Endokrynologia Polska
DOI: 10.5603/EP.a2020.0014
Volume/Tom 71; Number/Numer 3/2020
ISSN 0423–104X

Effect of peptide receptor radionuclide therapy (PRRT) with tandem isotopes — [^{90}Y]Y/[^{177}Lu]Lu-DOTATATE in patients with disseminated neuroendocrine tumours depending on [^{18}F]FDG PET/CT qualification in Polish multicentre experience — do we need [^{18}F]FDG PET/CT for qualification to PRRT?

Anna Zemczak[1], Maciej Kołodziej[2], Paweł Gut[3], Leszek Królicki[4], Beata Kos-Kudła[1], Grzegorz Kamiński[2], Marek Ruchała[3], Dariusz Pawlak[5], Jolanta Kunikowska[4]

[1]*Department of Endocrinology and Neuroendocrine Tumours, Department of Pathophysiology and Endocrinology, Medical University of Silesia, Katowice, Poland*
[2]*Department of Endocrinology and Radioisotope Therapy, Military Institute of Medicine, Warsaw, Poland*
[3]*Department of Endocrinology, Metabolism, and Internal Medicine, Poznan University of Medical Sciences, Poznan, Poland*
[4]*Nuclear Medicine Department, Medical University of Warsaw, Poland*
[5]*Radioisotope Centre POLATOM, National Centre for Nuclear Research, Otwock–Swierk, Poland*

Abstract

Introduction: Peptide receptor radionuclide therapy (PRRT) using radiolabelled somatostatin analogues is a treatment option for patients with disseminated neuroendocrine tumours (NET). The aim of the study was the evaluation of the role of [^{18}F]FDG PET/CT in predicting response, progression-free survival (PFS) and overall survival (OS) after tandem therapy [^{90}Y]Y/[^{177}Lu]Lu-DOTATATE.

Material and methods: Seventy-five patients with histopathologically proven NET G1 and G2 were included in the study. Before treatment [^{68}Ga]Ga-DOTATATE PET/CT and [^{18}F]FDG PET/CT was performed. Patients were treated with [^{90}Y]Y/[^{177}Lu]Lu-DOTATATE (1:1) with mixed amino-acid infusion for kidney protection.

Results: Progression-free survival was 22.2 months for [^{18}F]FDG-positive patients and 59.3 months for [^{18}F]FDG-negative patients ($p = 0.003$). The OS from diagnosis (OS-D) and from the start of PRRT (OS-T) was not reached in [^{18}F]FDG-negative patients, and in [^{18}F]FDG-positive patients it was 71.8 months and 55.8 months, respectively.

The observed overall one-year survival in [^{18}F]FDG-positive *vs.* [^{18}F]FDG-negative patients was 96.8% *vs.* 99.1%, two-year survival was 88.9% *vs.* 96%, and five-year survival was 58.8% *vs.* 88%, respectively. The one-year and two-year risk of progression was 15% *vs.* 58.9% in [^{18}F]FDG-positive patients and 11% *vs.* 32% in [^{18}F]FDG-negative patients. The objective response rate (ORR) [^{18}F]FDG-positive *vs.* [^{18}F]FDG-negative patients was 41.7% *vs.* 17%.

Conclusions: [^{18}F]FDG-positive patients have statistically significant shorter survival parameters than [^{18}F]FDG-negative patients. The risk of progression in [^{18}F]FDG-positive *vs.* [^{18}F]FDG-negative patients in one-year follow-up is comparable, whereas in two-year follow-up it is nearly two times higher for [^{18}F]FDG PET/CT-positive patients. **(Endokrynol Pol 2020; 71 (3): 240–248)**

Key words: *PRRT; [^{90}Y]Y/[^{177}Lu]Lu-DOTATATE; [^{18}F]FDG PET/CT; tandem therapy; neuroendocrine tumours*

Introduction

Neuroendocrine tumours (NET) deriving from cells of diffuse endocrine system (DES) are a rare, heterogeneous group of the digestive system and lungs [1–3]. According to epidemiological data from recent years, the incidence and detection rate of those tumours has significantly increased [1, 2, 4, 5].

Histopathological examination determines the diagnostic and treatment protocol. The most important histopathological feature of clinical importance is the grading (G), assessed based on proliferation index Ki-67 and number of mitotic figures. Grading is an independent parameter dividing tumours into three groups: G1 with low, G2 with medium, and G3 with high malignancy [1].

In 2017, according to the 8th Edition of Union for International Cancer Control (UICC) and World Health Organisation (WHO) classification, new neuroendocrine neoplasia (NEN) classification, divided into

Anna Zemczak, Department of Endocrinology and Neuroendocrine Tumours, Department of Pathophysiology and Endocrinology, Medical University of Silesia, 40–514 Katowice, Ceglana St. 35, Poland, tel./fax: (+48) 32 35 81 366; e-mail: aniazemczak@poczta.onet.pl

well-differentiated NET G1 (Ki-67 < 3%), G2 (Ki-67 3–20%), and G3 (Ki-67 21–55%), as well as poorly-differentiated NEC (Ki-67 > 55%), was implemented [1, 6–9].

Currently, the gold standard in functional imaging for NET is somatostatin receptor imaging (SRI) with positron emission tomography PET/CT using ^{68}Ga-labelled somatostatin analogues [1, 10]. This examination is crucial for the assessment of expression of somatostatin receptors before planned radioisotope treatment in patients with advanced well-differentiated G1 and G2 NET.

Until now it was considered that [^{18}F]FDG PET/CT is not very useful in NET diagnosis, which, due to slow its growing behaviour, are not characterised by increasing uptake of glucose. On the other hand, increased metabolism of glucose appears in the case of many other neoplasms and correlates with the degree of malignancy. Based on publications, increased uptake in [^{18}F]FDG PET/CT in NET is currently considered as a crucial negative prognostic factor [1, 10–14].

For heterogeneous presentation and behaviour over time, NEN management should be discussed in multidisciplinary meetings [15].

The aim of the study was to evaluate the role of [^{18}F]FDG PET/CT in predicting response, progression-free survival (PFS), and overall survival (OS) after simultaneous use of [^{90}Y]Y- and [^{177}Lu]Lu-DOTATATE in tandem peptide receptor radionuclide therapy ([^{90}Y]Y/[^{177}Lu]Lu-DOTATATE) in patients with disseminated NET G1 and G2 in a multicentre trial. Additionally, we assessed survival parameters in relation to disease grading.

The main objective of this study was to evaluate PFS and OS depending on [^{18}F]FDG PET/CT after simultaneous use of [^{90}Y]Y- and [^{177}Lu]Lu-DOTATATE.

Material and methods

This multi-institution study was approved by the Ethical Committees of theMedical University of Warsaw, Military Institute of Medicine, Warsaw, and the University of Medical Sciences, Poznan. All patients gave written, informed consent.

Patients

Seventy-five patients (males and females with mean age 56.8 [± 11.6 SD] years) with diffused, histologically confirmed NET were included in the study.

Tumours were categorised according to the current TNM staging and grading system for NET.

All patients met the following inclusion criteria:

— histological confirmation of NET G1 or G2 tumour; metastatic disease;
— preserved haematological, liver, and renal parameters: haemoglobin ≥ 10 g/dL, white blood cell (WBC) count ≥ 3 × 10^9/L, platelet count ≥ 90 × 10^9/L, bilirubin ≤ 1.5 × upper limit of normal (ULN), ALT < 2.5 × ULN, and estimated creatinine clearance (CrCl) > 40 mL/min;
— positive somatostatin receptor imaging (SRI): PET/CT using [^{68}Ga]Ga-DOTATATE with uptake equal to or higher than liver;
— Karnofsky index ≥ 70, ECOG performance status ≤ 2;
— age > 18 years;
— life expectancy > 3 months;
— no pregnancy or lactation.

The exclusion criteria were as follows:

— patients with mismatch lesion: positive in [^{18}F]FDG and negative in [^{68}Ga]Ga-DOTATATE PET/CT.

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

[^{68}Ga]Ga-DOTATATE and [^{18}F]FDG PET/CT

The PET/CT examinations (vertex to upper thigh) were performed 60-70 minutes after intravenous injection of 120-200 MBq [^{68}Ga]Ga-DOTATATE and 300-370 MBq of [^{18}F]FDG on a Biograph 64 TruePoint PET/CT scanner (Siemens Medical Solutions, Knoxville). To increase renal washout, 20 mg of furosemide was administered intravenously after injection of [^{68}Ga]Ga-DOTATATE.

All patients were requested to drink 1.5 L of water and to void before the PET/CT examination.

Patients were imaged in a supine position with arms raised, according to standard CT practice. A continuous CT was acquired in spiral mode using 120 kV, 170 mAs, 2 mm slice thickness, and a pitch of 0.8. Patient position and topogram of the PET/CT examination was identical to that of CT, at a rate of three minutes per bed position for [^{68}Ga]Ga-DOTATATE and two minutes for [^{18}F]FDG, 6-7 bed positions depending on the size of the patient.

Emission data was reconstructed on a 168 × 168 matrix, using ordered subsets expectation maximisation algorithm (three iterations, 21 subsets for [^{68}Ga]Ga-DOTATATE and two iterations, 14 subsets for [^{18}F]FDG). Attenuation was corrected with the CT. The PET/CT images, which consisted of half body attenuated and non-attenuated PET, CT, and fused images, were transferred to a multimodal workstation (MMWS) (Syngo TrueD Siemens Medical Solutions) for analysis.

Study treatment and radiopeptide administration

In 6- to 12-week intervals between cycles all patients received intravenous infusions of tandem [^{90}Y]Y/[^{177}Lu]Lu-DOTATATE with amino-acid infusion for nephroprotection, with treatment procedure as previously described [16].

Tandem therapy [^{90}Y]Y/[^{177}Lu]Lu-DOTATATE consisting of 50% radioactivity of [^{90}Y]Y-DOTATATE (1.48–1.85GBq) and 50% radioactivity of [^{177}Lu]Lu-DOTATATE (1.48-1.85GBq) with a treatment ratio of 1:1, was prepared using previously described methods with ^{90}Y and ^{177}Lu (ItraPol, LutaPol, POLATOM, Poland) [17–19].

Peptide receptor radionuclide therapy was performed in patients receiving long-acting somatostatin analogue 4-5 weeks after completing therapy with octreotide (Sandostatin LAR; Novartis) and 5-7 weeks after completing therapy with lanreotide (Somatuline Autogel; Ipsen). The interval between chemotherapy and PRRT was longer than three months. Sixty-two patients were treated with "cold" somatostatin analogues (41 with octreotide and 21 with lanreotide) before PRRT, during radioisotope therapy, and at follow-up.

Post-therapy imaging

Twenty-four hours after the therapy post-therapy imaging was performed, enabling biodistribution to be monitored during the treatment. The acquisition was made with an energy window ± 10% centred on ^{177}Lu photopeaks (208 keV), as described previously [17–19].

Images analysis

PET images analysis was performed using a Siemens Workstation (True D, Siemens Medical Solutions Inc., USA).

The PET/CT images were reviewed by two certified nuclear medicine physicians, and CT/MRI was performed by the radiologist, both with more than five years' experience.

Attenuation-corrected PET images and PET/CT images were analysed. Nonattenuation corrected PET images were also reviewed. On visual analysis, abnormal uptake was determined as a positive lesion when it exhibited non-physiological increased uptake that was discernible above background activity seen on coronal, transaxial, and sagittal views. Linear and tubular areas of increased uptake in the gastrointestinal tract were ascribed to physiological activity and considered negative for malignancy. For quantitative analysis, the maximal standard uptake value (SUVmax) of a positive lesion was measured on [^{68}Ga]Ga-DOTATATE and [^{18}F]FDG PET/CT images with spherical volumes of interest (VOIs).

Assessment of treatment results and clinical benefits

All patients underwent staging by contrast-enhanced CT or MRI, [^{18}F]FDG PET/CT, and [^{68}Ga]Ga-DOTATATE PET/CT.

The monitoring of treatment response after completing PRRT was done at 3-6, 12 months, and every 12 months thereafter, using blood markers and diagnostic imaging.

Restaging was performed 12 months after completing PRRT using the Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 criteria for radiological evaluation and SRI.

Blood tests for complete blood cell count and kidney and liver function parameters were repeated every 7-21 days after each therapy cycle, at 3, 6, and 12 months, and every 12 months after completing the therapy. Toxicity was recorded using the Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Kidney function was estimated using the Modification of Diet in Renal Disease formula.

Statistical methods

Mean values and standard deviations, medians, and quartiles or frequencies depending on the parameter distribution were used to summarise patients' characteristics.

Overall survival from the disease diagnosis was defined as the time from the first diagnosis of the tumour to death from any cause (OS-D). OS from the start of the treatment was defined as the time from the first cycle of [^{90}Y]Y/[^{177}Lu]Lu-DOTATATE treatment to death from any cause (OS-T).

OS, PFS, probability of a one-year, two-year, and five-year OS, and one-year and two-year risk of progression were calculated using the Kaplan-Meier estimator and compared using the log-rank test. Calculations were done using GraphPad PRISM 5 (GraphPad Software Inc.).

Results

Patients' characteristics

Peptide receptor radionuclide therapy was the first line of systemic therapy only in one patient. Of the remaining 74 patients before PRRT, 56 patients underwent surgery, 62 patients were treated with long-acting somatostatin analogues, and 15 patients had received chemotherapy.

Detailed patients' data are shown in Table 1.

Table 1. *Patients' characteristics*

Characteristics	Value
Total no. of patients	75
Age (years)	
Mean	56.8
Range	26-77
Gender	
Male	25
Female	50
Primary tumour site	
Pancreas	24
Small intestine	22
Large intestine	16
Lung	4
Unknown	9
Grade	
1	27
2	48
[^{18}F]FDG PET/CT positivity	
Positive	27
Negative	48

Results of [^{90}Y]Y/[^{177}Lu]Lu-DOTATATE tandem therapy based on [^{18}F]FDG PET/CT scans

Patients were usually treated with four cycles of 3.7 GBq of [^{90}Y]Y/[^{177}Lu]Lu-DOTATATE per injection at 6–12 week intervals, depending on clinical status, laboratory results, and radiopharmaceutical availability. The administered cumulative activity was 7.4-14.8 GBq [^{90}Y]Y/[^{177}Lu]Lu-DOTATATE. Two patients received only two doses due to lack of cooperation, and withdrew from treatment continuation. Four patients received three doses with cumulative activity of 9.3–11.1 GBq, one due to deterioration of leucocytes during therapy and three due to low body mass (below 50 kg). At the time of restaging, one year after therapy, four patients died.

All patients had positive [^{68}Ga]Ga-DOTATATE PET/CT study in all defined lesions. [^{18}F]FDG was positive in 5% of patients with grade 1 NET and in 31% of patients with grade 2 NET.

The median follow-up duration was 45.3 months (range 7.2-122.8) for [^{18}F]FDG-positive and 59.6 months (range 11.1-116.7) for [^{18}F]FDG-negative patients.

Twenty-seven patients had positive [^{18}F]FDG PET/CT scans with a median overall survival time from diagnosis (OS-D) of 71.8 months (range 13.8-166), and 48 patients had negative [^{18}F]FDG PET/CT scans without reaching median survival time from diagnosis (range 27.9–207.3 months). Survival times for [^{18}F]FDG PET/CT-negative patients were significantly longer than those for [^{18}F]FDG-positive patients ($p = 0.003$) (Tab. 2).

Analysing outcomes since the start of radioisotope treatment overall survival (OS-T) was 55.8 months [^{18}F]FDG PET/CT-positive patients, and wasn't reached at [^{18}F]FDG PET/CT-negative ($p = 0.002$) (Fig. 1).

Table 2. *[18F]FDG positive vs. [18F]FDG negative*

	[18F]FDG+ (n = 27)	[18F]FDG– (n = 48)	p
PFS	22.2	59.3	0.0027
OS-T	55.8	ND	0.0021
OS-D	71,8	ND	0.0031

PFS — progression-free survival; OS-T — overall survival from the time of therapy; OS-D — overall survival from diagnosis; ND — no data

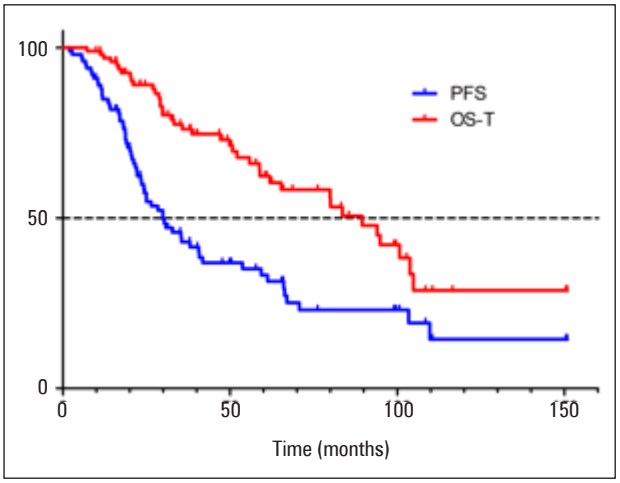

Figure 1. *Tandem [90Y]Y/[177Lu]Lu-DOTATATE therapy: Kaplan-Meier estimators of progression-free survival (PFS) in relation to the overall survival from the time of therapy (OS-T)*

Progression-free survival time (PFS) was 22.2 months in [18F]FDG PET/CT-positive patients and 59.3 months for [18F]FDG PET/CT-negative patients (p = 0.003) (Fig. 2).

The observed overall one-year survival in [18F]FDG PET/CT-positive *vs.* [18F]FDG PET/CT-negative patients was 96.8% *vs.* 99.1%, two-year survival was 88.9% *vs.* 96%, and five-year survival was 58.8% *vs.* 88%, respectively.

The one-year and two-year risk of progression was 15% *vs.* 58.9 % in [18F]FDG PET/CT-positive patients and 11% *vs.* 32% in [18F]FDG PET/CT-negative patients.

By the time of restaging one year after the therapy, three patients had died from the [18F]FDG PET/CT-positive group and one from the [18F]FDG PET/CT-negative group.

At 12-month follow-up in [18F]FDG PET/CT-positive *vs.* [18F]FDG PET/CT-negative patients, the following was observed: complete response (CR) 1/24 (4.2%) *vs.* 1/47 (2.1%); partial response (PR) 9/24 (37.5%) *vs.* 7/47 (14.9%), and stable disease (SD) 10/24 (41.7%) *vs.* 32/47 (68.1%), respectively.

Disease control rate (DC), defined as in the proportion of patients achieving PR or CR, and SD, at [18F]FDG PET/CT-positive *vs.* [18F]FDG PET/CT-negative patients was 83.4% *vs.* 85.1%.

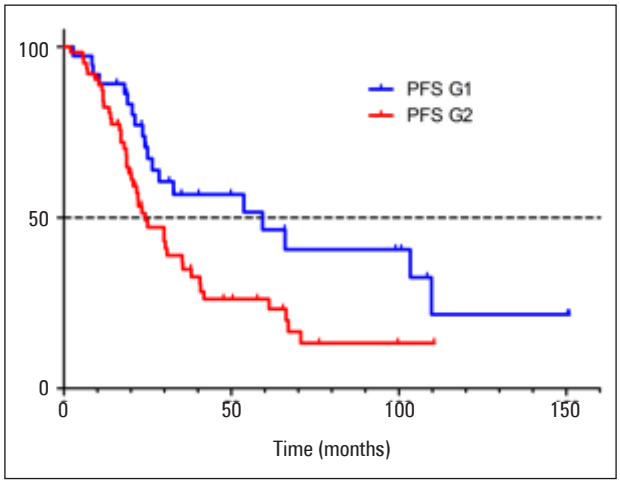

Figure 2. *Tandem [90Y]Y/[177Lu]Lu-DOTATATE therapy: Kaplan-Meier estimators of progression-free survival (PFS) in relation to the disease grade*

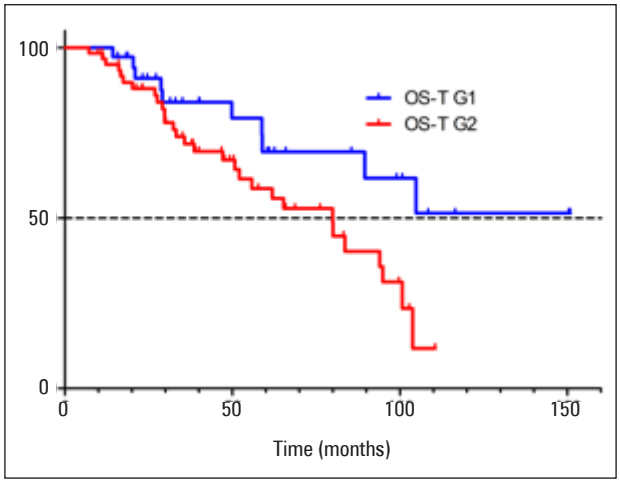

Figure 3. *Tandem [90Y]Y/[177Lu]Lu-DOTATATE therapy: Kaplan-Meier estimators of overall survival from the time of PRRT (OS-T) in relation to the disease grade*

The objective response rate (ORR), defined as in the proportion of patients achieving PR or CR, at [18F]FDG PET/CT-positive *vs.* [18F]FDG PET/CT-negative patients, was 41.7% *vs.* 17%.

Impact of G1 vs. G2

When the proliferation index of tumours (G1, n = 27; G2, n = 48) was taken into consideration, the Kaplan–Meier curve analysis did not show a significant impact on survival parameters (Tab. 3).

The observed overall one-year survival in G1 *vs.* G2 was 96.9% *vs.* 96.2%, two-year was 88.9% *vs.* 91.5%, and five-year survival was 65.5% *vs.* 64.6%, respectively.

Table 3. *Impact of G1 vs. G2*

	G1 (n = 27)	G2 (n = 48)	p
PFS	53.7	30.3	NS
OS-T	ND	80.0	NS
OS-D	ND	102.6	NS

PFS — progression-free survival; OS-T — overall survival from the time of therapy; OS-D — overall survival from diagnosis; ND — no data; NS — non significant

The one-year and two-year risk of progression was 11.8% and 32.4% in G1 patients and 12.6 and 43.4% in G2 patients, respectively.

In the G1 group 55% showed progression after PRRT, and in the G2 group, 69%.

Group of patients with G1 NET

G1: [18F]FDG positive *vs.* [18F]FDG negative

The distinction between [18F]FDG-positive (n = 4) and [18F]FDG-negative (n = 23) patients with G1 was significant for PFS; the median PFS was 23.1 months *vs.* 59.3 months (p = 0.049), respectively, for OS-T and OS-D was not significant (Tab. 4).

The observed overall one-year survival for G1 [18F]FDG-positive patients *vs.* [18F]FDG-negative was 85.7% *vs.* 96.4%, two-year survival was 63.3% *vs.* 91.3%, and five-year survival was 25% *vs.* 76.4%, respectively.

The one-year *vs.* two-year risk of progression was 83.7% *vs.* 68.4% in [18F]FDG-positive patients and 13.7% *vs.* 31% in [18F]FDG-negative patients.

Group of patients with G2 NET

G2: [18F]FDG-positive *vs.* [18F]FDG-negative

The distinction between [18F]FDG-positive (n = 23) *vs.* [18F]FDG-negative (n = 25) patients with G2 was significant for all survival parameters; the median PFS was 22.2 months *vs.* 40.6 months (p = 0.030), OS-t 55.8 months *vs.* not reached (p = 0.020), OS-D 71.8 months and not reached (p = 0.010), respectively (Tab. 5).

Table 4. *Group of patients with G1 NET: [18F]FDG positive vs. [18F]FDG negative*

	[18F]FDG+ (n = 4)	[18F]FDG– (n = 23)	p
PFS	23.1	59.3	0.0499
OS-T	43.8	ND	NS
OS-D	55.2	ND	NS

PFS — progression-free survival; OS-T — overall survival from the time of therapy; OS-D — overall survival from diagnosis; ND — no data; NS — non significant

Table 5. *Group of patients with G2 NET: [18F]FDG positive vs. [18F]FDG negative*

	[18F]FDG+ (n = 23)	[18F]FDG– (n = 25)	p
PFS	22.2	40.6	0.0284
OS-T	55.8	ND	0.0209
OS-D	71.8	ND	0.0146

PFS — progression-free survival; OS-T — overall survival from the time of therapy; OS-D — overall survival from diagnosis; ND — no data

The observed overall one-year survival in [18F]FDG-positive *vs.* [18F]FDG-negative patients was 91.5% *vs.* 100%, two-year was 82.6% *vs.* 100%, and five-year survival was 43.3% *vs.* 84.9%, respectively.

The one-year and two-year risk of progression was 17.5 % *vs.* 57.1% in [18F]FDG-positive patients and 9.1% *vs.* 32.8% in [18F]FDG-negative patients.

Examples of therapeutic effects are presented in Figure 4, 5.

Side effects

PRRT was well tolerated by all patients, without any serious acute adverse events. During the treatment transient leukocytopaenia and thrombocytopaenia occurred in two patients (3%).

According to the CTCAE criteria, after PRRT, 11 (15%) patients had anaemia (nine patients were grade 1, two patients were grade 2); 17 (23%) patients had leukopaenia (grade 1 was observed in 16 patients and grade 2 in one patient); five (7%) patients had thrombocytopaenia (grade 1 in four patients and grade 2 in one patient). One patient (1%) developed myelodysplastic syndrome. Grade 1 nephrotoxicity was seen in nine patients (12%) and grade 2 in one patient (1%).

No other grade 3 or 4 haematological or renal toxicity or any grade hepatic toxicity were observed.

Discussion

Peptide receptor radionuclide therapy is a valid, therapeutic option for advanced or inoperable NET, which is used with different schedules in several protocols [13, 20, 21]. Various studies showed efficacy of PRRT in the gastroenteropancreatic NET (GEP-NET) with an objective response rate of approximately 30%. A few retrospective studies demonstrated that overall remission rates in metastatic pulmonary neuroendocrine tumours were comparable to those in GEP-NET [22–26].

In this retrospective study we analysed the survival outcome data from the group of 75 patients with NET G1 and G2 undergoing tandem PRRT with simultaneous use of [90Y]Y- and [177Lu]Lu-DOTATATE.

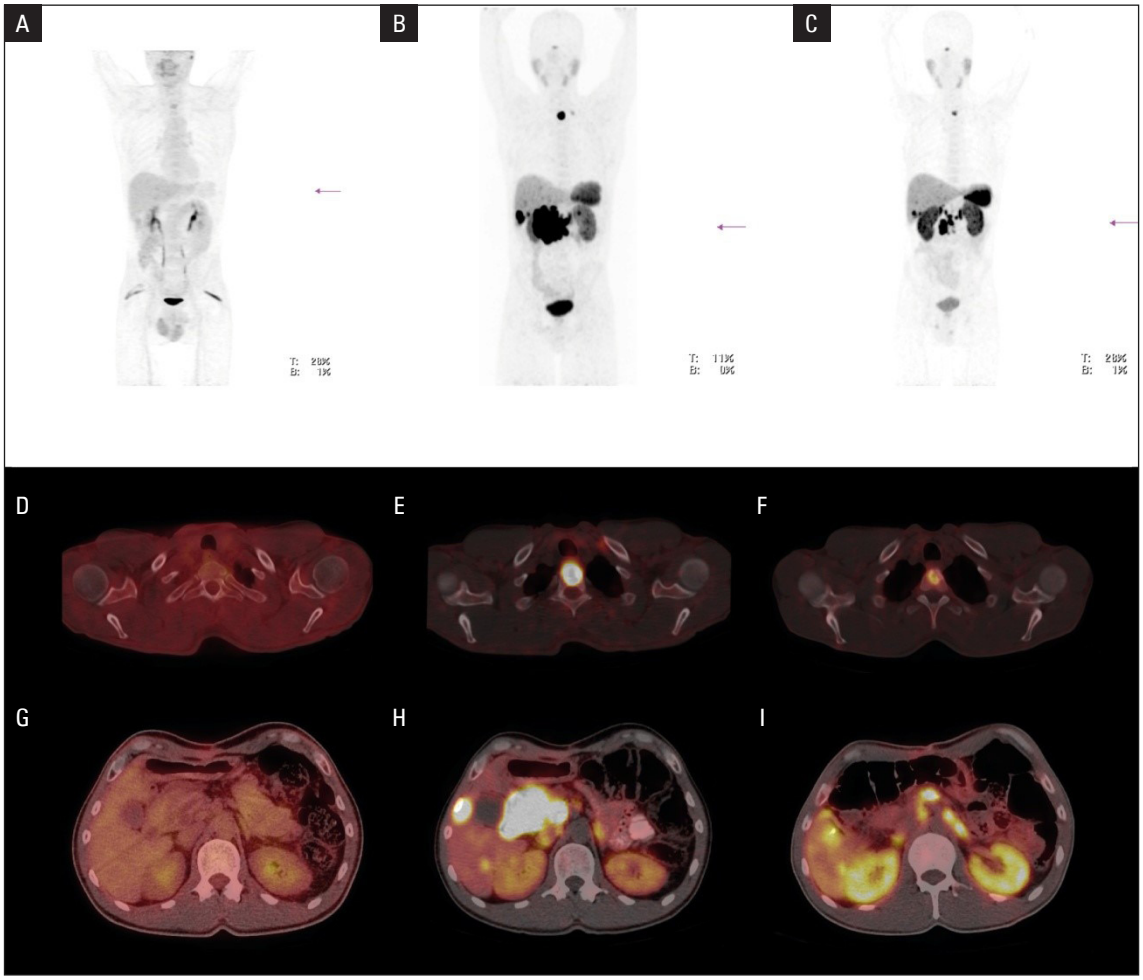

Figure 4. *Example of tandem [^{90}Y]Y/[^{177}Lu]Lu-DOTATATE therapy effect. A 37-year-old woman with non-functional pancreatic NET G2 with lymph nodes and multiple liver metastases after surgical treatment.* **A** *— [^{18}F]FDG PET MIP (maximum intensity projection);* **B** *— [^{68}Ga]Ga-DOTATATE PET MIP;* **C** *— [^{68}Ga]Ga-DOTATATE PET MIP;* **D, G** *— [^{18}F]FDG PET/CT before treatment showing uptake in the metastatic lesions in lymph nodes and the liver;* **E, H** *— [^{68}Ga]Ga-DOTATATE PET/CT before treatment showing uptake in the metastatic lesions in lymph nodes and the liver;* **F, I** *— [^{68}Ga]Ga-DOTATATE PET/CT after 12 months of follow-up showed partial treatment response within lymph nodes and liver metastases*

We observed statistically significantly better survival parameters for [^{18}F]FDG-negative patients ([^{18}F]FDG-positive *vs.* negative: PFS 22.2 *vs.* 59.3 months, OS-D 71.8 *vs.* not reached, OS-T 55.8 months *vs.* not reached). Of note, in our group [^{18}F]FDG was positive only in 5% of patients with G1 NET and in 31% of patients with G2 NET.

To the best of our knowledge, this is the first paper to consider the impact of [^{18}F]FDG for simultaneous use of both isotopes ^{90}Y and ^{177}Lu for tandem [^{90}Y]Y/[^{177}Lu]Lu-DOTATATE.

One of first reports on the impact of [^{18}F]FDG on survival parameters was reported by Delpassard et al. Patients were treated with high doses of [^{111}In]In-pentetreotide with an average survival time of 18.9 months for [^{18}F]FDG-positive and 31.8 months for [^{18}F]FDG-negative scans. Survival times for [^{18}F]FDG-negative patients were significantly longer than those for [^{18}F]FDG-positive patients [21].

Our results are in line with the studies by Severi et al. and Sansovini et al., who used a single isotope for treatment [^{177}Lu]Lu-DOTATATE. According to their results, PFS in [^{18}F]FDG PET/CT-positive patients was 20 and 21.1 months whereas in the [^{18}F]FDG PET/CT-negative group it was 32 and 68.7 months, respectively [11, 13].

Most papers on radioisotope treatment consider the impact of [^{18}F]FDG to be related to NET grade 1 and 2.

Nicolini et al. focused on GEP-NEN patients with high Ki-67 proliferation index, who underwent [^{177}Lu]Lu-DOTATATE therapy. Progression-free survival in the [^{18}F]FDG PET-positive group of patients with Ki-67 ≤ 35% and with Ki-67 > 35% was 23.0 months *vs.* 6.8 months, respectively. Importantly, PFS in [^{18}F]FDG PET-negative patients (all with Ki-67 ≤ 35%) was much longer than for [^{18}F]FDG PET-positive patients [27]. Nevertheless, on the Ki-67 index [^{18}F]FDG PET showed a strong impact in survival parameters.

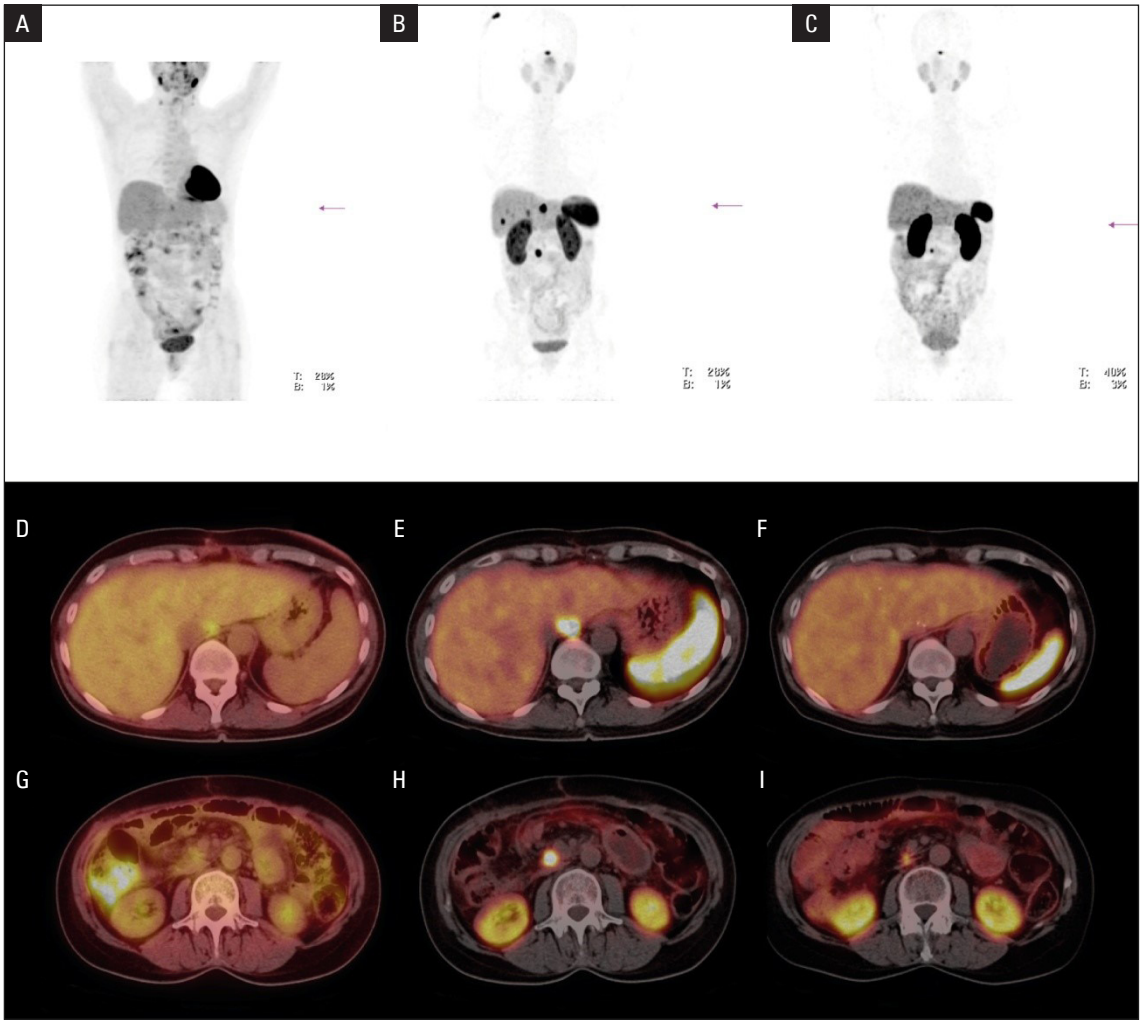

Figure 5. *Example of tandem [^{90}Y]Y/[^{177}Lu]Lu-DOTATATE therapy effect. A 31-year-old man with primarily non-resectable, non-functional pancreas NET G1 with metastases to lymph nodes, bones, and the liver.* **A** *— [^{18}F]FDG PET MIP;* **B** *— [^{68}Ga]Ga-DOTATATE PET MIP;* **C** *— [^{68}Ga]Ga-DOTATATE PET MIP;* **D, G** *— [^{18}F]FDG PET/CT before treatment without uptake in the primary tumour and bone metastases;* **E, H** *— [^{68}Ga]Ga-DOTATATE PET/CT before treatment with high uptake in the primary pancreas tumour and bone metastases;* **F, I** *— [^{68}Ga]Ga-DOTATATE PET/CT after 6 months of follow-up showed partial treatment response within the primary tumour and bone metastases*

In bronchial NET, which has different clinical and biochemical behaviour than GEP-NET PFS in the [^{18}F]FDG PET-positive *vs.* [^{18}F]FDG PET-negative group was shorter than in GEP-NET (15.3 months *vs.* 26.4 months, respectively). Progression-free survival in patients with typical *vs.* atypical carcinoids and [^{18}F]FDG-postive scans was 12.9 *vs.* 15.7 months, respectively. However, within the group of [^{18}F]FDG-negative patients, PFS was 26.4 in the case of typical carcinoids and 48.9 in the case of atypical carcinoids [28].

In the prospective, randomised phase 3 NETTER-I trial, the influence of PRRT on survival parameters was proven for the first time. The estimated PFS was 40 months in the midgut NET group with [^{177}Lu]Lu-DOTATATE and octreotide LAR compared to 8.4 months in the group to whom octreotide LAR was administered alone. In that study a 79% reduction in disease progression risk was observed in the group patients treated with [^{177}Lu]Lu-DOTATATE [29].

Another serious problem is the impact of [^{18}F]FDG on the disease control rate and the objective response rate. In our study, for [^{18}F]FDG-positive *vs.* [^{18}F]FDG-negative patients the DC rate was quite similar, at 83.4% *vs.* 85.1%, but the ORR was 41.7% *vs.* 17%, respectively.

In other studies DC rates in [^{18}F]FDG PET-positive groups of patients were 76-78% and in [^{18}F]FDG PET-negative groups of patients 96-100% [11, 13].

Nicolini et al., in a high-Ki-67 patient group, confirmed that DC in [^{18}F]FDG PET/CT-positive patients with Ki-67 ≤ 35% was 93%, and 17% in the group of [^{18}F]FDG PET/CT-positive patients with Ki-67 > 35%. DC in [^{18}F]FDG PET/CT-negative patients (all Ki-67 ≤ 35%) was 86% [27].

In typical carcinoids the DC rate was 80%, whereas in patients with atypical carcinoids DC was achieved in 47% (all patients had SD). The authors herein did not analyse DC rates depending on [^{18}F]FDG PET/CT scan [28].

Differences in treatment response may result from different treatment response criteria (RECIST 1.1 *vs.* SWOG) and different groups of patients.

Another important parameter with an impact on treatment is grading and concordance with [^{18}F]FDG. Our analysis of outcomes according to the histopathological type showed significantly longer PFS in [^{18}F]FDG-negative patients with G1 NET. However, OS-T and OS-D were not statistically significant. The distinction between [^{18}F]FDG-positive *vs.* [^{18}F]FDG-negative patients with G2 was significant for all survival parameters.

In retrospective analysis, Ezziddin et al. confirmed that in patients with pancreatic neuroendocrine tumours treated with [^{177}Lu]Lu-DOTATATE, NET G1 was associated with longer PFS and OS (patients with NET G1 *vs.* NET G2: PFS 45.0 *vs.* 28.0 months; OS was not reached *vs.* 49 months, respectively) [30].

Similar results were presented research by Severi et al. in which PFS in a group of NET G1 [^{18}F]FDG PET-positive patients was not reached *vs.* 26 months in [^{18}F]FDG PET-positive with NET G2 [11].

Data concerning clinical experience with NEN G3 patients are limited. Zhang et al. reported that the PRRT is effective in grade 3 neuroendocrine neoplasm in patients after failing prior chemotherapy, as well as with Ki-67 ≤ 55% [31, 32].

The present study has some strengths and limitations. The main limitation is its retrospective nature. Additionally, the treatment was carried out on a small heterogeneous sample size, with the primary focus on different parts of the digestive tract and lungs, which may also have had an impact on the outcomes. The lack of a control group of patients treated with yttrium or lutetium only may also be a restraint. The main advantage of this study is high percentage of disease control rates, long PFS and OS, and low incidence of serious adverse events.

Conclusions

[^{18}F]FDG PET/CT-positive patients have statistically significant shorter survival parameters (PFS, OS-T, OS-D) than [^{18}F]FDG PET/CT-negative patients.

The risk of progression in [^{18}F]FDG PET/CT-positive *vs.* [^{18}F]FDG PET/CT-negative patients in one-year follow-up is comparable, whereas in two-year follow up it is nearly two times higher for [^{18}F]FDG PET/CT-positive patients. Hence, [^{18}F]FDG PET/CT-positive patients need careful follow-up.

[^{18}F]FDG PET/CT is an additional useful tool for qualification of patients to PRRT.

Acknowledgments

We thank the radiochemistry group at the Nuclear Medicine department, the nursing staff, and the technologists from the Medical University of Warsaw, Military Institute of Medicine and Poznan University of Medical Sciences for their support.

Compliance with ethical standards

All authors declare that they have no conflict of interest in relation to this article.

This article does not contain any studies with animals performed by any of the authors.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

Funding

This study was partially supported by Research Grants (6 P05 2004 C/6453 and 4/85195/1210/529) from the Ministry of Health and Ministry of Education.

References

1. Kos-Kudła B, Blicharz-Dorniak J, Strzelczyk J, et al. Consensus Conference, Polish Network of Neuroendocrine Tumours. Diagnostic and therapeutic guidelines for gastro-entero-pancreatic neuroendocrine neoplasms (recommended by the Polish Network of Neuroendocrine Tumours). Endokrynol Pol. 2013; 64(6): 418–443, doi: 10.5603/EP.2013.0028, indexed in Pubmed: 24431116.
2. Plöckinger U, Rindi G, Arnold R, et al. European Neuroendocrine Tumour Society. Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumours. A consensus statement on behalf of the European Neuroendocrine Tumour Society (ENETS). Neuroendocrinology. 2004; 80(6): 394–424, doi: 10.1159/000085237, indexed in Pubmed: 15838182.
3. Ramage JK, Ahmed A, Ardill J, et al. UK and Ireland Neuroendocrine Tumour Society. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut. 2012; 61(1): 6–32, doi: 10.1136/gutjnl-2011-300831, indexed in Pubmed: 22052063.
4. Yao JC, Hassan M, Phan A, et al. One hundred years after „carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008; 26(18): 3063–3072, doi: 10.1200/JCO.2007.15.4377, indexed in Pubmed: 18565894.
5. Ramage JK, De Herder WW, Delle Fave G, et al. Vienna Consensus Conference participants. ENETS Consensus Guidelines Update for Colorectal Neuroendocrine Neoplasms. Neuroendocrinology. 2016; 103(2): 139–143, doi: 10.1159/000443166, indexed in Pubmed: 26730835.
6. Kvols LK, Brendtro KL. North American Neuroendocrine Tumor Society (NANETS). The North American Neuroendocrine Tumor Society (NANETS) guidelines: mission, goals, and process. Pancreas. 2010; 39(6): 705–706, doi: 10.1097/MPA.0b013e3181eb7451, indexed in Pubmed: 20664469.
7. Maroun J, Kocha W, Kvols L, et al. Guidelines for the diagnosis and management of carcinoid tumours. Part 1: the gastrointestinal tract. A statement from a Canadian National Carcinoid Expert Group. Curr Oncol. 2006; 13(2): 67–76, indexed in Pubmed: 17576444.

8. Amin MB, Edge S, Greene F. AJCC Cancer Staging Manual. Eighth Edition. Springer 2017.
9. Brierley JD, Gospodarowicz MK, Wittekind CT. TNM Classification of Malignant Tumours. Eighth Edition. Wiley Blackwell 2017.
10. Binderup T, Knigge U, Loft A, et al. Functional imaging of neuroendocrine tumors: a head-to-head comparison of somatostatin receptor scintigraphy, 123I-MIBG scintigraphy, and 18F-FDG PET. J Nucl Med. 2010; 51(5): 704–712, doi: 10.2967/jnumed.109.069765, indexed in Pubmed: 20395333.
11. Severi S, Nanni O, Bodei L, et al. Role of 18FDG PET/CT in patients treated with 177Lu-DOTATATE for advanced differentiated neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2013; 40(6): 881–888, doi: 10.1007/s00259-013-2369-z, indexed in Pubmed: 23443937.
12. July M, Santhanam P, Giovanella L, et al. Role of positron emission tomography imaging in Multiple Endocrine Neoplasia syndromes. Clin Physiol Funct Imaging. 2018; 38(1): 4–9, doi: 10.1111/cpf.12391, indexed in Pubmed: 27677981.
13. Sansovini M, Severi S, Ianniello A, et al. Long-term follow-up and role of FDG PET in advanced pancreatic neuroendocrine patients treated with Lu-DOTATATE. Eur J Nucl Med Mol Imaging. 2017; 44(3): 490–499, doi: 10.1007/s00259-016-3533-z, indexed in Pubmed: 27704193.
14. Binderup T, Knigge U, Loft A, et al. 18F-fluorodeoxyglucose positron emission tomography predicts survival of patients with neuroendocrine tumors. Clin Cancer Res. 2010; 16(3): 978–985, doi: 10.1158/1078-0432.CCR-09-1759, indexed in Pubmed: 20103666.
15. Kunikowska J, Zemczak A, Górska M, et al. TeleNEN as a telemedicine model for neuroendocrine neoplasm management in case of Meckel's diverticulum NET. Endokrynol Pol. 2018; 69(3): 313–317, doi: 10.5603/EP.2018.0033, indexed in Pubmed: 29952421.
16. Rolleman EJ, Valkema R, de Jong M, et al. Safe and effective inhibition of renal uptake of radiolabelled octreotide by a combination of lysine and arginine. Eur J Nucl Med Mol Imaging. 2003; 30(1): 9–15, doi: 10.1007/s00259-002-0982-3, indexed in Pubmed: 12483404.
17. Kunikowska J, Królicki L, Hubalewska-Dydejczyk A, et al. Clinical results of radionuclide therapy of neuroendocrine tumours with 90Y-DOTATATE and tandem 90Y/177Lu-DOTATATE: which is a better therapy option? Eur J Nucl Med Mol Imaging. 2011; 38(10): 1788–1797, doi: 10.1007/s00259-011-1833-x, indexed in Pubmed: 21553086.
18. Kunikowska J, Pawlak D, Bąk MI, et al. Long-term results and tolerability of tandem peptide receptor radionuclide therapy with Y/Lu-DOTATATE in neuroendocrine tumors with respect to the primary location: a 10-year study. Ann Nucl Med. 2017; 31(5): 347–356, doi: 10.1007/s12149-017-1163-6, indexed in Pubmed: 28316066.
19. Kunikowska J, Zemczak A, Kołodziej M, et al. Tandem peptide receptor radionuclide therapy using Y/Lu-DOTATATE for neuroendocrine tumors efficacy and side-effects - polish multicenter experience. Eur J Nucl Med Mol Imaging. 2020; 47(4): 922–933, doi: 10.1007/s00259-020-04690-5, indexed in Pubmed: 31980909.
20. Kwekkeboom DJ, de Herder WW, Kam BL, et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. J Clin Oncol. 2008; 26(13): 2124–2130, doi: 10.1200/JCO.2007.15.2553, indexed in Pubmed: 18445841.
21. Delpassand ES, Samarghandi A, Zamanian S, et al. Peptide receptor radionuclide therapy with 177Lu-DOTATATE for patients with somatostatin receptor-expressing neuroendocrine tumors: the first US phase 2 experience. Pancreas. 2014; 43(4): 518–525, doi: 10.1097/MPA.0000000000000113, indexed in Pubmed: 24632546.
22. Parghane RV, Talole S, Prabhash K, et al. Clinical Response Profile of Metastatic/Advanced Pulmonary Neuroendocrine Tumors to Peptide Receptor Radionuclide Therapy with 177Lu-DOTATATE. Clin Nucl Med. 2017; 42(6): 428–435, doi: 10.1097/RLU.0000000000001639, indexed in Pubmed: 28319500.
23. Sabet A, Dautzenberg K, Haslerud T, et al. Specific efficacy of peptide receptor radionuclide therapy with (177)Lu-octreotate in advanced neuroendocrine tumours of the small intestine. Eur J Nucl Med Mol Imaging. 2015; 42(8): 1238–1246, doi: 10.1007/s00259-015-3041-6, indexed in Pubmed: 25808630.
24. Bodei L, Cremonesi M, Grana CM, et al. Peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE: the IEO phase I-II study. Eur J Nucl Med Mol Imaging. 2011; 38(12): 2125–2135, doi: 10.1007/s00259-011-1902-1, indexed in Pubmed: 21892623.
25. van Essen M, Krenning EP, Bakker WH, et al. Peptide receptor radionuclide therapy with 177Lu-octreotate in patients with foregut carcinoid tumours of bronchial, gastric and thymic origin. Eur J Nucl Med Mol Imaging. 2007; 34(8): 1219–1227, doi: 10.1007/s00259-006-0355-4, indexed in Pubmed: 17260141.
26. Bodei L, Cremonesi M, Kidd M, et al. Peptide receptor radionuclide therapy for advanced neuroendocrine tumors. Thorac Surg Clin. 2014; 24(3): 333–349, doi: 10.1016/j.thorsurg.2014.04.005, indexed in Pubmed: 25065935.
27. Nicolini S, Severi S, Ianniello A, et al. Investigation of receptor radionuclide therapy with Lu-DOTATATE in patients with GEP-NEN and a high Ki-67 proliferation index. Eur J Nucl Med Mol Imaging. 2018; 45(6): 923–930, doi: 10.1007/s00259-017-3925-8, indexed in Pubmed: 29387927.
28. Ianniello A, Sansovini M, Severi S, et al. Peptide receptor radionuclide therapy with (177)Lu-DOTATATE in advanced bronchial carcinoids: prognostic role of thyroid transcription factor 1 and (18) F-FDG PET. Eur J Nucl Med Mol Imaging. 2016; 43(6): 1040–1046, doi: 10.1007/s00259-015-3262-8, indexed in Pubmed: 26611427.
29. Strosberg J, El-Haddad G, Wolin E, et al. NETTER-1 Trial Investigators. Phase 3 Trial of Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med. 2017; 376(2): 125–135, doi: 10.1056/NEJMoa1607427, indexed in Pubmed: 28076709.
30. Ezziddin S, Khalaf F, Vanezi M, et al. Outcome of peptide receptor radionuclide therapy with 177Lu-octreotate in advanced grade 1/2 pancreatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2014; 41(5): 925–933, doi: 10.1007/s00259-013-2677-3, indexed in Pubmed: 24504504.
31. Zhang J, Kulkarni HR, Singh A, et al. Peptide Receptor Radionuclide Therapy in Grade 3 Neuroendocrine Neoplasms: Safety and Survival Analysis in 69 Patients. J Nucl Med. 2019; 60(3): 377–385, doi: 10.2967/jnumed.118.215848, indexed in Pubmed: 30115686.
32. Rogowski W, Wachuła E, Gorzelak A, et al. Capecitabine and temozolomide combination for treatment of high-grade, well-differentiated neuroendocrine tumour and poorly-differentiated neuroendocrine carcinoma - retrospective analysis. Endokrynol Pol. 2019; 70(4): 313–317, doi: 10.5603/EP.a2019.0010, indexed in Pubmed: 30843182.