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Original

Re-treatment with [^{177}Lu]Lu-DOTA-TATE or [^{177}Lu]Lu-DOTA-TATE and [^{90}Y]Y-DOTA-TATE of patients with progressive neuroendocrine neoplasm

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Abstract

Background: Neuroendocrine neoplasms (NENs) are heterogeneous groups of tumours derived from neuroendocrine cells of the ectoderm or endoderm. They are considered rare, with an estimated incidence and prevalence of 6/100,000 and 35/100,000 respectively, and a noticeable upward trend. Radioligand therapy (RLT) using beta-radiation-emitters combined with somatostatin analogues is an effective and relatively safe treatment method. It is usually used as a second-line therapy in case of progressive disease.

Material and methods: In retrospective analysis covering eight years of observation (2015–2023) of patients treated in a single highest-reference NEN centre, a subgroup of 13 who received RLT re-treatment (^{177}Lu or ^{177}Lu/^{90}Y-mixture) was identified. Epidemiological aspects, renal, hepatic, haematological parameters and chromogranin A serum concentration were analysed.

Results: The median PFS after the first cycle of RLT was 53.8 months (IQR = 19.3). Directly after the second cycle of RLT disease stabilization and progression was observed in 11/13 (84.6%) and 2/13 (15.4%) patients respectively. After the second cycle of RLT median observation time for the study group was 16.2 months. Eight out of 13 patients were reachable for long-term observation and stabilization was confirmed in 62.5 % (5/8), progression in 12.5% (1/8) and death in 25% (2/8) patients. Median survival time in patients with confirmed death was 7 months. During observation, an increase in creatinine concentration with a decrease in glomerular filtration rate (GFR) was noticed, however, the values were at a statistical trend level ($p = 0.056$; $p = 0.071$). The increase of liver parameters was statistically, but not clinically significant. The decrease in albumin concentration and fasting glucose concentration were not significant. An increase in chromogranin A concentration correlated, although not statistically, with the progression of the disease. A statistically significant decrease in the number of all bone marrow cell lines was observed. The first RLT cycle caused a higher decrease in blood parameters than the second. There were no differences in PFS or laboratory parameters depending on the radioligand ([^{177}Lu]Lu-DOTA-TATE *vs.* [^{177}Lu]Lu-DOTA-TATE/[^{90}Y]Y-DOTA-TATE).

Conclusions: In follow-up after RLT re-treatment stabilization was observed in 62.5%, progression in 12.5% and death in 25% of patients. Decrease of glomerular filtration, and bone marrow parameters resulted from the cumulative adverse effect of RLT, the natural ageing process, and the progression of the disease. Side effects were mainly caused by the first treatment cycle. There was no significant influence on the measured parameters, depending on the radioisotope used. Re-treatment of RLT seems to be a reliable and relatively safe method, thus should be considered in patients who underwent one cycle of RLT and responded to the treatment.

KEYwords: neuroendocrine neoplasms; NEN; RLT; PRRT; ^{177}Lu; ^{90}Y; re-treatment

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Introduction

Neuroendocrine neoplasms (NENs) are a heterogeneous group of tumours that originate from neuroendocrine cells of the neuroectoderm and endoderm [1]. These tumours are rare diseases, with their global incidence and prevalence estimated at 6/100,000 and 35/100,000 respectively. There is a noticeable worldwide increase in the incidence and prevalence of NENs, which leads to rising costs of diagnosis and treatment, and a demand for a higher number of specialistic excellence NEN centres [2, 3]. Despite their common embryonic origin, neuroendocrine tumours differ significantly in terms of function (for example secretion of hormones such as serotonin, insulin or gastrin), disease course, and treatment outcomes [4, 5]. The most common location of these tumours is the small intestine, although primary tumour location shows significant geographic distribution difference [6–10]. In many cases (even up to 20%), the primary location of the tumour is unknown, and the disease is diagnosed only by the presence of local or distant metastases [11–13]. Surgical removal of the primary lesion and/or metastases is the first choice in the majority of cases. The alternative in small lesions is endoscopic alcoholization [14]. Subsequently, in the presence of somatostatin receptors detected in functional tests (PET/CT with ^{68}Ga or somatostatin receptor scintigraphy with ^{99m}Tc), chronic treatment with long-acting somatostatin analogues such as octreotide or lanreotide is initiated [15]. Further therapeutic options include radioligand therapy, chemotherapy — which is preferred in NEN G3 with a high proliferation index (Ki-67) and neuroendocrine carcinomas (NEC), targeted therapy using a selective inhibitor of m-TOR (mammalian target of rapamycin) — everolimus, or a tyrosine kinase inhibitor (TKI) — sunitinib. Currently recommended chemotherapy regimens are usually two-component, e.g. streptozocin (STZ) with 5-fluorouracil (5-FU) or capecitabine + temozolomide (CAPTEM) [15–19]. The above therapies are limited by national drug availability, the patient's clinical condition, and other factors related to patient individualization of the therapeutic process. Radioligand therapy (RLT), previously called peptide receptor radionuclide therapy (PRRT), is a therapeutic method most commonly used as a second-line treatment (in case of disease progression), but also in the absence of the possibility of primary surgical treatment. Treatment can be applied in cases of advanced disease with grades: G1 (Ki-67 1–2%), G2 (Ki-67 3–20%), or G3 (Ki-67 > 20%) with confirmed somatostatin receptor expression in scintigraphy with ^{99m}Tc or in PET/CT with ^{68}Ga [15]. The radiopharmaceuticals commonly used in treatment are ^{177}lutetium in monotherapy — [^{177}Lu]Lu-DOTA-TATE — or tandem therapy using a mixture of ^{177}lutetium and ^{90}yttrium isotopes — [^{177}Lu]Lu-DOTA-TATE/[^{90}Y]Y-DOTA-TATE [20]. The differences between ^{177}lutetium and ^{90}yttrium isotopes depend on their physical properties. Beta (β) radiation of ^{177}lutetium has a range of 2 mm, a maximum energy of 0.497 MeV, and a half-life of 6.647 days, while the β-radiation of ^{90}yttrium has an energy of 2.27 MeV, a range of 11 mm, and a half-life of 2.67 days [21]. It is claimed that the usefulness of ^{90}Y is limited due to the higher potential of side effects (due to the cumulative effect of range and energy). However, previous studies have not conclusively confirmed the superiority of one radioisotope over the other and their mixture, and they have also indicated the possible greater potential and ability to reduce tumour mass during treatment with a ^{177}lutetium or mixture of ^{177}lutetium and ^{90}yttrium. To establish clear recommendations and guidelines, longer population observations are required [22–24]. Nevertheless, the most current international standards propose a single cycle of four administrations (four courses) of 7.4 GBq [^{177}Lu]Lu-DOTA-TATE every 8–12 weeks as the basis for treating the progression of neuroendocrine tumours, while maintaining continuous treatment with a somatostatin analogue (lanreotide 120 mg or octreotide 30 mg) every 4 weeks [25].

Material and methods

During eight-year observation (May 2015–March 2023) of patients treated with radioligand therapy for neuroendocrine tumours in the Department of Endocrinology and Radioisotope Therapy, Military Institute of Medicine — National Research Institute, 13 individuals who underwent the RLT re-treatment were identified. Patients during their treatment received more than four standard courses of RLT. Patients were administrated with either ^{177}lutetium in monotherapy (7.4 GBq [^{177}Lu]Lu-DOTA-TATE), or tandem therapy (1.85 GBq [^{177}Lu]Lu-DOTA-TATE) + 1.85 GBq [^{90}Y]Y-DOTA-TATE). Three patients received 1 additional course of RLT (total: 5 courses of RLT), five received 2 additional courses (total: 6 courses of RLT), three received 3 additional courses (total: 7 courses of RLT), and two — 4 additional courses of treatment (total: 8 courses of RLT). In a subgroup of patients with 7–8 courses, the median time between the 6th and 7th RLT was 5 months (IQR = 4).

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Military Medical Chamber, number 154/17. In all patients, intravenous nephroprotection with amino acid infusion (Nephrotec®, Fresenius Kabi) was used during therapeutic courses according to the centre's protocol — 1000 mL during the RLT and 500 mL the day after radioisotope administration. Detailed data of the study group is presented in Table 1.

Statistical analysis

Statistical analysis was performed by using IBM SPSS (v29 2022) software. Due to the relatively small sample size, the results were presented as medians (Med) with interquartile range (IQR). The U Mann–Whitney and the Wilcoxon test were used for data analysis. A significance level of $p < 0.05$ was accepted.

Laboratory tests

Venal blood samples were taken on an empty stomach between 7:30 and 8:30 in the Department of Endocrinology and Radioisotope Therapy and analysed in the Department of Medical Diagnostics of the Military Institute of Medicine. Morphology was evaluated using the Sysmex Corporation XN 1000 automatic haematology analyser (Japan). Biochemistry was analysed using the Roche Diagnostics Assays (Germany) and Hitachi High-Tech Corporation COBAS c503 PRO Automatic Analyzer (Japan) using dedicated reagents. Chromogranin A (CgA) was measured using the LDN Company ELISA test (Germany). The sensitivity of the method for this parameter was 1.4 μg/L. Glomerular filtration rate (GFR) was measured by CKD-EPI (2021) formula.

The reference ranges for the laboratory tests discussed in the paper are presented in the Supplementary Table 1.

Table 1. Details of the study group

	Gender	Age of patient at I treatment	NEN grading	Tumour location	Tumour function	Ki-67 [%]	Previous surgery	Previous chemotherapy or targeted therapy	RLT I cycle	RLT II cycle
1.	F	73	G2	Unknown	Non-functioning	3	No	No	4 × 7.4 GBq [^{177}Lu]Lu-DOTA-TATE	1 × 7.4 GBq [^{177}Lu]Lu-DOTA-TATE
2.	M	63	G1	Unknown	Carcinoid	2	No	Yes	4 × 1.85 GBq [^{90}Y]Y-DOTA-TATE + 1.85 GBq [^{177}Lu]Lu-DOTA-TATE	2 × 1.85 GBq [^{90}Y]Y-DOTA-TATE + 1.85 GBq [^{177}Lu]Lu-DOTA-TATE
3.	M	76	G2	Unknown	Carcinoid	20	Yes	No	4 × 1.85 GBq [^{90}Y]Y-DOTA-TATE + 1.85 GBq [^{177}Lu]Lu-DOTA-TATE	3 × 1.85 GBq [^{90}Y]Y-DOTA-TATE + 1.85 GBq [^{177}Lu]Lu-DOTA-TATE
4.	F	70	G2	Unknown	Non-functioning	5	No	No	4 × 1.85 GBq [^{90}Y]Y-DOTA-TATE + 1.85 GBq [^{177}Lu]Lu-DOTA-TATE	2 × 1.85 GBq [^{90}Y]Y-DOTA-TATE + 1.85 GBq [^{177}Lu]Lu-DOTA-TATE
5.	M	50	G2	Unknown	Carcinoid	15	No	No	4 × 1.85 GBq [^{90}Y]Y-DOTA-TATE + 1.85 GBq [^{177}Lu]Lu-DOTA-TATE	1 × 1.85 GBq [^{90}Y]Y-DOTA-TATE + 1.85 GBq [^{177}Lu]Lu-DOTA-TATE
6.	F	66	G1	Unknown	Carcinoid	1	No	No	4 × 1.85 GBq [^{90}Y]Y-DOTA-TATE + 1.85 GBq [^{177}Lu]Lu-DOTA-TATE	4 × 1.85 GBq [^{90}Y]Y-DOTA-TATE + 1.85 GBq [^{177}Lu]Lu-DOTA-TATE
7.	M	64	G1	Small intestine	Carcinoid	1	Yes	No	4 × 1.85 GBq [^{90}Y]Y-DOTA-TATE + 1.85 GBq [^{177}Lu]Lu-DOTA-TATE	2 × 1.85 GBq [^{90}Y]Y-DOTA-TATE + 1.85 GBq [^{177}Lu]Lu-DOTA-TATE
8.	M	63	G2	Small intestine	Non-functioning	7	No	No	4 × 7.4 GBq [^{177}Lu]Lu-DOTA-TATE	3 × 7.4 GBq [^{177}Lu]Lu-DOTA-TATE
9.	F	62	G1	Large intestine	Carcinoid	2	Yes	Yes	4 × 7.4 GBq [^{177}Lu]Lu-DOTA-TATE	2 × 7.4 GBq [^{177}Lu]Lu-DOTA-TATE
10.	F	66	G2	Large intestine	Non-functioning	10	Yes	Yes	4 × 7.4 GBq [^{177}Lu]Lu-DOTA-TATE	3 × 7.4 GBq [^{177}Lu]Lu-DOTA-TATE
11.	F	62	G2	Large intestine	Non-functioning	3	Yes	Yes	4 × 7.4 GBq [^{177}Lu]Lu-DOTA-TATE	1 × 7.4 GBq [^{177}Lu]Lu-DOTA-TATE
12.	F	56	G2	Paraganglia	Paraganglioma	3	No	No	4 × 1.85 GBq [^{90}Y]Y-DOTA-TATE + 1.85 GBq [^{177}Lu]Lu-DOTA-TATE	2 × 1.85 GBq [^{90}Y]Y-DOTA-TATE + 1.85 GBq [^{177}Lu]Lu-DOTA-TATE
13.	F	40	G1	Retroperitoneal space	Non-functioning	2	Yes	Yes	4 × 7.4 GBq [^{177}Lu]Lu-DOTA-TATE	4 × 7.4 GBq [^{177}Lu]Lu-DOTA-TATE

F — female; M — male; NEN — neuroendocrine neoplasms; RLT — radioligand therapy

Results

In the analysed group of 13 patients, there were eight (61.54%) women and five (58.46%) men. The median age was 63 years (IQR = 4). In five (38.46%) patients, the tumour was diagnosed in grade G1 and eight (61.54%) in grade G2. In six patients, the tumour had an unknown point of origin, in two the small intestine and in three the primary point was the large intestine, in one case it was a disseminated paraganglioma, and in one case it was the retroperitoneal space. The median Ki-67 was 3% (IQR = 5). Six (46.15%) patients underwent primary tumour resection or its metastases before the RLT , while seven cases (53.85%) were not eligible for surgery. Before radioisotope therapy five (38.46%) patients underwent chemotherapy or targeted therapy: three of them received CAPTEM (capecitabine + temozolomide), one E/P (etoposide + cisplatin), and one EVE (everolimus). Ten (76.92%) patients also received lanreotide (Somatuline Autogel 120 mg), while three (23.08%) octreotide (Sandostatin LAR 30 mg) in monthly injections. Before treatment, nine (69.23%) patients were diagnosed with diabetes or prediabetes, seven (53.85%) had hypertension, and seven (53.85%) had hyperlipidemia. Seven patients (53.85%) received tandem therapy, while six (46.15%) received ^{177}Lu in monotherapy in both the first and second cycles of the treatment. Carcinoid syndrome was diagnosed in six patients (46.15%).

The median progression-free survival (PFS) before the first RLT (previous treatment) was 22.0 months (IQR = 33.3). All patients were in the stage of metastatic disease at the time of radioisotope qualification. The median overall observation time (from the first RLT administration to the last follow-up checkup) was 74.0 months (IQR = 15.5). The median PFS after the first RLT cycle (PFS_{RLT-I}) was 53.8 months (IQR = 19.3). Directly after the second cycle of treatment, 11 patients showed stabilization of their clinical condition and tumour growth, while two patients had a clinical and/or radiological progression. In follow-up after the second cycle of RLT (re-treatment) eight out of 13 patients were reachable for long-term observation and the median observation time for the whole study group was 6.5 (IQR 8.5) months. Stabilization was confirmed in 62.5% (5/8) patients (median — 16.2 months), and progression was noted in 12.5% (1/8) after 12.2 months (patient received chemotherapy as a next line of treatment). Death was confirmed in 25% (2/8) patients (median — 10.7 months). The unknown status was in 5 patients.

Comparing laboratory tests before the first and the last RLT (median number of courses — 6; IQR = 1), an increase in creatinine concentration was observed, with a simultaneous decrease in the GFR. Median creatinine concentration increased by 0.4 mg/dL (from 0.8 to 1.2 mg/dL), and GFR decreased by 9.5 mL/min/1.73m^2 (from 81.5 to 75 mL/min/1.73m^2) (p = 0.056 and p = 0.1291, respectively). The first cycle of treatment caused a lower reduction of GFR and an increase of creatinine concentration than the second cycle (−3 mL/min/1.73m^2 and 0.1 mg/dl *vs.* −6.5 mL/min/1.73m^2 and 0.3 mg/dL respectively), but results were statistically non-significant (Tab. 2, 3 and 4).

An increase in liver parameters before the first and before the last RLT was also observed, with aspartate aminotransferase (AST) concentration increasing by 13 IU/L and alanine aminotransferase (ALT) concentration increasing by 7 IU/L (p = 0.019 and p = 0.171 respectively). Although statistical significance was achieved for the increase of AST (p = 0.019), it should be noted that these values remained within the normal range. Albumin concentration decreased by 0.2 mg/dL, but the results were not statistically significant. There were no statistical differences between the first and second cycles of treatment.

An increase in the median glucose concentration from 100.5 mg/dL to 110 mg/dL was also observed, although the results were not statistically significant (p = 0.363). The increase in glucose concentration was mainly caused by the first cycle of treatment, and surprisingly the second cycle showed an even decrease in parameters, but again — the results were not significant.

Also noticeable increase of chromogranin A concentration was observed — on average by 296.25 ng/mL — in this case, the results were also not statistically significant. There was a higher increase in CgA concentration observed during the first cycle, but the results were non-significant.

Table 2. Medians with IQRs of laboratory parameter values measured before the first course of the first cycle and before the first course of the second cycle of RLT

	I cycle $_{1st\ course}$		II cycle $_{1st\ course}$		Δ	p
	Median	IQR	Median	IQR		
CREA [mg/dL]	0.8	0.3	0.9	0.4	0.1	0.147
GFR [mL/min/1.73 m^2]	84.5	32.5	81.5	41.7	−3	0.236
AST [IU/L]	22.5	10.2	26.0	9.7	3.5	0.079
ALT [IU/L]	18.5	7.0	20.5	17.7	2	0.301
ALB [mg/dL]	4.5	0.6	4.5	0.4	0	0.345
GLU [mg/dL]	100.5	32.0	114.5	18.7	14	0.255
CgA [mg/dL]	368.1	822.4	595.5	2144.3	227.4	0.171
WBC [1000/μL]	6.1	3.5	4.6	2.8	−1.5	0.056
RBC [mln/μL]	4.41	1.3	3.7	1.2	−0.7	**0.013**
HBG [g/dL]	13.7	2.8	11.0	2.0	−2.7	**0.032**
PLT [1000/μL]	233.0	104.2	190.0	120.7	−43.0	**0.034**

ALB — albumin; ALT — alanine aminotransferase; AST — aspartate aminotransferase; CgA — chromogranin A; CREA — creatinine; GFR — glomerular filtration rate of the kidneys; GLU — glucose; HGB — haemoglobin; PLT — platelets; RBC — red blood cells; WBC — white blood cells; Δ — difference of medians, p — statistical significance level; statistically significant results (< 0.05) are shown in bold

Table 3. Medians with IQRs of laboratory parameter values measured before the first course of the second cycle and before the last course of the second cycle of RLT

	II cycle $_{1st\ course}$		II cycle $_{last\ course}$		Δ	p
	Median	IQR	Median	IQR		
CREA [mg/dL]	0.9	0.4	1.2	0.5	0.3	0.184
GFR [mL/min/1.73 m^2]	81.5	41.7	75.0	58.5	−6.5	0.312
AST [IU/L]	26.0	9.7	35.5	29.5	9.5	0.261
ALT [IU/L]	20.5	17.7	25.5	36.0	5.0	0.254
ALB [mg/dL]	4.5	0.4	4.3	0.4	−0.2	0.291
GLU [mg/dL]	114.5	18.7	110.0	24.5	−4.5	0.345
CgA [mg/dL]	595.5	2144.3	664.3	1917.3	68.8	0.500
WBC [1000/μL]	4.6	2.8	4.1	1.7	−0.5	0.201
RBC [mln/μL]	3.7	1.2	3.5	1,0	−0.2	0.452
HBG [g/dL]	11.0	2.0	10.6	1.5	−0.4	0.409
PLT [1000/μL]	190.0	120.7	168.0	93.0	−22.0	0.255

ALB — albumin; ALT — alanine aminotransferase; AST — aspartate aminotransferase; CgA — chromogranin A; CREA – creatinine; GFR — glomerular filtration rate of the kidneys; GLU — glucose; HGB — haemoglobin; PLT — platelets; RBC — red blood cells; WBC — white blood cells; Δ — difference of medians, p — statistical significance level; statistically significant results (< 0.05) are shown in bold

Table 4. Medians with quartile ranges, laboratory parameter values measured during the therapy (before the first course of the first cycle and last course last cycle of re-treatment)

	I cycle $_{1st\ course}$		II cycle $_{last\ course}$		Δ	p
	Median	IQR	Median	IQR		
CREA [mg/dL]	0.8	0.3	1.2	0.5	0.4	0.056
GFR [mL/min/1.73 m^2]	84.5	32.5	75.0	58.5	−9.5	0.129
AST [IU/L]	22.5	10.2	35.5	29.5	13.0	0.019
ALT [IU/L]	18.5	7.0	25.5	36.0	7.0	0.171
ALB [mg/dL]	4.5	0.6	4.3	0.4	−0.2	0.261
GLU [mg/dL]	100.5	32.0	110.0	24.5	9.5	0.363
CgA [mg/dL]	368.1	822.4	664.3	1917.3	296.2	0.184
WBC [1000/μL]	6.1	3.5	4.1	1.7	−2.0	0.003
RBC [mln/μL]	4.4	1.3	3.5	1.0	−0.9	0.011
HGB [g/dL]	13.7	2.8	10.6	1.5	−3.1	0.016
PLT [1000/μL]	233.0	104.2	168.0	93.0	−65.0	0.009

ALB — albumin; ALT — alanine aminotransferase; AST — aspartate aminotransferase; CgA — chromogranin A; CREA — creatinine; GFR — glomerular filtration rate of the kidneys; GLU — glucose; HGB — haemoglobin; PLT — platelets; RBC — red blood cells; WBC — white blood cells; Δ — difference of medians, p — statistical significance level; statistically significant results (< 0.05) are shown in bold

A decrease in all bone marrow cell lines, as well as haemoglobin concentration, was also observed. The comparison of the results before the first and last radioisotope administration showed a median decrease in leukocyte count of 2.01 thousand/μL (p = 0.003), erythrocytes of 0.94 million/μL (p = 0.011), blood platelets of 65 thousand/μL (p = 0.009) and haemoglobin of 3.02 g/dL (p = 0.016). The bone marrow injury was almost completely the results of the first cycle of RLT, and the p-values for WBC, RBC, HGB and PLT decrease were compared to ones during the second cycle as follows: 0.056 *vs.* 0.201, 0.013 *vs.* 0.452, 0.032 *vs.* 0.409, 0.034 *vs.* 0.255 respectively. No statistically significant differences were found in the observed patient group regarding progression-free survival, and laboratory results, regarding the radioisotope used (Tab. 5).

The box plots of the results, showing differences between the two cycles are summarized in Figure 1.

Discussion

Re-treatment of RLT as a kind of "beyond the standard" procedure showed that potential benefits like prolonging progression-free survival, clearly outweigh the possible complications of the treatment. In the authors' observation, the median prolongation of PFS over 3 years after the first cycle of treatment indicates the validity of considering the second radioisotope therapy cycle as an effective and relatively safe procedure. Despite a small study group of 13 patients, of whom only 8 were reachable in long-term follow-up, the effects of re-treatment were noticeable — in 62.5% of patients was observed stabilization, in 12.5% progression, and in 25% death. As every prolongation of life in advanced, metastatic disease has great significance for patients those results can be considered as a form of treatment success.

Table 5. Comparison of the median difference of the laboratory parameters during the therapy (between the first course of the first cycle and the last course of the re-treatment) depending on the radioisotope used

	[^{177}Lu]Lu-DOTA-TATE	[^{177}Lu]Lu-DOTA-TATE/[^{90}Y]Y-DOTA-TATE	p
	Δ	Δ	
CREA [mg/dL]	0.1	0.1	0.936
GFR [mL/min/1.73 m^2]	−4.0	−7.0	0.332
AST [IU/L]	7.0	17.0	0.373
ALT [IU/L]	9.0	7.0	0.999
ALB [mg/dL]	−0.2	0.0	0.741
GLU [mg/dL]	2.0	0.0	0.568
CgA [mg/dL]	76.0	144.4	0.681
WBC [1000/μL]	−0.7	−1.6	0.307
RBC [mln/μL]	−0.8	−1.0	0.726
HGB [g/dL]	−1.6	−1.8	0.794
PLT [1000/μL]	−39.0	−64.0	0.748

ALB — albumin; ALT — alanine aminotransferase; AST — aspartate aminotransferase; CgA — chromogranin A; CREA — creatinine; GFR — glomerular filtration rate of the kidneys; GLU — glucose; HGB — haemoglobin; PLT — platelets; RBC — red blood cells; WBC — white blood cells; Δ — difference of medians, p — statistical significance level; statistically significant results (< 0.05) are shown in bold

Previous studies also indicate for satisfactory effect and outcome of RLT with the use of beta-emitters like ^{177}Lu or ^{90}Y. A meta-analysis from 2017 included 30 studies on patients with neuroendocrine tumours treated with somatostatin analogues, chemotherapy, radioligand therapy or targeted therapy. Results showed that the combined mean PFS in those patients was 11.0 months (range 4.5–26.7 months) [26]. In the randomized RADIANT-4 study, in which 205 out of 302 patients received everolimus at a dose of 10 mg per day and 97 received placebo, the median progression-free survival was 11.0 months in the everolimus group compared to 3.9 months in the placebo group [27]. In the study of Yalchin et al. [28] in 133 patients with midgut neuroendocrine tumours, RLT with 7.4 Gbq of [^{177}Lu]Lu-DOTA-TATE or 7.4 GBq of [^{90}Y]Y-DOTA-TATE gave a progression-free survival of 28.5 months. Predictive factors for prolongation of progression-free survival were a greater number of treatment courses and earlier resection of liver metastases. In 2022 Pusceddu et al. [29] presented results of population analysis where a group of 508 patients, of whom 329 (64.8%) received RLT, and 179 (35.2%) received chemotherapy or targeted therapy, was observed. The target comparative group consisted of 222 patients (111 in each treated group — RLT subgroup *vs.* chemotherapy/targeted therapy one). The median progression-free survival was longer in the RLT group than in the chemotherapy or targeted therapy group (2.5 years *vs.* 0.7 years) and in the comparative group (2.2 years *vs.* 0.6 years). There were no significant differences in median overall survival (OS) between RLT and chemotherapy and targeted therapy in unmatched (12.0 years *vs.* 11.6 years) and comparative groups (12.2 years *vs.* 11.5 years) [29]. Another retrospective analysis of patients (based on the ELIOS group) showed a median progression-free survival of 33 months for the group of patients treated with everolimus (n = 31), 20 months for the group treated with chemotherapy (n = 17), and 30 months for the group treated with RLT (n = 15), compared to patients treated with only somatostatin analogues (SSA) [30].

The decrease of glomerular filtration rate and increase of creatinine serum concentration observed in the present study among patients undergoing radioligand therapy is consistent with the known negative impact of the treatment, but it can also be related to the natural decline in GFR values with age, estimated at approximately 1% in the Central European population [31–33]. The authors' prospective study published in 2023 showed a sustained decrease of GFR of about 10% one year after radioligand therapy of NEN patients [34]. Given that the kidneys are the critical organ for radioligand therapy, the greatest concerns and limitations of this treatment arise from the potential injury of the kidneys and permanent reduction in glomerular filtration [35]. The liver function parameters observed in the present study, although statistically significant, have no clinical relevance. The authors' previous studies and others did not indicate significant liver-related risks associated with radioligand therapy [36]. Therefore, concerns about liver injury related to the expression of somatostatin receptors in its cells appear to be unconfirmed.

The potential impact of radioligand therapy on the bone marrow is mainly related to the circulation time of the radioisotope in the blood. In the evaluation of 2,225 NET patients, of whom 2,104 were treated with RLT alone and 121 with combined RLT and chemotherapy, with an observation period ranging from 6 to 62 months, short-term bone marrow injury was found in 221 patients (10%). Acute bone marrow complications reached grade 3–4 WHO CTCEA v. 5.0 (World Health Organization — Common Terminology Criteria for Adverse Events) and were mainly manifested as a self-limiting reduction in platelet count, especially during the first administration of the radioisotope. The myelodysplastic syndrome was a rare complication that occurred in only 32 (1.4%) patients. Risk factors for bone marrow injury included age > 70 years, impaired kidney function, pre-existing cytopenia, and previous chemotherapy or radiotherapy [37]. The authors' previous study also confirmed that bone marrow function after the RLT was significantly disturbed [34, 38]. During RLT a decrease in each bone marrow cell line was observed, however, statistically significant results regarded only leukocytes and lymphocytes. The adverse events categorized according to the CTCAE v. 5.0 reached only G1–G2 grade. Long-term haematological complications were noted, mainly

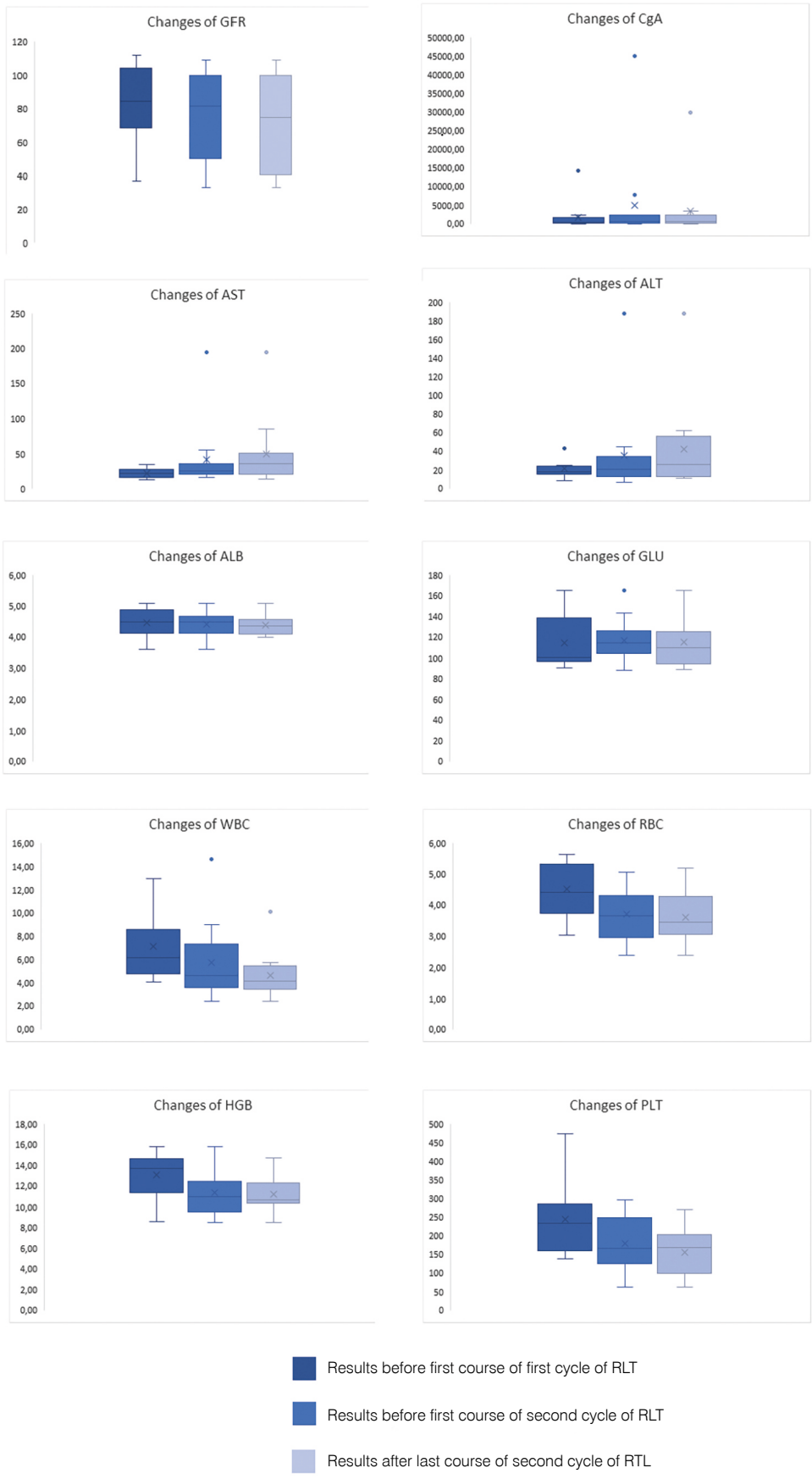

Figure 1. Box plots of laboratory parameters during treatment and observation; ALB — albumin; ALT — alanine aminotransferase; AST — aspartate aminotransferase; CgA — chromogranin A; GFR — glomerular filtration rate; GLU — glucose; HGB — haemoglobin; PLT — platelets; RBC — red blood cells; WBC — white blood cells

noticed in the lymphocyte line. There were no demographic or clinical factors that correlated with a higher decrease in blood parameters in that study (data not shown).

Disorders of carbohydrate metabolism (diabetes or prediabetes) are overlooked in descriptions of potential complications of RLT. In previous studies, Teunissen observed a long-term (up to 24 months) increase in average HbA1c values from 5.7% to 6.0% ($p < 0.05$) in a group of 79 patients treated with ^{177}Lu. Unfortunately, plasma glucose levels were not evaluated during the study [39]. Despite the lack of statistical significance in the present study, the increase of median fasting glucose concentration in patients treated with RLT may indicate the need for studies based on larger groups of patients to clearly establish the impact of the therapy on disturbances of carbohydrate metabolism.

Chromogranin A (CgA) concentration was used as a non-specific NEN biomarker of neoplastic disease control. Due to the lack of standardization of CgA testing, its potential and usefulness are not yet fully validated, however, results performed in single-centre with the use of the same method could be helpful and repeatable. Previous studies in patients with pancreatic NENs have shown that an increase in CgA concentration may correlate with disease progression, while in patients with NENs of the small and large intestine, chromogranin A concentration may be a predictive marker for progression-free survival [40].

The present observation did not show statistical differences in progression-free survival and laboratory results depending on the radioisotope used. Nevertheless, a noticeable trend indicating a higher therapeutic potential of tandem therapy but with possible greater systemic complications was observed. The results of the previous studies are partially in concordance with these findings [41].

Due to the increasing worldwide incidence of neuroendocrine neoplasms and higher demand for radioligand therapy, knowledge of possible results and complications of the treatment will be required. This awareness of potential outcomes of the treatment will enable more effective and proper qualification for individualized therapy tailored to each patient.

Conclusions

In the present study, the first cycle (4 courses) of RLT resulted in a median PFS of over 36 months. The extension of progression-free survival time to over 3 years of generalized cancer disease, as the NEN is a valuable therapeutic outcome.

Precise values of PFS and OS after re-treatment were calculated with limited data, but generally, 62.5% of patients beneficially responded to the treatment, 12.5% noted progression after over a year, and 25% died due to progression of the disease.

During observation, a decrease in glomerular filtration, all bone marrow cell line counts and an increase in fasting glycaemia were observed. The deterioration of these parameters after the first cycle of RLT was acceptable and did not disqualify patients from the second RLT cycle. The effect was most likely due to the cumulative effect of radioligand therapy, the natural ageing process, and the generalized progression of the disease.

There were no statistical differences between the results of patients treated with different types of radioisotopes, thus no data supports the predominance of any specific radiopharmaceutical. However, slight differences, such as higher CgA concentration and deeper GFR decrease when tandem therapy was used, could be suggestive for clinicians on how to individualize the therapy for these patients.

The present study suggests that the second cycle of RLT could be an efficient and safe method of treatment and should be considered when the progression of NEN is confirmed, and other treatment methods seem to be inappropriate or not available.

Limitations

The limitation of the study is its small group, as well as the limited number of patients in the final follow-up. However, repeated RLT is a non-standard procedure, performed in a very small number of patients. Therefore, it is believed that the presentation of the results above has a high substantive value in terms of future therapies in patients with progressive NENs.

Article information and declarations

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Author contributions

Conceptualization — A.D.D., M.S.; methodology — A.D.D. M.S.; formal analysis — A.D.D., M.S.; investigation — A.D.D., M.K, K.J.-P., W.Ż., B.D., A.M.; resources — A.D.D., M.K., K.J.-P., W.Ż., B.D., A.M.; data curation — A.D.D.; writing: original draft preparation — A.D.D., M.S.; writing: review and editing — A.D.D., M.S., G.K.; visualization — A.D.D., M.S., G.K.; supervision — M.S., G.K. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the local Ethics Committee, Protocol Code 154/17; date of approval: 15 December 2017.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Conflicts of interest

The authors declare no conflict of interest.

Supplementary material

The Supplementary material for this article can be found online at https://journals.viamedica.pl/nuclear_medicine_review/article/view/96672.

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