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Original Article

Radioactivity of biological samples of patients treated with ^{90}Y-DOTATOC

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ABSTRACT

Dosimetric studies in Nuclear Medicine are very important, especially with new therapeutic methods, the number of which has increased significantly with the Theranostic approach (determining diagnostic-therapeutic pairs where similar molecules are labelled with different isotopes in order to diagnose and treat malignant diseases). Peptide receptor radionuclide therapy (PRRT) has been used successfully for many years to treat neuroendocrine tumors (NET). ^{90}Y-DOTATOC is one of the radiopharmaceuticals used frequently in this type of therapy.

In this work, blood and urine samples from 13 patients treated with ^{90}Y-DOTATOC were measured by a liquid scintillation beta counter (LSC). Calibration of the beta counter for this type of measurement was done and all results are presented in the paper. The presented paper also provides a methodology for determining the measurement uncertainty for this type of measurement.

Immediately after the administration of radiopharmaceuticals, the activity in the blood was different from 6.31% to 88.9% of the applied radioactivity, while 3 *h* after the termination of the application, the average value of radiopharmaceuticals in the blood was only 3.84%. The activity in the excreted urine depended on the time when the patients urinated after the therapy. It was measured that as much as 58% of the applied radioactivity was excreted in the first urine after the therapy in a patient who urinated 4.5 *h* after the completed application of the therapy. In most patients, the highest urine activity was in the first 10 *h* after the application, while the activities after that time were negligibly low.

The described methodology of measuring and evaluating activity in blood and excreted urine can be applied to other radiopharmaceuticals used in nuclear medicine. It could be useful for researchers for dosimetric assessments in clinical application of PRRT.

1. Introduction

Yttrium 90 (^{90}Y) is an isotope that is widely used in nuclear medicine for therapeutic purposes. It is used in peptide radionuclide therapy to treat neuroendocrine tumors (NET) and lymphoma. It is also used with or nanospheres for selective internal radiation therapy (SIRT) in ablation of liver tumors [1,2] and in radiosynovectomy for the treatment of degenerative changes in the joints.

^{90}Y is an almost pure beta emitter (99.989%) and is therefore difficult to detect on standard nuclear medicine equipment. The half-life is 64.1 *h*, and the maximum energy of beta particles is 2278.7 *keV*, while the mean energy is 926.7 *keV*. It can be detected as bremstrahlung radiation on gamma cameras, but such images do not meet the quality criteria for dosimetric calculations [3–6]. More recently, there have been studies where ^{90}Y has been measured by using combination of two techniques, bremstrahlung SPECT-CT and TOF-PET-CT, thanks to the fact that in 0.003% there is decay through β^+ emission [7, [8]]. Therefore, it is very important to measure blood and urine samples in therapies where this isotope is administered intravenously and where renal excretion is dominant.

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The range of ^{90}Y beta particle in soft tissues is a maximum of 11.2 *mm* and it is recommended to use this isotope in well-differentiated neuroendocrine tumors larger than 2 *cm* in diameter (NET) as Peptide Receptor Radionuclide Therapy (PRRT) [9,10]. For smaller tumors, the use of Lutecium 177 is recommended. PRRT therapy is used in neuroendocrine tumors that are well suppressed by somatostatin receptor subtype 2 (SST2) and somatostatin receptor subtype 5 (SST5) receptors [11] and is applied in several cycles. The characteristic of PRRT is that the peptide molecules are transported very quickly to the tumor, while the unbound residue is excreted in the urine. Therapy is renotoxic [12.13.14.15], and Grade 3–4 myelotoxicity may be observed in up to 10–13% of patients, and cases of myelodysplastic syndrome or acute myelogenous leukemia have been reported [12–20]]. Therefore, it is very important to perform measurements of ^{90}Y in blood and urine for the assessment of absorbed doses in critical organs that should be performed in all patients [16].

There are recommendations that the absorbed doses in the kidneys, when using PRRT, should be limited [7,21,22] and the biologically effective dose should not exceed 28 *Gy* [16]. It is also important to evaluate the absorbed doses in the tumor in order to achieve a good therapeutic effect.

Liquid scintillation counters are considered as a gold standard for measuring of low beta emitter activity of various radionuclides in drinking water and various foods [23] as in the urine of healthy people to determine the presence of some radionuclides [24]. Their advantage is the high efficiency for beta emitters, while the disadvantage is the limit in count rate, so high activities cannot be measured with such equipment's. Liquid scintillation counters use Cherenkov light that occurs in the tube in which the sample is measured. The detector measures the intensity of the emitted light and determines its wavelength, so the counter can also be used as a spectrometer.

The aim of this paper was to present the ^{90}Y sampling methodology, measurement and calculation of activity in blood and urine and the obtained results.

2. Materials and method

2.1. Sampling of biological materials from patients

In this study, blood and urine samples of 13 patients were measured, in whom PRRT ^{90}Y-DOTATOC was administered at the University Clinical Center Kragujevac, Center for Nuclear Medicine. Applied activities were between 2700 *MBq* and 5550 *MBq*. The patients were hospitalized for three days and during that time their biological samples were collected. A number of parameters such as sex, year of birth, diagnosis, dose used were also collected. The Ethics Committee of the Clinical Center Kragujevac, Serbia (decision number 01/20–655, date August 03, 2020) approved the protocol and the study was performed in accordance with the Declaration of Helsinki. Informed and written consent were obtained from all individual participant included in the study.

All ^{90}Y doses were delivered from the Isotope Laboratory of the Vinča Institute of Nuclear Sciences, Belgrade, where DOTATOC labeling was performed according to the manufacturer's protocol; all necessary measurements and quality control of the obtained ^{90}Y-DOTATOC radiopharmaceutical were performed [25]. Then, the prepared doses were transported the same day to KC Kragujevac, Center for Nuclear Medicine, where radiopharmaceuticals were administered to patients in the afternoon. On the packaging of the bottle, the sticker shows the activity of the preparation, which was measured at the Vinča Institute of Nuclear Sciences; this activity was taken as the applied activity, and the end time of the application was taken as zero time. For all samples a correction for ^{90}Y physical decay was considered.

Patients received therapy intravenously into the lateral cubital vein, in 150 *ml* of saline for 30 *min*. One hour before PRRT administration, during administration and 3 *h* after, a solution of positively charged amino acids is administered into the contralateral cubital vein, which is recommended for use as a renoprotective agent [26]. 2–3 *ml* of blood was sampled from the contralateral cubital vein immediately after the PRRT administration was completed, then for the first 6 *h* every hour, and then every 12 *h* for a total of 3 days, as long as, the patients were hospitalized. Urine samples were sampled by the patients themselves, by explaining in advance that each time they urinate into a plastic beaker from which they would read the volume of wet urine and then take a sample in a numbered syringe left for that purpose. They would then enter the values in the table left for them in their patient room, taking care that the ordinal number in the table matches the ordinal number of urination and the ordinal number of numbered syringes. Patients entered the date and exact time of urination and the volume of wet urine in the table.

2.2. Measurements of blood and urine samples of patients

Samples of blood and urine were measured by a liquid scintillation beta counter RACKBETA 1219, Wallac (LKB, Finland) after three days, considering the physical decay of ^{90}Y. Depending on the sample type, the biological material usually has to be pretreated before adding the scintillation cocktail. In our case, ethanol was first added to suppress protein precipitation in serum and in urine if proteins were present. For the same reason, measurements of radioactivity samples were done within a few hours of sample preparation. In addition, this dilution of the samples allowed minimizing the effect of color quenching. Further, scintillation cocktail which consists of organic solvent - toluene and scintillators (PPO (2, 5 - diphenyloxazole) and POPOP [1–4, bis-2- (5-Phenyloxazolyl) -benzene]) was added. Toluene belongs to the classic aromatic organic solvent used in liquid scintillation counting and plays as a target for β-emission, capturing the energy of the nuclear decay. Scintillator PPO directly transfers the energy between solvent and the POPOP molecules, which then re-emits this energy at a higher wavelength, as a visible light. This light is detected by the photomultiplier tube of the liquid scintillation counter (LSC). Plastic shatterproof vials of 5 *ml* was used in experiments, and the total volume of the mixture which was added to the sample was 4 *ml*. This allows optimal homogenization of samples by vortex which is essential for precise radioisotope detection by LSC.

2.3. Determination of activity in whole volume of blood and urine

The problem is to determine the activity in the total blood volume for all measuring points. The total volume of blood in the human body varies depending on the sex, tissue structure, body weight and height of the patient, so it is considered that a muscular man has 75 *ml* of blood per kilogram of body weight, while a normal man with average musculature has about 70 *ml*, and lean men are 65 *ml* and obese 60 *ml* per kilogram of body weight. Similar values are given for women and children. However, this method is highly subjective and imprecise, so the total blood volume of patients was calculated by the formula [27]:

$$\begin{aligned} BVL &= 31.9\cdot HT + 26.3\cdot WT - 2402 \ (for \quad men) \\ BVL &= 56.9\cdot HT + 14.4\cdot WT - 6460 \ (for \quad women) \end{aligned} \tag{1}$$

Where *BVL* is volume of blood, *HT* is body height (in *cm*), *WT* is body mass (in *kg*).

Activity in urine was obtained in the following way: results by LSC obtained in counts/min were recalculated in *MBq*, and then multiplied with the volume of urine, for each urination. Correction on the physical decay was also taken into account.

3. Results and Discussion

3.1. Calibration of LSC

Before the study, calibration of LSC was performed to determine the measurement efficiency i.e. the *count-Bq* ratio. A calibration source with activity of 50 *MBq* in a volume of 1 *ml* (POLATOM, Poland) calibrated at 14 *h* on the day of measurement was used. The measurement was completed on the calibration day at 17 *h* 04 *min*, so no decay correction was considered. The calibration source and blood and urine samples were placed in the same manner for measurement. To the Plastic vials, 10 μl of the original sample was placed with an automatic pipette and then 2 *ml* of alcohol, 2 *ml* of scintillation cocktail 0.1 *g* of POPOP [1.4-bis [2-(5-Phenyloxazoly) benzene]] and 4 *g* of PPO (2.5 Diphenyloxazole), dissolved in 1 *l* of Toluol were added by automatic pipette. After homogenization on a vortex machine, the samples were ready for measurement. The problem which appear when high activity is measured is lost of counts due to the dead counter time. The beta counter used has a count limit of 10^7 *cpm*, so the maximum number of counts that can be measured is 9 999 999 counts per minute. In order to estimate lost counts five batches of 10 samples in different dilution ratios of 1:10:100:1000:10 000 were set up. The results obtained are given in Table 1.

Table 1 shows the beta counter calibration results for various level of dissolution - five measuring series. The first series was pipetted from the original sample in order to measure it which activity was order of 0.5 *MBq*; however, this activity was too large and the liquid scintillation beta counter could not measure it (Column 3-over limit). Then, the sample was diluted in 1:10 and activity of dissoluted sample was measurable on used LSC (Results are given in column 5 of Table 1). However, dilute sample had still large activity, which caused some losses of counts due to the finite dead time of the counter. The samples were diluted further 1:100 and measured again. This was repeated until dissolution 1: 10 000 was achieved. It has been found that *counts* per *MBq* increased with dissolution level because lost counts become less and less. However all results shown in Table 1 (for all dissolution level) were taken into account to determine the beta counter efficiency.

From calibration measurements, the efficiency of the beta counter can be calculated. The efficiency is equal to the mean value of the number of counts measured per second per *Bq*, multiplied by the beta particle yield, which is 0.9982 for ^{90}Y. Efficiency was calculated using the following equation:

$$\varepsilon = \frac{N_{average}}{A} \cdot Y[\cdot 100\%] \tag{2}$$

Where, $N_{average}$ is average number of counts per second, A is activity and Y is yield. It has found that the absolute efficiency is 90.34%.

Such high efficiency of the beta counter confirms the good choice of detectors for measuring ^{90}Y activity. The mean count rate per minute per *MBq* for ^{90}Y is $5.41 \cdot 10^7$. Using the data given in Table 1, the graph was plotted in (Fig. 1) showing the dependence of count rate vs activity. First, the mean values of measured number of counts were calculated for each activity separately, and then were plotted in a logarithmic scale. Then, the fit of the experimental data was done with a linear function, which gives the opportunity to approximate the number of counts measured for an activity that is not explicitly specified.

Standard deviation was calculated also according to Eq. (3). As follows

$$\sigma = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n}(x_i - \bar{x})^2} \tag{3}$$

Where n is the number of the measurement, x_i observed values of the sample, $\bar{x}$ is the mean value of these measurements.

In Table 2, the following is given: mean values $\bar{x}$ and standard deviation σ, $\Delta\bar{x}$ the absolute error of the difference between the measured value and the true value and δ[%] the relative error expressed in percent. From the table we can see that for small

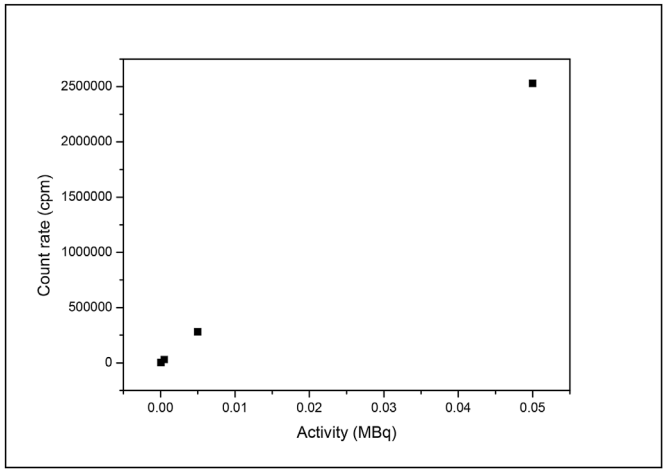

Fig. 1. Count rate versus activity.

Table 1
Calibration of LSC. Count rate - counts per minute (*cpm*) obtained on LSC for different dissolution of ten original samples.

Series	First series		Second series		Third series		Fourth series		Fifth series	
	Activity [*MBq*]	Number of measured counts [*cpm*]	Activity [*MBq*]	Number of measured counts [*cpm*]	Activity [*MBq*]	Number of measured counts [*cpm*]	Activity [*MBq*]	Number of measured counts [*cpm*]	Activity [*MBq*]	Number of measured counts [*cpm*]
1	$5 \cdot 10^{-1}$	Over limit	$5 \cdot 10^{-2}$	2 532 008	$5 \cdot 10^{-3}$	274847.9	$5 \cdot 10^{-4}$	27817.7	$5 \cdot 10^{-5}$	2763.53
2	$5 \cdot 10^{-1}$	Over limit	$5 \cdot 10^{-2}$	2540367.4	$5 \cdot 10^{-3}$	280625.2	$5 \cdot 10^{-4}$	28158.8	$5 \cdot 10^{-5}$	2846.72
3	$5 \cdot 10^{-1}$	Over limit	$5 \cdot 10^{-2}$	2652306.5	$5 \cdot 10^{-3}$	285461.5	$5 \cdot 10^{-4}$	28 313	$5 \cdot 10^{-5}$	2937.87
4	$5 \cdot 10^{-1}$	Over limit	$5 \cdot 10^{-2}$	2586783.7	$5 \cdot 10^{-3}$	283 811	$5 \cdot 10^{-4}$	28 201	$5 \cdot 10^{-5}$	2873.52
5	$5 \cdot 10^{-1}$	Over limit	$5 \cdot 10^{-2}$	2588936.5	$5 \cdot 10^{-3}$	280004.7	$5 \cdot 10^{-4}$	28 808	$5 \cdot 10^{-5}$	3031.02
6	$5 \cdot 10^{-1}$	Over limit	$5 \cdot 10^{-2}$	2619042.9	$5 \cdot 10^{-3}$	286333.1	$5 \cdot 10^{-4}$	28 820	$5 \cdot 10^{-5}$	2864.55
7	$5 \cdot 10^{-1}$	Over limit	$5 \cdot 10^{-2}$	2670612.9	$5 \cdot 10^{-3}$	283 392	$5 \cdot 10^{-4}$	27603.1	$5 \cdot 10^{-5}$	2806.1
8	$5 \cdot 10^{-1}$	Over limit	$5 \cdot 10^{-2}$	2579606.1	$5 \cdot 10^{-3}$	279713.6	$5 \cdot 10^{-4}$	28361.41	$5 \cdot 10^{-5}$	3001.3
9	$5 \cdot 10^{-1}$	Over limit	$5 \cdot 10^{-2}$	2613307.9	$5 \cdot 10^{-3}$	280073.2	$5 \cdot 10^{-4}$	27913.41	$5 \cdot 10^{-5}$	2700.09
10	$5 \cdot 10^{-1}$	Over limit	$5 \cdot 10^{-2}$	2 584 709,6	$5 \cdot 10^{-3}$	278521.5	$5 \cdot 10^{-4}$	28809.73	$5 \cdot 10^{-5}$	2835.83

Table 2
The mean, standard deviation (SD) and error of repeated measures.

Activity [*MBq*]	$\bar{x}$	σ	$\Delta\bar{x} = 3\sigma$	$\delta(\%)$
$5\cdot10^{-1}$	0	0	0	0
$5\cdot10^{-2}$	$2.53\cdot10^{6}$	43821.8	131 465	5.06
$5\cdot10^{-3}$	$2.81\cdot10^{5}$	3477.41	10432.2	3.71
$5\cdot10^{-4}$	$2.83\cdot10^{4}$	432.81	1298.44	4.59
$5\cdot10^{-5}$	$2.87\cdot10^{3}$	101.98	305.95	10.67

activities, the beta counter error is greater than for larger activities. Standard deviation and statistical measurement error is an integral part of the measurement uncertainty budget given by the following formula.

The uncertainty budget was calculated according to the formula:

$$\frac{\Delta A}{A} = \sqrt{\left(\frac{1}{\sqrt{N}}\right)^2 + \left(\frac{\Delta V}{V}\right)^2 + \left(\frac{\Delta K}{K}\right)^2} \tag{4}$$

Where N is number of counts, $\Delta V/V$ is relative uncertainty of blood and urine volume, which is taken as 5%, $\Delta K/K$ is uncertainty of calibration source, which was 10% according to manufacturer POLATOM. The average measurement uncertainty for all measurements was 12.8%. For most measurements, the measurement uncertainty did not exceed 11%, while for some measurements at very low activities, the measurement uncertainty was 20%.

3.2. Results of blood analysis

Results of ^{90}Y measurements in blood are presented in Fig. 2 and Table 3.

In average, only 3.84% of applied activity was measured in blood of patients, after 3 *h*. However, the range of values is large; for example it was 12.79% in one of examined patient. Since ^{90}Y-DOTATOC is rapidly distributed from the blood to other organs of the human body, the first blood sampling was performed immediately after the application of radiopharmaceuticals, which in all cases 30 *min*. In some cases, a large percentage of the radiopharmaceutical in the first blood sample was measured. In patients with GEP-NET (Gastroenteropancreatic-Neuroendocrine tumor) in the first blood sample was measured from 6.31% to 67.47% of the total applied activity, while in patients with MTC (medullary thyroid cancer) this percentage was slightly higher and ranged in the range of 37.7%–88.9% of the applied activity.

In a study [28], the time of "cleansing" peptides from blood was studied. They found that the effective half-life of radiopharmaceuticals in the blood was 1 *h*. Measurements performed in this study show that after 2 *h*, most patients have about 10% of the applied activity. In all patients, there was a small non-zero amount of activity in the blood in the later hours after the application of a therapeutic dose (Table 3). This indicates that re-entry of bound peptide molecules from critical organs and a tumor into the bloodstream was likely to occur.

3.3. Results of urine analysis

Results of urine analysis are shown in Table 4 And Fig. 4.

PRRT therapy was recognized as suitable for the treatment of neuroendocrine tumors because it has rapid biokinetics [28], binds rapidly to tumor tissue, and unbounded residue is excreted in the urine, as it is shown on Fig. 3.

Table 4 shows the activities and volume of the patient's urine. Activities (in *MBq*) were calculated by multiplying the number of counts per minute, obtained by LSC, with the appropriate calibration factor, and then multiplied by the volume of urine soaked for each measurement (patients recorded volume in provided form).

The second column shows the values that patients urinated in

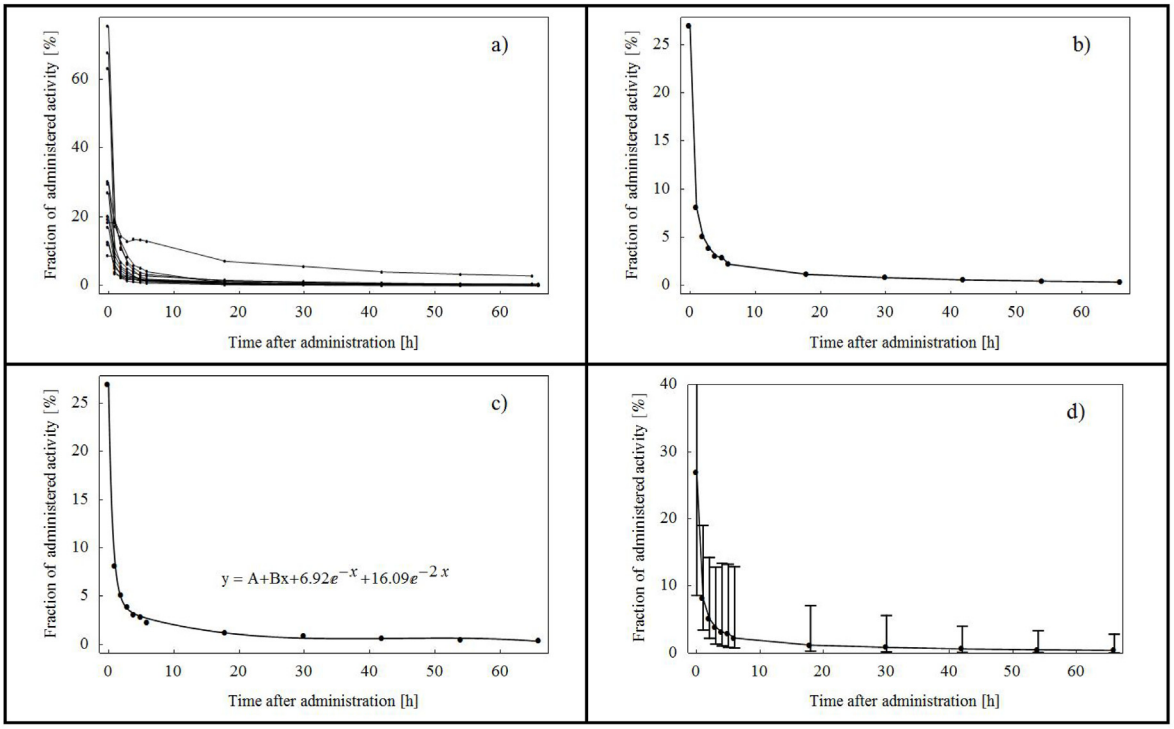

Fig. 2. Fraction of ^{90}Y activity in total blood volume, a) for all patients, (b) mean, (c) Fitted curve by $3.88\text{-}0.24x + 0.01x^2\text{-}0.00004x^3 + 16.09e^{-2x} + 6.92e^{-x}$, (d) bars show the range of values for all patients.

Table 3
Activity of ^{90}Y in blood of 13 patients.

Patient					Activity of ^{90}Y in patients blood											
No	Sex	Age	Administered activity [*MBq*]	Activity	Time [*h*]											
No	Sex	Age			0	1	2	3	4	5	6	18	30	42	54	66
1	f	52	2700	[*MBq*]	341.02	106.81	58.52	35.19	27.86	22.56	19.97	8.42	4.46	2.73	1.75	1.77
				[%]	12.63	3.96	2.17	1.30	1.03	0.84	0.74	0.31	0.17	0.10	0.06	0.06
2	f	71	3700	[*MBq*]	706.88	345.85	244.16	179.88	135.12	110.60	102.36	56.53	39.77	28.70	18.63	17.33
				[%]	19.10	9.35	6.60	4.86	3.65	2.99	2.77	1.53	1.07	0.78	0.50	0.47
3	f	47	4500	[*MBq*]	1352.88	774.03	555.67	373.81	262.754	224.90	178.43	25.70	11.37	7.27	4.20	4.95
				[%]	30.10	17.20	12.30	8.30	5.80	5.00	4.00	0.60	0.03	0.2	0.10	0.10
4	f	47	4500	[*MBq*]	measurement	824.8 0	494.97	272.52	183.13	114.24	86.22	34.60	19.45	13.22	8.37	6.58
				[%]	error	18.30	11.00	6.10	4.10	2.50	1.90	0.80	0.40	0.30	0.20	0.10
5	m	65	4500	[*MBq*]	3392.61	856.26	470.01	298.57	220.39	167.05	143.63	60.66	35.38	24.71	16.75	12.36
				[%]	75.40	19.00	10.40	6.60	4.90	3.70	3.20	1.30	0.80	0.50	0.40	0.30
6	f	33	5100	[*MBq*]	3218.64	942.49	726.56	652.43	681.37	674.60	656.23	358.76	284.12	202.56	168.50	142.68
				[%]	63.11	18.48	14.25	12.79	13.36	13.22	12.87	7.03	5.57	3.97	3.30	2.80
7	m	54	3700	[*MBq*]	746.85	259.77	154.72	108.40	84.36	70.18	57.35	25.92	15.23	10.93	8.05	7.83
				[%]	20.19	7.02	4.18	2.92	2.28	1.90	1.55	0.70	0.41	0.30	0.21	0.21
8	m	55	5550	[*MBq*]	477.61	472.47	268.09	194.61	139.40	110.64	88.40	48.53	25.85	19.97	14.24	11.71
				[%]	8.61	8.51	4.83	3.51	2.51	1.99	1.59	0.87	0.47	0.36	0.26	0.21
9	m	62	4650	[*MBq*]	3137.17	159.87	110.87	90.95	86.81	80.86	77.25	57.35	39.17	28.50	22.20	17.68
				[%]	67.47	3.44	2.38	1.96	1.87	1.74	1.66	1.23	0.84	0.61	0.48	0.38
10	m	55	3500	[*MBq*]	939.79	204.93	97.17	60.87	63.01	44.96	48.81	31.84	14.92	11.02	7.77	6.69
				[%]	26.85	5.86	2.78	1.74	1.80	1.28	1.39	0.90	0.43	0.31	0.22	0.19
11	f	39	5230	[*MBq*]	1543.34	581.40	281.40	208.16	139.74	88.65	67.76	14.61	7.25	3.68	2.81	2.5
				[%]	29.51	11.12	5.38	3.98	2.67	1.70	1.30	0.28	0.14	0.07	0.05	0.05
12	f	57	5330	[*MBq*]	898.54	301.29	153.51	132.42	131.35	94.81	50.60	38.32	26.78	21.02	15.42	0.09
				[%]	16.86	5.65	2.88	2.48	2.46	1.78	0.95	0.72	0.50	0.39	0.29	0.001
13	f	59	5400	[*MBq*]	640.66	268.38	188.03	128.09	93.39	90.05	75.34	23.16	16.03	13.51	10.37	8.72
				[%]	11.86	4.97	3.48	2.37	1.73	1.67	1.40	0.43	0.30	0.25	0.19	0.16

Table 4
Measured activity in urine samples after PRRT application. The fraction of activity in urine in relation to the applied activity is given in brackets in percent.

No.	Activity in the first urination [*MBq*]	V [*ml*]	Total activity urinated after 24^{h} [*MBq*]	V [*ml*]	Cumulative Activity [*MBq*]	V [*ml*]	Administered activity [*MBq*]
1.	160 (6%)	400	600 (22%)	1620	660 (24%)	3345	2700
2.	710 (19%)	350	1000 (27%)	1270	1100 (30%)	2700	3700
3.	2100 (47%)	250	2300 (51%)	1200	2400 (53%)	3000	4500
4.	2600 (58%)	500	2700 (60%)	2650	2700 (60%)	8250	4500
5.	1700 (38%)	300	2200 (49%)	1300	2300 (51%)	7950	4500
6.	550 (11%)	450	1300 (25%)	1800	1800 (35%)	4750	5100
7.	350 (9%)	500	590 (16%)	1300	700 (19%)	3110	3700
8.	1600 (29%)	300	2200 (40%)	1200	2300 (41%)	3250	5550
9.	250 (5%)	300	780 (17%)	2870	1100 (24%)	6170	4650
10.	240 (7%)	200	460 (13%)	900	580 (16%)	2630	3500
11.	1200 (23%)	390	2400 (46%)	2600	2900 (55%)	6360	5230
12.	370 (7%)	250	700 (13%)	850	1000 (19%)	4200	5330
13.	180 (3%)	400	1000 (19%)	2850	1300 (24%)	3800	5400

the first urination after the application of radiopharmaceuticals. The third column shows the values of total activity that patients urinated in 24 *h*, and the fourth column presents the values of total activity that patients urinated during their stay in the hospital, i.e. during approximately 72 *h*. These values were obtained by summing the activity for each individual urination during these time intervals. In brackets, next to the number representing the activity in *MBq*, the percentage of the applied activity is given. The last column shows the value of the applied activity for each patient.

The original measurements in the liquid scintillation beta counter are in counts per minute (*cpm*). Table 4 gives the values converted to *MBq* with included measurement error.

In all patients, the highest activity was in the first urination after the radiopharmaceutical application, up to 29% of the applied activity (range 3% in the patient who urinated immediately after the end of radiopharmaceutical application up to 58% in patients whose first urination was 4.5 h after application of a therapeutic dose of ^{90}Y-DOTATOC (Table 4) and with a relatively small tumor.

It is noticeable that after a few hours, the curves start to flatten out, which means that there is no more secretion of radiopharmaceuticals, i.e. the unbound residue is excreted and that significant part of the activity is related to the tumor tissue [29]. This is a good feature of PRRT and gives a desirable therapeutic effect. It has been observed that in patients diagnosed with medullary thyroid carcinoma, radiopharmaceuticals excrete slightly more in the urine than in patients with GEP-NET, probably because the tumor are smaller. In Fig. 4 the following is presented (a) the percentage of cumulative radioisotope activity in urine for all patients in *MBq*, (b) the mean value, (c) the fitted mean curve (d) bars show range of values.

4. Conclusion

From this results a conclusion can be drawn that PRRT has a very fast biokinetics, that the activity is quickly bound to tumor and that the unbound part is excreted in a few hours.

Although medullary thyroid carcinoma and gastrointestinal neuroendocrine carcinomas belong to the same group of neuroendocrine tumors and are treated in the same way, there is a

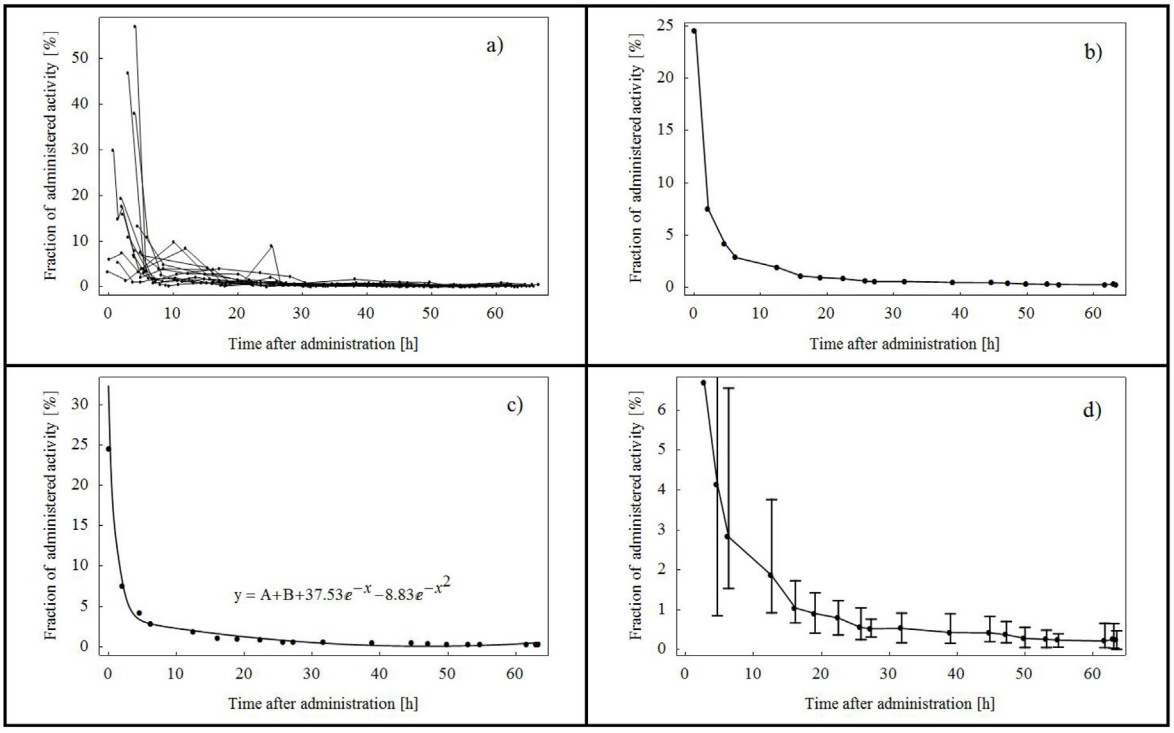

Fig. 3. Percentage of ^{90}Y activity in total urine volume over time, (a) for all patients, (b) mean, (c) fitted by *3.65-0.15x + 0.002x2 + 37.53e-x-8.83e-x2*, (d) bars show the range of values among patients.

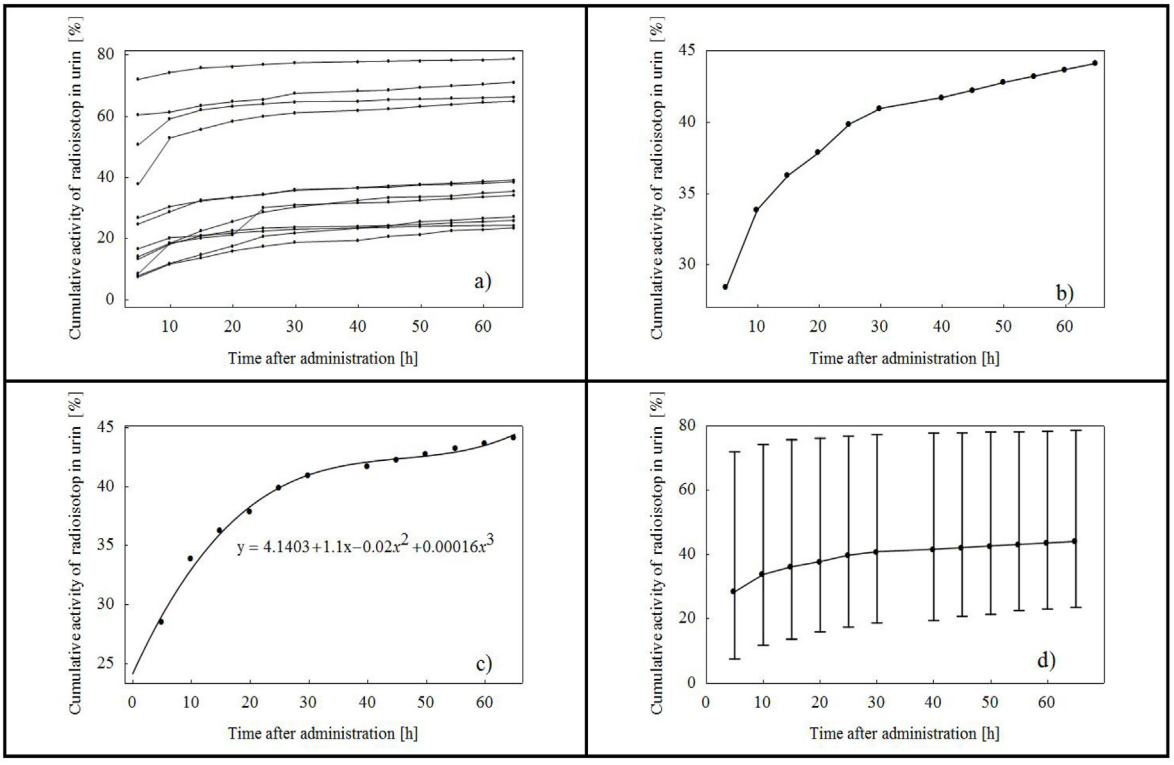

Fig. 4. Percentage of cumulative radioisotope activity in urine in *MBq* (a) for all patients, (b) mean, (c) fitted curve and (d) bars are range of results among patients.

difference in biokinetics, but for better understanding it is necessary to conduct a study on a larger number of patients.

Our analyzes and the results can help other researchers in determining blood and urine activity for dosimetric assessments based on biokinetic models in the form of multi-compartment models.

This methodology of measuring and evaluating activity in blood and excreted urine can also be applied to other radiopharmaceuticals used in nuclear medicine, where isotopes ^{131}I, ^{177}Lu, ^{188}Re are used, as well as to cocktail therapy that involves the simultaneous use of ^{90}Y and ^{177}Lu.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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