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Nephrotoxicity after PRRT — still a serious clinical problem? Renal toxicity after peptide receptor radionuclide therapy with ^{90}Y-DOTATATE and ^{90}Y/^{177}Lu-DOTATATE

Czy nefrotoksyczność po PRRT jest nadal poważnym problemem klinicznym? Analiza stopnia uszkodzenia nerek po terapii znakowanymi izotopowo analogami somatostatyny z zastosowaniem ^{90}Y-DOTATATE i ^{90}Y/^{177}Lu-DOTATATE

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Abstract

Introduction: The kidneys play an essential role in PRRT. The infusion of amino acids could reduce uptake in the kidney of radiolabelled peptides.
The purpose of this study was to determine the extent of kidney damage post PRRT.
Material and methods: 53 patients, with disseminated neuroendocrine tumours (NET), received 3–5 cycles of up to a maximum 7.4 GBq/m^2 calculated dose of ^{90}Y-DOTATATE (n = 25) and ^{90}Y/^{177}Lu-DOTATATE (n = 28). Creatinine levels were measured and glomerular filtration rates (GFR) were calculated. A mixed amino acid infusion was used for nephroprotection.
Results: Patients treated with ^{90}Y-DOTATATE had a mean creatinine level of 0.77 ± 0.19 mg/dL and a mean GFR (mL/min/1.73 m^2) of 103.6 ± 30.8. Patients treated with ^{90}Y/^{177}Lu-DOTATATE had a mean creatinine level of 0.92 ± 0.33 mg/dL and a mean GFR of 84.7 ± 26.3. In the follow up, among patients treated with ^{90}Y-DOTATATE and ^{90}Y/^{177}Lu-DOTATATE, the mean GFR level at 12 months was 101.2 ± ± 31.3 v. 83.9 ± 25.2, at 24 months 80.2 ± 32.7 v. 77.2 ± 31.1, at 36 months 78.9 ± 42.1 v. 67.5 ± 9.7, and 48 months 59.7 ± 15.2 v. 72.6 ± 11.2. The mean yearly decrease in GFR was 4.5 mL in all treated patients; for patients treated with ^{90}Y-DOTATATE and ^{90}Y/^{177}Lu-DOTATATE it was 6.8 v. 3.0, respectively.
Conclusions: ^{90}Y/^{177}Lu-DOTATATE treatment induced statistically significantly less change in kidney function compared to ^{90}Y-DOTATATE.
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Key words: *somatostatin receptors, peptide receptor radionuclide therapy, neuroendocrine tumours, nephrotoxicity, ^{90}Y-DOTATATE, tandem ^{90}Y/^{177}Lu-DOTATATE*

Streszczenie

Wstęp: Narządem krytycznym w leczeniu guzów neuroendokrynnych z zastosowaniem znakowanych radioizotopowo analogów somatostatyny (PRRT) są nerki. Działanie nefrotoksyczne można ograniczyć, podając roztwór aminokwasów w formie wlewu dożylnego. Celem pracy była analiza stopnia uszkodzenia nerek po PRRT w ciągu pierwszych czterech lat po leczeniu.
Materiał i metody: Do badania włączono 53 chorych, z rozpoznanym rozsianym procesem neuroendokrynnym (NET). Chorzy otrzymali 7,4 GBq/m^2 ^{90}Y-DOTATATE (n = 25) lub ^{90}Y/^{177}Lu-DOTATATE (n = 28) w 3–5 cyklach. Radiofarmaceutyk podawano w trakcie wlewu *i.v.* roztworu aminokwasów. Oceniano stężenie kreatyniny, na podstawie którego obliczano wartość filtracji kłębuszkowej (GFR).
Wyniki: Przed leczeniem w grupie chorych leczonych ^{90}Y-DOTATATE stężenie kreatyniny wynosiło 0,77 ± 0,19 (mg/dl), natomiast GFR 103,6 ± 30,8 (ml/min/1,73 m^2). W grupie leczonej ^{90}Y/^{177}Lu-DOTATATE stężenie kreatyniny wynosiło 0,92 ± 0,33 i GFR 84,7 ± 26,3. Nie stwierdzono statystycznie znamiennej różnicy w wartościach badanych parametrów między obydwiema grupami.
Po 12 miesiącach wartość GFR w grupie leczonej ^{90}Y-DOTATATE i grupie leczonej ^{90}Y/^{177}Lu-DOTATATE wynosiła odpowiednio: 101 ± ± 31,3 oraz 83,9 ± 25,2. Po 24 miesiącach odpowiednio: 80,2 ± 32,7 i 77,2 ± 31,1. Po 36 miesiącach odpowiednio 78,9 ± 42,1 i 67,5 ± 9,7. Po 48 miesiącach odpowiednio: 59,7 ± 15,2 i 72,6 ± 11,2. Średni spadek GFR dla wszystkich chorych wynosił 4,5 ml/rok, dla chorych leczonych ^{90}Y-DOTATATE – 6,8 ml/rok, natomiast dla chorych leczonych ^{90}Y/^{177}Lu-DOTATATE — 3,0 ml/rok
Wnioski: Leczenie z zastosowaniem ^{90}Y/^{177}Lu-DOTATATE jest związane z istotnie mniejszym statystycznie uszkodzeniem czynności nerek w porównaniu do leczenia z zastosowaniem ^{90}Y-DOTATATE. **(Endokrynol Pol 2013; 64 (1): 13–20)**

Słowa kluczowe: *receptory somatostatynowe, terapia znakowanymi izotopowo analogami somatostatyny, guzy neuroendokrynne, nefrotoksyczność, ^{90}Y-DOTATATE, ^{90}Y/^{177}Lu-DOTATATE*

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Introduction

PRRT, using radiolabelled somatostatin analogues, has shown promising results in the treatment of patients with inoperable or metastatic NET. However, PRRT may adversely affect the kidneys due to the re-absorption of radiolabelled somatostatin analogues in the proximal tubules of nephrons [1, 2] and the expression of somatostatin receptors [3].

Clinically, renal failure and end-stage renal disease (ESRD) have been documented post PRRT with ^{90}Y-DOTATOC [4, 5]. Furthermore, renal damage may occur during external beam radiation therapy when absorbed doses reach 23 Gy or higher [6]. This was confirmed by Milano: a group of patients (n = 47) treated with ^{90}Y-DOTATOC received a cumulative kidney dose of 27 Gy during six courses [7].

Co-administration of amino acids L-lysine and/or L-arginine competitively inhibit the proximal tubular re-absorption of radiopeptides, reducing uptake by 40%, thus offering significant nephroprotection [8]. Moreover, succinylated gelatin plasma expander Gelofusine co-injected with lysine can reduce kidney radiopeptide uptake by 62–70% [9, 10].

Renal malfunction may appear several years post PRRT, potentially coinciding with chronic kidney diseases found more often in the elderly. The age-associated decline in GFR during the third decade of life, from a peak of about 120 mL/min/1.73 m^2, is approximately 1 mL/min/y/1.73 m^2, reaching a mean value of 70 mL/ /min/1.73 m^2 at the age of 70 [11]. GFR also declines in patients with additional risk factors: hypertension 2.32–4.1 mL/min/1.73 m^2 [12,13], diabetes 4.7–7.2 mL/min/1.73 m^2 [14,15], and cisplatin chemotherapy ≤ 6 mL/min/1.73 m^2 per year [16]. In addition, post PRRT renal failure may be insidious; stages 1–3 of kidney failure are for the most part clinically silent. Consequently, it is important to observe long term renal function following PRRT.

In our study, we analysed changes in renal function post PRRT with ^{90}Y-DOTATATE and tandem ^{90}Y/^{177}Lu-DOTATATE.

Material and methods

This study was approved by the ethical committee of the Medical University of Warsaw. All patients gave written informed consent.

53 patients with diffuse NETs were enrolled in an uncontrolled study. The ^{90}Y-DOTATATE treatment group consisted of 25 patients (11 males and 14 females) with a mean age of 57.4 ± 9.9 years, ranging from 37–75 years. The ^{90}Y/^{177}Lu-DOTATATE treatment group consisted of ten males and 18 females, totalling 28 patients, with a mean age of 55 ± 10.9 years, ranging from 39–78 years.

The patients in our study were not randomised, but were treated first using ^{90}Y DOTATATE; patients who presented later were treated with ^{90}Y/^{177}Lu DOTATATE. Subsequently, Cox analysis was used to evaluate the effects of relevant prognostic factors on the survival times in each treatment group, as well as the independency of these variables.

GFR was calculated using creatinine-based approximations based on the modification of diet in renal disease (MDRD) [17]. Basal creatinine values ranged from 0.5 to 1.3 mg/dL in the ^{90}Y-DOTATATE treatment group, and from 0.5 to 1.9 mg/dL in the ^{90}Y/^{177}Lu-DOTATATE treatment group. Basal calculated GFR ranges were 171 to 43 mL/min in the ^{90}Y-DOTATATE group, and 137 to 40 mL/min in the ^{90}Y/^{177}Lu-DOTATATE group.

The progression of disease, in both groups, was confirmed by CT and by an increase of chromogranin A (CgA) concentration in blood. Response to treatment was observed by CT and stratified according to the Response Evaluation Criteria in Solid Tumours (RECIST). The following inclusion criteria for therapy were used:

— Somatostatin receptor imaging (^{99m}Tc-HYNIC-TATE or ^{68}Ga-DOTATATE) positive uptake by tumour and metastases at least three months prior to inclusion;
— Histological confirmation of NET tumour, determined to be inoperable or metastatic;
— Haemoglobin level (Hb) ≥ 10 g/dL; leukocytes (WBC) ≥ 2 × 10^9/L; thrombocytes (PLT) ≥ 90 × 10^9/L;
— Calculated GFR > 40 mL/min;
— Karnofsky Performance Status ≥ 60;
— Life expectancy > 3 months;
— No pregnancy or lactation;
— Interval between chemotherapy and PRRT of at least three months.

Treatment

Therapy was performed on an outpatient basis. Treatment sessions were repeated with a total calculated maximum dose of 7.4 GBq /m^2. The injected activity per course equaled 2.2–3.7 GBq. Four patients from the ^{90}Y-DOTATATE treatment group and two from the ^{90}Y/^{177}Lu-DOTATATE treatment group received two additional cycles due to recurrence of disease.

With regards to ^{90}Y/^{177}Lu-DOTATATE, 50% of the activity was attributed to ^{90}Y-DOTATATE and the other 50% to ^{177}Lu-DOTATATE. The median period between the treatments was 40 and 49 days, respectively. A mixed amino-acid infusion, consisting of 11.3 g of arginine and 9.0 g lysine (1,000 mL Vamin 18, Fresenius Kabi) and Ringer's solutions (500 mL), was infused over eight hours in addition to 200 ml prior to administration of the treatment [18, 19]. Ondansetron (8 mg, Zofran, Glaxo Wellcome, Atossa, Anpharm S. A.) was given intravenously to prevent nausea and vomiting prior to the administration of radiopharmaceuticals.

Evaluation of Results and Assessment of Clinical Benefit

Creatinine level was assessed prior to treatment and reassessed seven, and 21–30 days after each cycle of therapy, and then after three, six, 12, 24, 36, and 48 months. Renal toxicity was defined by the National Cancer Institute.

Statistical methods

Means, standard deviations, and frequencies were used to summarise patient characteristics. Linear multi-parameters regression models were used to analyse the influence of risk factors over time, depending on the changes of GFR. Overall survival (OS), event free survival (EFS), and time to progression (TTP) were calculated using the Kaplan-Meier estimator. They were then compared using the log-rank test. Calculations were done using Stata v.10.1 software (Stata Statistical Software: Release 10, College Station, TX, Stata Corporation LP 2007).

Results

Patient characteristics

The study included 53 Caucasian patients with metastatic NETs. Medical history revealed common risk factors for kidney disease: age > 60 years, diabetes, hypertension, and positive family history. Additionally, previous chemotherapy (etoposide + cisplatin or streptozocin + 5-fluourouracyl) was evaluated. Refer to Table I for detailed patient characteristics.

Table I. *Patient characteristics*

Tabela I. *Charakterystyka pacjentów*

	^{90}Y-DOTATATE N = 25	^{90}Y /^{177}Lu -DOTATATE N = 28
Age range Mean ± SD	37–75 57.4 ± 9.9	39–73 55 ± 10.9
Sex: Female	14 (56%)	18 (64%)
Age > 40	22 (88%)	25 (89%)
Age > 60	10 (40%)	13 (46%)
Chemotherapy	9 (36%)	9 (32%)
Diabetes mellitus	5 (20%)	8 (29%)
Hypertension	15 (60%)	20 (71%)
Primary tumours		
Foregut	16 (64%)	14 (50%)
Midgut	6 (24%)	9 (32%)
Hindgut	2 (8%)	1 (4%)
Unknown primary	1 (4%)	2 (7%)
Other	0	2 (7%)

Outcome of therapy

Median OS, of patients treated with ^{90}Y-DOTATATE, was 34.2 months and 49.8 months for patients treated with ^{90}Y/^{177}Lu-DOTATATE ($p > 0.05$). The median EFS time in the ^{90}Y-DOTATATE and the ^{90}Y/^{177}Lu-DOTATATE group was 19.3 v. 24.3 months, respectively, while the median TTP was 24.2 compared to 24.3 months for the ^{90}Y-DOTATATE and the ^{90}Y/^{177}Lu-DOTATATE group respectively. The differences were not statistically significant.

Kidney function after treatment with ^{90}Y-DOTATATE and ^{90}Y/^{177}Lu-DOTATATE

Treatment was well tolerated without severe adverse events. Baseline mean creatinine level was 0.77 ± 0.19 mg/dL and GFR (mL/min/1.73 m^2) was 103.6 ± 30.8 in patients treated with ^{90}Y-DOTATATE. In contrast, baseline mean creatinine level of 0.92 ± 0.33 mg/dL and GFR of 84.7 ± 26.3 were noted in patients treated with ^{90}Y/^{177}Lu-DOTATATE (Fig. 1).

Upon follow up, patients in the ^{90}Y-DOTATATE and ^{90}Y/^{177}Lu-DOTATATE group had, at six months, creatinine levels (mg/dL) of 0.77 ± 0.24 v. 0.86 ± 0.32, at 12 months 0.8 ± 0.25 v. 0.94 ± 0.43, at 24 months 0.97 ± 0.36 v. 1.07 ± 0.55, at 36 months 1.07 ± 0.55 v. 1.03 ± 0.22, and at 48 months 1.3 ± 0.5 v. 0.96 ± 0.16.

The mean GFR level (mL/min/1.73 m^2) at six months was 105.6 ± 35.1 v. 92.6 ± 33.9, at 12 months 101.2 ± 31.3 v. 83.9 ± 25.2, at 24 months 80.2 ± 32.7 v. 77.2 ± 31.1, at 36 months 78.9 ± 42.1 v. 67.5 ± 9.7, and at 48 months 59.7 ± 15.2 v. 72.6 ± 11.2.

The median changes of GFR at 48 months are presented in Figure 2 and detailed changes in particular patients in both treatment groups in Tables II and III.

The yearly mean increase in creatinine level for the entire study group was 0.056 mg/dL. The yearly decrease in GFR, calculated by a linear regression model, was 4.5 mL/min/1.73 m^2 in all treated patients. The decrease in GFR in patients treated with ^{90}Y-DOTATATE and ^{90}Y/^{177}Lu-DOTATATE was 6.8 v. 3 mL/min/1.73 m^2 per year ($p < 0.05$).

It was observed that patients from both groups with more than two risk factors demonstrated the largest statistically significant changes in GFR (Fig. 3). Multi-parameter regression models (including previous reported risk factors) revealed GFR statistically significant changes depending on the type of therapy, hypertension and previous chemotherapy (Table IV). GFR declination percent upon follow-up was significantly lower in the group treated with ^{90}Y/^{177}Lu-DOTATATE (Fig. 4).

Grade 1 nephrotoxicity was seen in 2/25 patients treated with ^{90}Y-DOTATATE and 2/28 in the group treated with ^{90}Y/^{177}Lu-DOTATATE. Grade 2 nephrotoxicity was seen in 3/25 patients and 1/28 patients, respectively. Grade 3 and 4 nephrotoxicity was not observed in both groups.

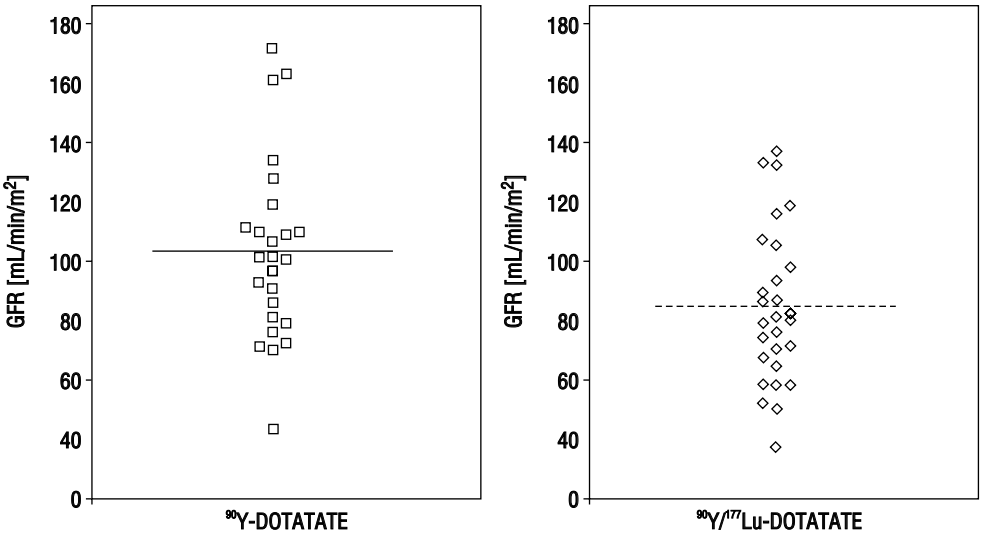

Figure 1. *Baseline GFR of persons in the two groups treated with ^{90}Y-DOTATATE and ^{90}Y/^{177}Lu-DOTATATE before PRRT. Line is presented as median*

Rycina 1. *Wyjściowe (przed terapią) wartości GFR dla obu grup leczonych ^{90}Y-DOTATATE lub ^{90}Y/^{177}Lu-DOTATATE. Linia prezentuje medianę*

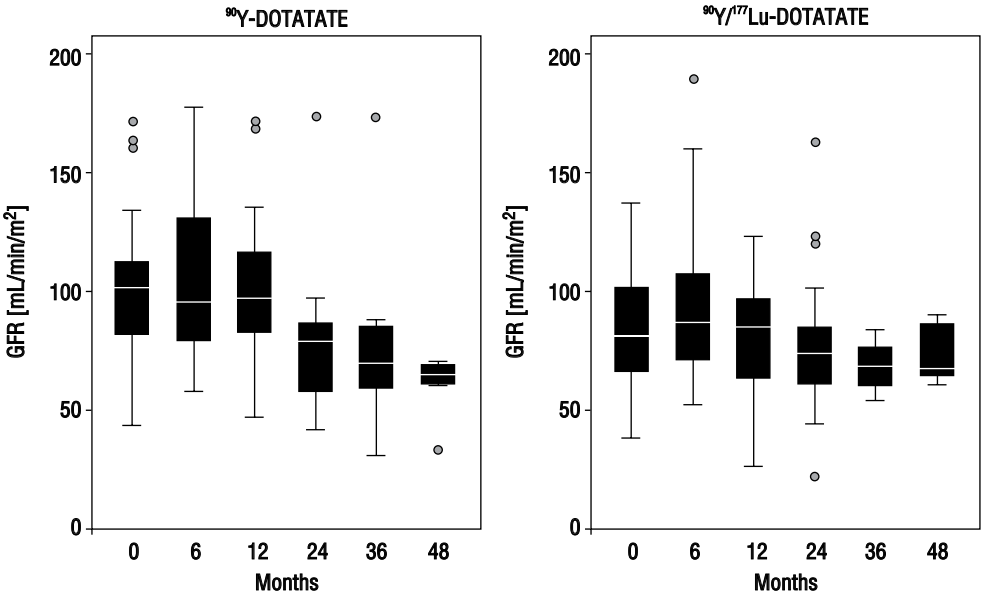

Figure 2. *Box-plot of changes in GFR at six, 12, 24, 36 and 48 months follow up in group treated with ^{90}Y-DOTATATE and ^{90}Y/^{177}Lu-DOTATATE. Line is presented as median changes*

Rycina 2. *Wykres zmian GFR w kontroli po 6, 12, 24 ,36 i 48 miesiącach w grupie leczonej ^{90}Y-DOTATATE lub ^{90}Y/^{177}Lu-DOTATATE. Linia prezentuje medianę*

Mild nausea occurred at equal frequencies in both groups; it affected 38% of the entire population and was reported upon administration of radiopharmaceuticals and amino-acids infusion. All cases of nausea and vomiting responded to ondansetron. Hyperkalemia was not observed clinically nor in blood tests.

Discussion

^{177}Lu and ^{90}Y demonstrate different physical properties. These differences include half-life, path length, and type of energy emission. ^{90}Y emits β-particles with longer path lengths and higher energies. ^{177}Lu has a shorter β-particle range, and longer half-life, resulting in lower kidney re-absorption and reduction of renal toxicity [20]. In the literature, nephrotoxicity after PRRT with ^{90}Y -DOTATOC has been recognised as an important clinical problem which limits therapy [21–25]. Cumulative experience with ^{90}Y-DOTATOC was reported by the Basel group [26]. Four cases of early renal insufficiency and two additional cases of delayed renal failure in studies without infusion of amino acids for renal protection were observed. In later studies, only

Table II. *Number of risk factors and GRF changes after PRRT in group treated with ^{90}Y-DOTATATE*

Tabela II. *Występujące czynniki ryzyka i zmiany GFR po PRRT w grupie leczonej ^{90}Y-DOTATATE*

	Age	Number of risk factors	Age > 60	CHT	HA	DM	Total administered activity [GBq]	GFR baseline [mL/min/m^2]	GFR follow up [mL/min/m^2]
1	37	1		+			3.7	161.1	Death in first year
2	59	1			+		14.8	109.9	Death last follow up 12 months 86.2
3	63	1	+				13.3	96.8	Death last follow up 12 months 117.2
4	36	1		+			15	86.3	Death last follow up 24 months 86.3
5	59	1			+		17.8	134.2	134.2 (48 months)
6	70	2	+		+		7.4	90.9	Death in first year
7	50	2		+	+		13.3	76.3	70.4 (48 months)
8	64	2	+		+		12.6	107.0	59.3 (36 months)
9	58	2			+	+	22.6	109.1	Death last follow up 36 months 54.2
10	56	1			+		22.9	81.2	Death last follow up 24 months 55.7
11	68	3	+	+	+		14.8	101.7	69.7 (36 months)
12	65	4	+	+	+	+	13.3	43.7	Death last follow up 12 months 55.5
13	46	0					13.3	163.6	135.7 (24 months)
14	44	0					14.8	110.0	Death last follow up 12 months 120.2
15	61	2	+			+	14.8	171.7	Death last follow up 24 months 145.6
16	66	2	+		+		6.7	70.2	Death in first year
17	44	2			+	+	14.1	128.1	61 (48 months)
18	55	1		+			13.3	79.2	Death last follow up 36 months 64.1
19	55	1		+			13.3	111.5	Death last follow up 24 months 93.1
20	56	2		+	+		3.7	92.8	Death in first year
21	47	0					19.2	71.3	64.7 (48 months)
22	60	3	+	+	+		17.8	72.6	33.5 (48 months)
23	70	3	+		+	+	14.1	101.6	68.9 (48 months)
24	59	1			+		20.7	100.8	Death last follow up 24 months 69.7
25	68	1	+				11.8	119.3	69.7 (24 months)

CHT — chemotherapy; HA — hypertension; DM — diabetes mellitus

Table III. *Number of risk factors and GRF changes after PRRT in group treated with ^{90}Y /^{177}Lu-DOTATATE*
Tabela III. *Występujące czynniki ryzyka i zmiany GFR po PRRT w grupie leczonej ^{90}Y/^{177}Lu-DOTATATE*

	Age	Number of risk factors	Age > 60	CHT	HA	DM	Total administered activity [GBq]	GFR baseline [mL/min/m^2]	GFR follow up [mL/min/m^2]
1	39	2		+		+	14.1	133.4	Death last follow up 24 months 64.2
2	57	2		+	+		23.3	70.4	64.5 (48 months)
3	62	2	+		+		21.5	98.2	67.4 (48 months)
4	58	2			+	+	13.3	76.1	60.5 (48 months)
5	69	4	+	+	+	+	14.8	40.2	45.8 (36 months)
6	45	1				+	13	82.4	82.4 (24 months)
7	72	3	+		+	+	13.3	79.5	67.1 (48 months)
8	62	2	+		+		13	67.4	77.2 (48 months)
9	62	2	+		+		11.1	86.4	Death last follow up 24 months 85.4
10	67	2	+		+		16.7	71.7	64.0 (36 months)
11	50	1			+		14.8	80.3	84.1 (48 months)
12	40	0					17	89.6	69.2 (48 months)
13	38	1		+			10.4	118.9	Death last follow up 24 months 118.9
14	67	2	+		+		14.8	87.3	76.0 (48 months)
15	57	2		+	+		14.8	116.2	Death last follow up 12 months 118.6
16	40	0					11.1	58.5	58.5 (48 months)
17	42	1			+		12.6	64.6	52.4 (48 months)
18	47	0					14.8	137.4	95.3 (36 months)
19	64	2	+		+		14.8	81.8	71.6 (48 months)
20	59	2		+	+		10.4	52.4	54.0 (48 months)
21	63	1	+				13	132.4	89.8 (24 months)
22	63	4	+	+	+	+	14.8	58	Death last follow up 24 months 54.3
23	44	1		+			13	93.5	Death last follow up 12 months 86.6
24	68	4	+	+	+	+	11.1	105.7	Death in first year
25	69	3	+		+	+	9.6	50.5	Death last follow up 24 months 22.2
26	60	2	+		+		14.1	58.1	63.0 (24 months)
27	52	1			+		13	107.4	123.4 (24 months)
28	53	1			+		14.1	74.4	Death in first year

CHT — chemotherapy; HA — hypertension; DM — diabetes mellitus

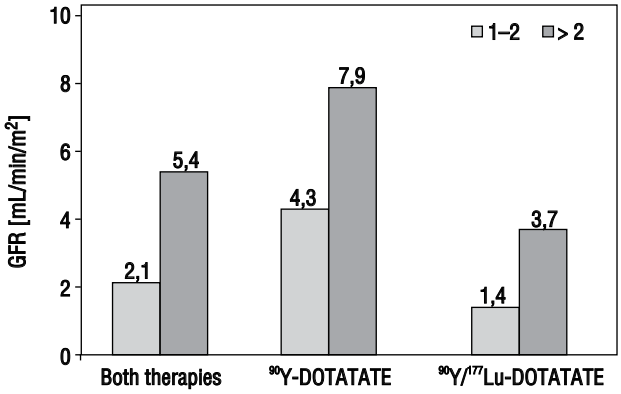

Figure 3. *Graph presenting changes per year in GFR (mL/min/m²) in patients with 1–2 risk factors and > 2 risk factors*

Rycina 3. *Wykres zmian GFR/rok(ml/min/m²) u pacjentów z 1–2 czynnikami ryzyka oraz > 2 czynników ryzyka*

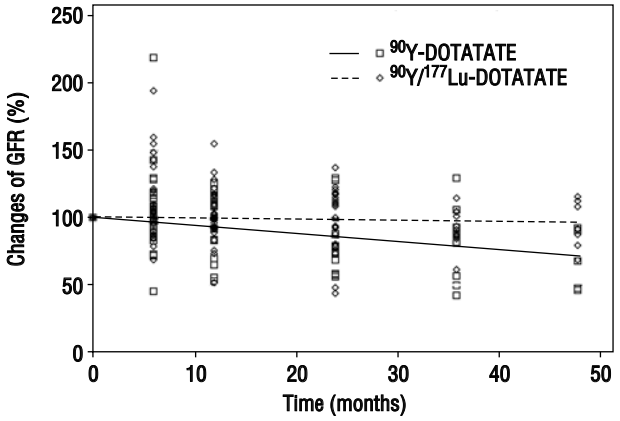

Figure 4. *Proportional changes in GFR at 6, 12, 24, 36 and 48 months follow up in group treated with ^{90}Y-DOTATATE and ^{90}Y/^{177}Lu-DOTATATE*

Rycina 4. *Proporcjonalne zmiany GFR w kontroli po 6, 12, 24, 36 i 48 miesiącach w grupie leczonej ^{90}Y-DOTATATE lub ^{90}Y/^{177}Lu-DOTATATE*

Table IV. ***Regression model — influence of risk factors on changes of GFR***

Tabela IV. ***Model regresji — wpływ czynników ryzyka na zmiany GFR***

GFR	P
Therapy	**0.008**
Age	0.09
Chemotherapy	**0.014**
Hypertension	0.001
Diabetes	0.426

a single patient developed late grade 2 renal toxicity when nephroprotecting agents, such as amino acids, were added during therapy [27]. In Milan's study, 256 patients received amino acids [28] and no acute renal toxicity was reported. One patient developed grade 2 toxicity, two patients developed grade 1 toxicity, and two patients developed transient grade 1 toxicity. Bodei at al. [29] observed patients treated with ^{90}Y-DOTATOC: 7/23 developed grade 1 toxicity, 1/23 patients developed grade 2 toxicity, and 1/23 patients developed grade 3 toxicity. A large study conducted by Imhof et al., consisting of 1,109 patients, demonstrated 9.2% permanent renal toxicity with grades 4 to 5; initial renal uptake was predictive for severe renal toxicity [30]. In the ^{177}Lu-DOTATATE treatment group, renal toxicity was not observed [31]. A 2.5% solution of arginine and lysine has been used for nephroprotection in published data. This solution was not available in Poland. Consequently, a commercially available mixed amino-acid solution was used. In our study, nephrotoxicity occurred at a similar rate compared to reported data. Grade 1 nephrotoxicity was observed in 2/25 patients treated with ^{90}Y-DOTATATE and 2/28 in the group treated with ^{90}Y/^{177}Lu-DOTATATE. Grade 2 nephrotoxicity was seen in 3/25 patients and 1/28 patients, respectively. Grades 3 and 4 were not observed.

Despite nephroprotection, loss of renal function can occur post PRRT, with a creatinine clearance loss of about 3.8% per year for ^{177}Lu-DOTATATE and 7.3% per year for ^{90}Y-DOTATOC [30]. Grade 4 and 5 kidney toxicity has been reported in 9.2% of patients treated with ^{90}Y-DOTATOC [32].

The influence of additional risk factors on nephrotoxicity presents another dilemma. The clinical observation of renal damage post PRRT, in the study by Valkema et al., revealed five risk factors: cumulative renal absorbed doses of more than 25 Gy, diabetes, hypertension, age > 60 years and a renal radiation dose > 14 Gy per cycle [32]. Similar negative influences of hypertension, diabetes mellitus and previous chemotherapy were observed by Barone et al. [33] and by Bodei et al. [29].

In our study, we observed significant influences of one type of radioisotope therapy, hypertension and previous chemotherapy. The influence of diabetes mellitus and an age > 60 years were not statistically significant. This could be connected to the proportion of older patients and good control of diabetes. The majority of patients in our study had one or more risk factors for renal disease. The significant GFR changes were observed among patients with two or more risk factors.

The reported biological effective dose threshold for renal toxicity in patients with risk factors was 28 Gy. In patients without risk factors, the threshold for toxicity was 40 Gy [29]. Clinical experience and earlier dosimetry studies have indicated that the renal dose threshold does not accurately correlate with the renal toxicity observed in patients undergoing PRRT [30].

The limitations of this study were the small number of patients and the lack of dosimetry. Dosimetry is still an open problem for yttrium and tandem therapy. For

PRRT with yttrium-90, dosimetry cannot be reconstructed from the bremsstrahlung images. For PRRT with tandem isotopes, different physical properties of isotopes used are presented. However, in our study there was no observed grade 3 and 4 renal toxicity, using 200 mCi (7.4 GBq) doses per m^2. Analysis of GFR decline demonstrated that the toxicity of PRRT is comparable to the influence of nephotoxicity as a consequence of other risk factors.

Reports of end-stage renal failure during PRRT treatment have appeared in the past, particularly in patients receiving doses > 200 mCi (7.4 GBq/m^2) [4,5]. Currently, this is not observed due to inclusion of nephroprotective agents during therapy. Infusion of amino acid used for nephroprotection can cause nausea, vomiting and hyperkalemia. Few adverse reactions were reported during this study. Mild nausea was observed in 38% of patients and vomiting in 19%, with equal frequency in both groups. Hyperkalemia did not occur in our investigation. Nonetheless, it was reported in previous studies in which patients received a total dose of 75 g lysine [8].

The evolution of nephroprotection during PRRT includes novel combinations of agents that reduce renal retention of radiolabelled peptides or the development of new somatostatin analogues less susceptible to renal retention. There is a need for standardisation of therapy protocols and multicentre studies in order to enhance the clinical value of PRRT in the advent of various other new oncological treatments.

Conclusions

^{90}Y/^{177}Lu-DOTATATE treatment induced statistically significantly less change in kidney function than ^{90}Y-DOTATATE**.** On the basis of published data regarding chronic kidney disease, the change of renal function in patients after PRRT is comparable to that of any other progressive chronic kidney disease.

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