc}$ -HYNICTOC was performed. SRS revealed multiple focal hepatic lesions and two paraaortic lymph nodes with overexpression of somatostatin receptors but still no sign of primary tumour location (Fig. 1). Ultimately, liver biopsy confirmed the diagnosis of NET G1. Since SRS had not shown the primary tumour site, further examination —  $^{68}\text{Ga}$ -DOTATATE PET/CT — was performed.



**Figure 1.**  $^{99\text{m}}\text{Tc}$ -HYNICTOC whole-body scan and SPECT/CT showing liver metastasis and paraaortic lymph node. Physiological distribution of radiopharmaceutical in rest of the liver, spleen, and urinary bladder. Injection of radiotracer in the right forearm

**Rycina 1.** W badaniu po podaniu  $^{99\text{m}}\text{Tc}$ -HYNICTOC całego ciała oraz SPECT/CT widoczne są przekroży do wątroby i okołoaortalnych węzłów chłonnych. Fizjologiczne gromadzenie radiofarmaceutyku w śledzionie, pęcherzu moczowym. W prawym przedramieniu miejsce wstrzyknięcia radioznacznika



**Figure 2.**  $^{68}\text{Ga}$  DOTATATE PET/CT showed multiple liver metastasis and paraaortic lymph node, which in part correspond with  $^{99\text{m}}\text{Tc}$ -HYNICTOC examination. On MIP (maximal image projection) additional foci in the intestine and pelvis was shown

**Rycina 2.** W badaniu  $^{68}\text{Ga}$  DOTATATE PET/CT widoczne są liczne przerzuty w wątrobie oraz okołoaortalnych węzłach chłonnych, które częściowo odpowiadają lokalizacji zmian w badaniu  $^{99\text{m}}\text{Tc}$ -HYNICTOC. Na MIP (maximal image projection) widoczne dodatkowe ogniska w jelicie (punkt wyjścia) i miednicy

It revealed previously known multiple metastases and paraaortic lymph nodes (SUVmax 14.5–97.5), as well as a new focal lesion of increased uptake in the small intestine (SUVmax 28.6), considered to be the primary tumour site, and focal lesions in both ovaries (SUVmax 12.1 and 14.1) (Fig. 2). Examinations carried out during the patient's stay in the Division of Endocrinology showed highly increased levels of chromogranin A ( $> 1500 \mu\text{g/l}$ , reference range  $< 125 \mu\text{g/l}$ ) and serotonin (1637 ng/ml, reference range 70–270 ng/ml) in blood and urinary excretion of 5-hydroxyindole acetic acid (5-HIAA) (61 mg/24h, reference range 2–9 mg/24h). Carcinoid syndrome was diagnosed.

In such a diagnostic statement, therapy with long-acting somatostatin analogue (Lanreotide:  $^{\text{®}}$ Somatuline Autogel, Ipsen) was started.

The clinical history of patient and imaging was discussed on TeleNEN Tumor Board (a novel model for the application of telemedicine in management of NEN). The modern TeleNEN platform is online consultations between the doctors most experienced in NEN patient care allow us to continually expand our knowledge, which is particularly important in tumors with such a diverse clinical course. The radiologist confirmed no visible anatomical changes in the small intestine, so classical surgery was not possible. According to the guidelines of the Polish Network of Neuroendocrine Tumours, due to the location of the primary tumour in the small intestine, gamma probe-guided surgery was taken into consideration [10]. Based on previous experience, the treatment plan included tandem peptide receptor radionuclide therapy (PRRT) three months after the surgery of the primary tumour [11].



**Figure 3.** Post-surgical appearance of tumour from Meckel's diverticulum

**Rycina 3.** Preparat pooperacyjny guza z uchyłka Meckela

The patient was directed to the surgical department of the Medical University of Warsaw with gamma probe surgery of NET experience. She underwent laparotomy guided with gamma probe (Sonda Neo 2000) after 80 MBq  $^{68}\text{Ga}$ -DOTATATE injection. During the surgery procedure, the primary tumour was hardly palpable in the tip of Meckel's diverticulum but clearly detected by gamma probe. Additionally, three hard, enlarged, mesenteric lymph nodes corresponding to lymph drainage from Meckel's diverticulum were resected, and a small

left ovary section was taken. The histopathological examination showed NET G1 of the Meckel's diverticulum pT3, N1, Mx, with focal angioinvasion and three metastatic lymph nodes; no malignancy in the ovary was recognised. After the surgery, the patient's condition was stable. The postoperative period was uncomplicated. The long-acting somatostatin analogue was continued after surgery.

Three months later the patient started tandem Peptide Receptor Radionuclide Therapy (PRRT) with  $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE according to the previously described protocol [16]. Between October 2016 and May 2017 patients received four doses of  $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE with total activity of 360 mCi (13.32 GBq) with amino-acid infusion for nephroprotection. The last dose was reduced to 60 mCi (2.22 GBq) due to decreasing of WBC to  $1.8 \times 10^9/\text{l}$ . The rest of the laboratory tests during the therapy were stable.

At the beginning of therapy ambulatory blood pressure monitoring (ABPM) was performed: mean 24-hour blood pressure (BP) was 104/69 mmHg — day BP 107/71 mmHg, and night BP 96/63 mmHg. Diurnal urinary excretion of catecholamine metabolites were within normal range — 717 ug/24 hours.

Both before and after the administration of radionuclide, facial and chest flushing were presented, with a slightly more intensive attack during the first few hours after each dose. The patient complained of insignificant nausea due to amino acid administration; however, no vomiting was observed. The symptoms were relieved by ondansetron.

The patient underwent three months of follow-up, which included clinical, biochemical, and hormonal tests as well as  $^{68}\text{Ga}$ -DOTATATE PET/CT.

Clinical symptoms of carcinoid syndrome are still present but are less intensive. Levels of chromogranin A (279  $\mu\text{g}/\text{l}$ ) and serotonin (735.5 ng/ml) are significantly lower, but measurements of 5-HIAA are in the same range (63 mg/24h).

$^{68}\text{Ga}$ -DOTATATE PET/CT examination has shown the patient to be stable.

## Discussion

The unique characteristic of NETs with the presence of somatostatin receptors allows us to localise even small tumours (especially located in the intestine) intraoperatively using a gamma probe. This technique is indispensable in the localisation of NETs that are difficult to find by palpation during traditional surgery, and it offers the immediate localisation of the primary NET.

The use of gamma probes in oncology began in 1949 when Selverstone et al. employed a Geiger-Muller probe counter for tumour localisation during brain

surgery [12]. But the real rise in their use dates as far back as the ninetieth century. Nowadays we use numerous radiotracers not only for mapping the sentinel lymph node but also, as in our case, for the localisation of the primary lesions.  $^{68}\text{Ga}$ -labelled peptides are especially useful in the localisation of the primary tumour site.

Radioguided surgery is considered to be a useful tool in localisation of NETs even as small as 0.5 cm. A study analysing the feasibility of RGS showed that it is especially valuable in the small intestine and mesenteric lymph nodes, where the correct identification of lesions reaches 81% [13]. In the same study 8.6% of lesions detected by gamma probe were neither possible for palpation nor visualisation by the surgeon [13].

Because the only curative method for gastrointestinal NETs is surgery it is really important to define the number and extent of lesions. It allows a radical surgery, which reduces recurrence and improves the quality of the patient's life.

As in all methods, the intraoperative use of gamma probe can have some limitations. The main limitation of the probe is its dependence on the positioning and therefore on the operator's skills. In some cases, high background activity due to the physiological uptake might be another problem. In some localisations of the tumours, e.g. the tail of the pancreas, it can hinder or even prevent tumour detection by the probe [13, 14].

Another problem could be the short half-life of the isotope used for that RGS, especially in cases of recurrence of diseases where the reoperation area may be hindered by adhesions. The optimum injection time has not yet been established because gamma camera reading can be done both too early and too late, disrupting the result.

The presented case shows the importance of the role of multidisciplinary team cooperation in patient management. Use of RGS is essential in cases like the one presented, in which the tumour cannot be localised only by surgical palpation.

## Conflict of interest

No conflict of interest

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