

Clinical results of radionuclide therapy of neuroendocrine tumours with ^{90}Y -DOTATATE and tandem $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE: which is a better therapy option?

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Abstract

Purpose Peptide receptor radionuclide therapy (PRRT) using radiolabelled somatostatin analogues is a treatment option for patients with disseminated neuroendocrine tumours (NET). A combination treatment using the high-energy ^{90}Y beta emitter for larger lesions and the lower energy ^{177}Lu for smaller lesions has been postulated in the literature. The aim of the study was to evaluate combined $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE therapy in comparison to ^{90}Y -DOTATATE alone.

Methods Fifty patients with disseminated NET were included in the study prospectively and divided into two groups: group A ($n=25$) was treated with ^{90}Y -DOTATATE, whereas group B ($n=25$) received the 1:1 $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE. The administered activity was based on 3.7 GBq/m² body surface area in three to five cycles, with amino acid infusion for nephroprotection.

Results The median overall survival time in group A was 26.2 months while in group B median survival was not reached. Overall survival was significantly higher in group

B ($p=0.027$). Median event-free survival time in group A was 21.4 months and in group B 29.4 months ($p>0.1$). At the 12-month follow-up, comparison of group A vs group B showed stable disease (SD) in 13 vs 16 patients, disease regression (RD) in 5 vs 3 patients and disease progression (PD) in 3 vs 4 patients; 4 and 2 patients died, respectively. The 24-month follow-up results were SD in nine vs ten patients, RD in one patient vs none and PD in four patients in both groups; three and four patients died, respectively. Side effects were rare and mild.

Conclusion The results indicate that therapy with tandem radioisotopes ($^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE) provides longer overall survival than with a single radioisotope (^{90}Y -DOTATATE) and the safety of both methods is comparable.

Keywords Somatostatin receptor · Peptide receptor radionuclide therapy · Neuroendocrine tumours · ^{90}Y -DOTATATE · ^{177}Lu -DOTATATE

Introduction

The choice of an appropriate treatment option as far as patients with inoperable or metastatic neuroendocrine tumours (NET) are concerned is limited. The response rate of chemotherapy is only at the level of 20–35% [1], effective in a minority of patients with poorly differentiated NETs and is completely ineffective in the majority of well-differentiated NETs. “Cold” somatostatin analogues exert a good clinical effect, decreasing flushing, diarrhoea and other symptoms of carcinoid syndrome [2, 3].

Worth mentioning is the fact that a prospective randomized study of the effect of octreotide LAR in the control of

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tumour growth in patients with metastatic midgut NETs (PROMID study) showed that octreotide LAR inhibits tumour growth in patients with well-differentiated metastatic midgut NETs [4].

Peptide receptor radionuclide therapy (PRRT) with radiolabelled somatostatin analogues has become an established method of treatment of disseminated NET. [^{111}In -diethylenetriaminepentaacetic acid (DTPA) 0]octreotide firstly was used in some clinical trials, with regression observed in 8% of patients. Because of the physical characteristics and short range of the Auger electrons of ^{111}In , the best results were observed in patients with small tumours and relatively high tumour uptake [5]. Recently, new somatostatin analogues that can be labelled with beta-emitting radionuclides have been developed. Currently ^{90}Y and ^{177}Lu are used. ^{90}Y emits beta particles with a high maximum energy (E_{max} 2.27 MeV) and long maximum particle range in tissues (10 mm), whereas ^{177}Lu has lower energy (E_{max} 0.497 MeV) and a shorter particle range in tissues (maximum 2–4 mm).

This isotope has a small γ -emission which makes it suitable for post-therapeutic scintigraphic imaging [133 keV (6.5%); 208 keV (11%)]. Studies that evaluated the efficacy of total doses of 7.4–20.2 GBq [^{90}Y -DOTA 0 ,Tyr 3] octreotide treatment have demonstrated a good response in 10–34% of patients [6–9]. Another large trial (MAURITIUS) which evaluated response post ^{90}Y -DOTA-(d)Na 1 -lanreotide (^{90}Y -DOTALAN) in 154 patients has shown a partial response (PR) and disease stabilization in 14 and 41% of patients, respectively [10].

Recent advances in somatostatin analogues have paved the way to the development of octreotate, which can be labelled with both ^{177}Lu and ^{90}Y radionuclides and is characterized by a higher affinity for somatostatin receptor type 2 leading to high tumour uptake.

The first clinical results of [^{177}Lu -DOTA 0 ,Tyr 3 ,Thr 8] octreotate (DOTATATE) therapy with a cumulative dose of 22.2–29.6 GBq were described in 34 patients with gastroenteropancreatic (GEP) NET. The patients were followed up 3–6 months after receiving the final dose [11]. At 3 months after the final administration, complete response (CR) was found in 1 patient (3%), PR in 12 patients (35%), stable disease (SD) in 14 patients (41%) and progressive disease (PD) in 7 patients (21%). The side effects of PRRT were few and mostly transient, with mild bone marrow suppression and nephrotoxicity, which were the most common finding.

de Jong et al. were the first to have described the use of combination treatment consisting of 50% ^{177}Lu -DOTATATE and 50% ^{90}Y -DOTATOC in rats, demonstrating that survival rates were three times longer [12, 13]. To our knowledge, there are no studies in the literature that evaluated the use of this combination treatment in human subjects.

The aim of this study was to evaluate combined $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE therapy in patients with tumours of various sizes and non-homogeneous receptor distribution in comparison to ^{90}Y -DOTATATE alone, using overall survival (OS) and progression-free survival (PFS) as primary clinical end points.

Materials and methods

The study was approved by the Ethics Committee of the Medical University of Warsaw. All patients gave written informed consent.

Patients

Fifty patients with histological confirmation of metastatic NETs (WHO II) were enrolled in the study. At the time of treatment all patients showed PD confirmed by CT examination, somatostatin receptor scintigraphy (SRS) and/or increasing blood concentration of chromogranin A (CgA).

Patients were divided into two groups. Group A consisting of 25 patients (11 men and 14 women) with a mean age (\pm SD) of 57.3 ± 10.6 years was treated with ^{90}Y -DOTATATE. Group B consisting of 25 patients (9 men and 16 women) with a mean age (\pm SD) of 56 ± 11.6 years was treated with a combination treatment including ^{90}Y and ^{177}Lu in one i.v. application.

The major criterion for inclusion into this study was the benefit from PRRT therapy. Because of the fact that it was the first PRRT study in Poland, patients had extended disease. The Karnofsky index was used for estimating the patients' general condition.

The following inclusion criteria for therapy were used:

- SRS-positive disease with uptake in the tumour and metastases higher than the liver, evaluated within 3 months before inclusion (qualitative analysis)
- Histological confirmation of NET; inoperable or metastatic disease
- Haemoglobin level (Hb) ≥ 10 g/dl; leucocytes (WBC) $\geq 2 \times 10^9/\text{l}$; thrombocytes (PLT) $\geq 90 \times 10^9/\text{l}$
- Calculated creatinine clearance (CrCl) > 40 ml/min
- Karnofsky performance status ≥ 60
- Life expectancy > 3 months
- No pregnancy or lactation

All patients underwent blood tests (full blood count, kidney, liver functions tests and CgA) and staging prior to therapy with the use of CT and SRS using $^{99\text{m}}\text{Tc}$ -HYNIC-TATE ($^{99\text{m}}\text{Tc}$ -HYNIC-Tyr 3 -octreotate) [14].

For patients receiving cold long-acting somatostatin analogues, the radionuclide therapy was performed 5 weeks

after the completion of octreotide (Sandostatin LAR, Novartis) and 3 weeks after lanreotide (Somatuline, Ipsen). Patients who received chemotherapy were not treated with PRRT until after a period of 3 months.

Patients were given a follow-up examination in the clinic post PRRT at 3, 6, 12, 24 and 36 months using blood tests, CT and ^{99m}Tc -HYNIC-TATE following the same protocols as the ones used prior to therapy.

Radiopharmaceuticals

^{99m}Tc -HYNIC-TATE: the detailed method of kit preparation and labelling with ^{99m}Tc was presented before [14, 15]. Briefly, the peptide conjugate HYNIC-Tyr³-octreotate (piChem, Graz, Austria) was prepared in the dried kit form under aseptic conditions (Institute of Atomic Energy POLATOM, Poland) after adding commercially available stannous chloride, mannitol, tricine, and *N,N'*-ethylenediaminediacetic acid. Quality control was performed by instant thin-layer chromatography silica gel (ITLC-SG) strips (Pall) developed in 0.9% saline for the determination of non-peptide-bound radioactivity.

The labelling yield efficiency exceeded 90% in all cases. Tests for sterility and bacterial endotoxins were routinely performed.

^{90}Y -DOTATATE and $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE dried kits containing 100 μg (DOTA-Tyr³-octreotate) (piChem, Graz, Austria) and 50.0 mg of commercially available ascorbic acid were prepared under aseptic conditions. For labelling the content of each kit vial was dissolved in not more than 0.5 ml of ^{90}Y no-carrier-added chloride of desired radioactivity (max. 6.5 GBq per kit) or ^{177}Lu carrier-added (specific activity of around 555 GBq/mg Lu) chloride solution, both isotopes provided by the Institute of Atomic Energy POLATOM, Poland. In case of low volume 0.9% NaCl was used to fill up to 0.5 ml. Incubation was carried out at 95°C for 25 min. After cooling down to room temperature, the volume was increased up to 1.5–2.0 ml with 0.9% NaCl. The preparation was sterilized by filtration with 0.22- μm filters (Millipore) to sterile glass vials followed by filter wash with 50 mg/ml ascorbic acid to the final radioactive concentration of 740 MBq/ml. The radiochemical purity (RCP) was assessed by HPLC (column: Synergy 4 Fusion RP 80A 150 \times 4.6 mm, flow rate 0.6 ml/min, UV detection at 220 nm and radiometric detection, solvent A: 0.1% trifluoroacetic acid in water, solvent B: acetonitrile, gradient: 0 min 18% B; 9 min 60% B; 12 min 60% B; 15 min 18% B; 21 min 18% B) and Sep-Pak C18 (Waters) mini-column separation according to the supplier's instructions. The limit for RCP was over 99.0% for each ^{90}Y - and ^{177}Lu -labelled DOTATATE. The specific activities obtained were on average 74.7 GBq/ μmol DOTATATE (in the range from 55.86 to 98.89 GBq/ μmol)

and 38.20 GBq/ μmol (in the range from 23.55 to 44.83 GBq/ μmol) for ^{90}Y - and ^{177}Lu -labelled DOTATATE, respectively. ^{90}Y -DOTATATE was administered as such while the mixed doses of $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE were prepared from each ^{90}Y - and ^{177}Lu -labelled DOTATATE solution with equal radioactivity (1 GBq ^{177}Lu /1 GBq ^{90}Y).

Treatment

Therapy was performed on an outpatients basis. Mixed amino acid (1,000 ml Vamin 18, Fresenius Kabi) and Ringer's solutions (500 ml) were infused over 8 h for kidney protection, with infusion of 200 ml prior to administration of the treatment [16–19]. Before administration of the radiopharmaceutical, ondansetron (8 mg, Zofran, Glaxo Wellcome, Atossa, Anpharm SA) was injected intravenously to prevent nausea and vomiting.

Treatment sessions were repeated, up to a total calculated dose of 7.4 GBq/m². The injected activity per one course was 2.2–3.7 GBq. With respect to $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE treatment, 50% activity of ^{90}Y -DOTATATE and 50% activity of ^{177}Lu -DOTATATE were injected. The median period between the treatment courses was 40 and 49 days, respectively.

Post-therapy imaging

A whole-body scan (256 \times 256 matrix, 8-min acquisition per cm) and single photon emission computed tomography (SPECT) acquisition of the abdomen (128 \times 128 matrix, 6° \times 60 s) were performed using the dual-head Varicam camera (GE) with parallel-hole, high-energy, general purpose collimators [energy window centred on ^{177}Lu photopeak (216 keV) and a $\pm 10\%$ window width].

Bremsstrahlung imaging whole-body scans in 256 \times 256 matrix, 8 cm/min was performed in ten patients 24 h post ^{90}Y -DOTATATE therapy again using the dual-head Varicam camera (GE) with a parallel-hole, low-energy, high-resolution collimator (energy window centred on 100 keV with a window width of $\pm 35\%$) [20].

Evaluation of results and assessment of clinical benefit

The staging of disease and treatment response were evaluated at 3, 6, 12, 24 and 36 months follow-up. Blood tests were repeated every 7 days, others between 14 and 21 days after each cycle of therapy, and finally 3, 6, 12, 24 and 36 months after the completion of the therapy. Response to treatment on CT was defined according to Response Evaluation Criteria in Solid Tumors (RECIST). Side effects were scored according to the WHO criteria.

Event-free survival (EFS) was defined as the time from PRRT to the first evidence of progression or relapse, or to death. OS was defined as the time from PRRT to death from any cause.

The following progression criteria were defined:

- In patients with clinical symptoms of carcinoid syndrome, aggravation of flushing, diarrhoea or lacrimation occurrence
- Increased level of CgA of more than 50% above a previously measured value on follow-up (3, 6 and 12 months following therapy)
- The increase of two-dimensional tumour diameters of more than 30% on enhanced three-phase CT
- The detection of new tumour foci on SRS with ^{99m}Tc -HYNIC-TATE on planar whole-body and SPECT imaging of the abdomen (if needed, SPECT of the chest)

Statistical methods

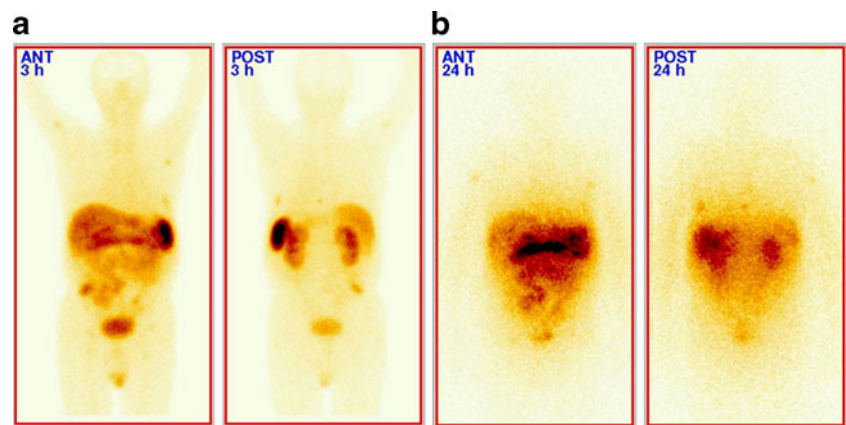
Means and standard deviations, medians and quartiles or frequencies depending on the parameters' distribution were used to summarize patient characteristics. The difference between comparable parameters was checked on the basis of Mann-Whitney and Wilcoxon tests.

OS, EFS and probability of 24-month survival were calculated on Kaplan-Meier estimator and compared via the log-rank test [21]. The multiple proportional hazards regression model (Cox analysis) was used for the analysis of OS and EFS. The association of chosen clinical predictors with OS and EFS was verified using the multiple proportional hazards regression model. No model reduction was performed to allow the adjustment of the effect of quality measurements for the effect of possible clinical predictors.

Table 1 Patient characteristics

	^{90}Y -DOTATATE ($n=25$)	$^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE ($n=25$)
Age range	37–75	31–73
Mean \pm SD	57.3 \pm 10.6	55 \pm 11.5
Sex: female	14 (56%)	16 (64%)
Female age range	37–75	39–73
Mean \pm SD	58.2 \pm 2.9	58.5 \pm 12.4
Male age range	37–70	39–64
Mean \pm SD	54.3 \pm 10.8	53.7 \pm 9.3
Foregut	12 (48%)	13 (52%)
Midgut	11 (44%)	8 (32%)
Hindgut	1 (4%)	1 (4%)
MEN 1	0	1 (4%)
von Hippel-Lindau syndrome	0	1 (4%)
Without primary	1 (4%)	1 (4%)
Size of lesion (CT in mm), range	10–166	16–155
Median (25%, 75%)	50 (39, 91)	47 (30, 75)
Number of lesions		
1	2 (8%)	0
1–10	9 (36%)	8 (32%)
>10	14 (56%)	17 (68%)
Site of metastases		
Liver	19 (76%)	20 (80%)
Bones	4 (16%)	7 (28%)
Lymph node	10 (40%)	7 (28%)
CgA (U/l)		
Range	5.1–11,477	24–4,572
Median (25%, 75%)	423 (272.6, 1,000)	179 (71, 417.8)
Surgery	20	19
Chemotherapy	8	12
“Cold” somatostatin analogues	9	6

Fig. 1 A 58-year-old man with multiple liver and peritoneum metastases of gastrinoma. **a** SRS with ^{99m}Tc -HYNIC-TATE before treatment with uptake in metastatic lesions in liver and peritoneum. **b** 24-h post-therapeutic image after administration of ^{90}Y -DOTATATE using bremsstrahlung



Model assumptions were tested on the basis of Schoenfeld residuals and in cases of violation the stratified model was fitted [22].

Calculations were done in Stata v.10.1 software (Stata Statistical Software: Release 10, Stata Corporation LP, College Station, TX, USA).

Results

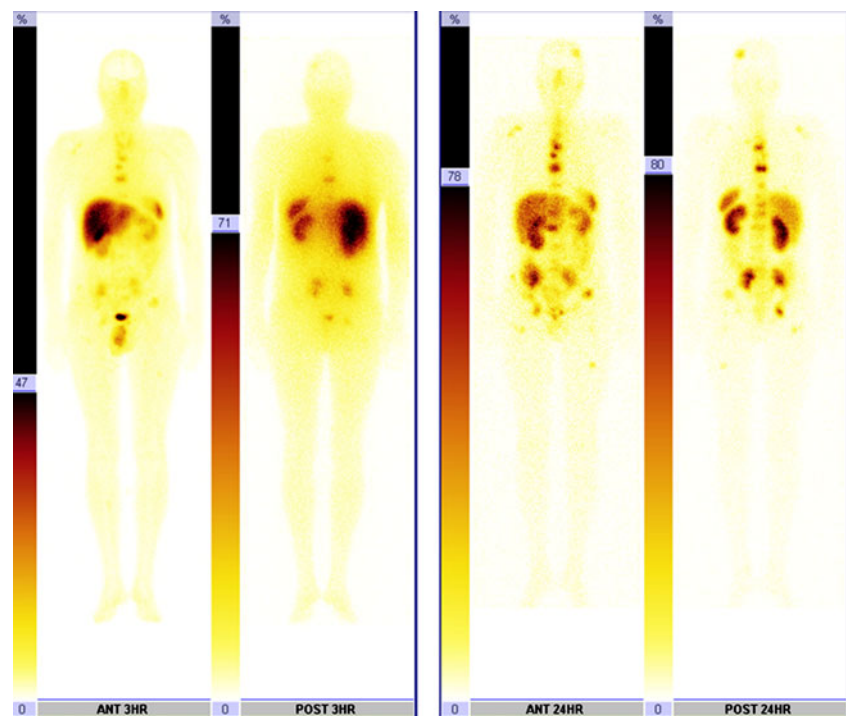
Patient characteristics

In the group treated with ^{90}Y -DOTATATE alone, 12 patients were diagnosed with foregut NETs (9 pancreas

NET: 3 gastrinoma, 1 insulinoma, 5 non-functioning tumours; 3 bronchial NET), 11 patients with midgut NETs (8 carcinoid, 3 small intestinal), 1 patient with hindgut NET (rectal NET) and 1 patient with unknown primary tumours.

In the group treated with a combination of $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE, 13 patients were diagnosed with foregut NETs (9 pancreas NET: 1 glucagonoma, 4 gastrinoma, 4 non-functioning tumours; 3 bronchial NET, 1 epiglottal NET), 8 patients with midgut NETs (7 carcinoids, 1 small intestinal), 1 patient with hindgut NET (rectal NET), 2 patients with other tumours [1 patient with multiple endocrine neoplasia (MEN 1), 1 patient with von Hippel-Lindau syndrome] and 1 patient with unknown primary tumours.

Fig. 2 A 42-year-old man with multiple bone metastases of atypical bronchial carcinoid tumour without hormonal activity. **a** SRS with ^{99m}Tc -HYNIC-TATE before treatment with uptake in metastatic lesions in bone. **b** 24-h post-therapeutic image after administration of $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE using ^{177}Lu photopeak



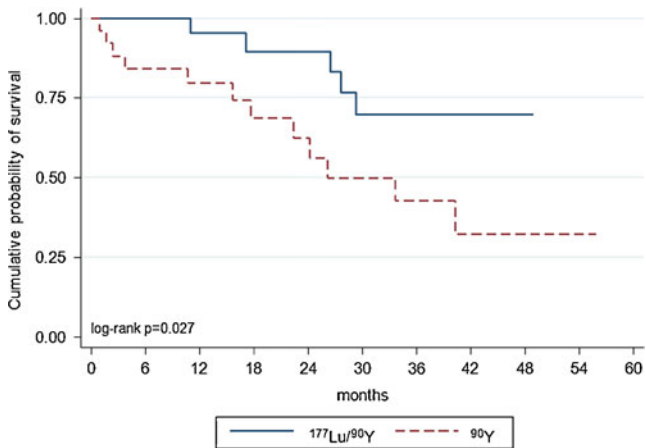


Fig. 3 Kaplan-Meier estimators of OS

There was no statistical difference in comparable parameters (age, sex, origin of tumours, size of metastases on CT, CgA, number and localization of metastases and treatment before PRRT). A Karnofsky performance status ≥ 80 was seen in the majority of patients; only two patients in both groups had a status ≥ 60 .

Detailed patient characteristics are listed in Table 1.

Post-therapeutic imaging

Post-therapeutic scans were performed to evaluate the biodistribution of tracer. In all cases increased uptake in the tumours and metastases was observed, compared to the liver background on qualitative analysis. The results of post-therapeutic images in all cases were comparable with the distribution of disease on ^{99m}Tc -HYNIC-TATE imaging (Figs. 1 and 2). Following post-therapeutic scans uptake in the majority of patients was unchanged. Only in two patients (one in group A and one in group B) were decreasing uptake and decrease in size of the liver metastatic lesions observed.

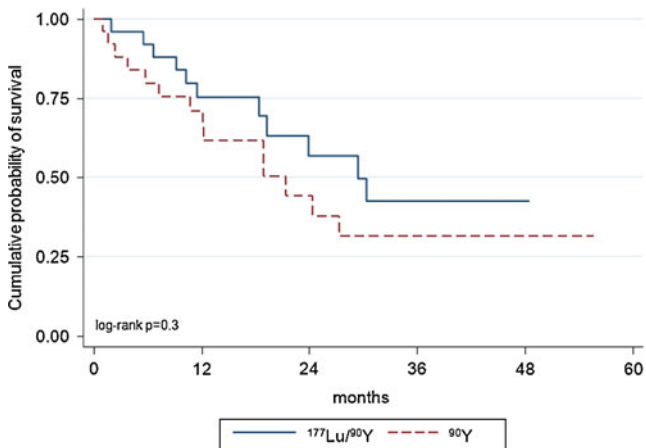


Fig. 4 Kaplan-Meier estimators of EFS

Results of therapy

The median follow-up observation period in group A was 37.7 months and the interquartile range (IQR) for the observation period was 20.5–46.7 months. In group B the median follow-up observation period was 34.6 months and the IQR was 25.2–39.5 months.

In the ^{90}Y -DOTATATE group of patients OS was 26.2 months. In patients treated with $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE, median survival was not reached, because less than 50% patients died. The survival plot depicting OS and the

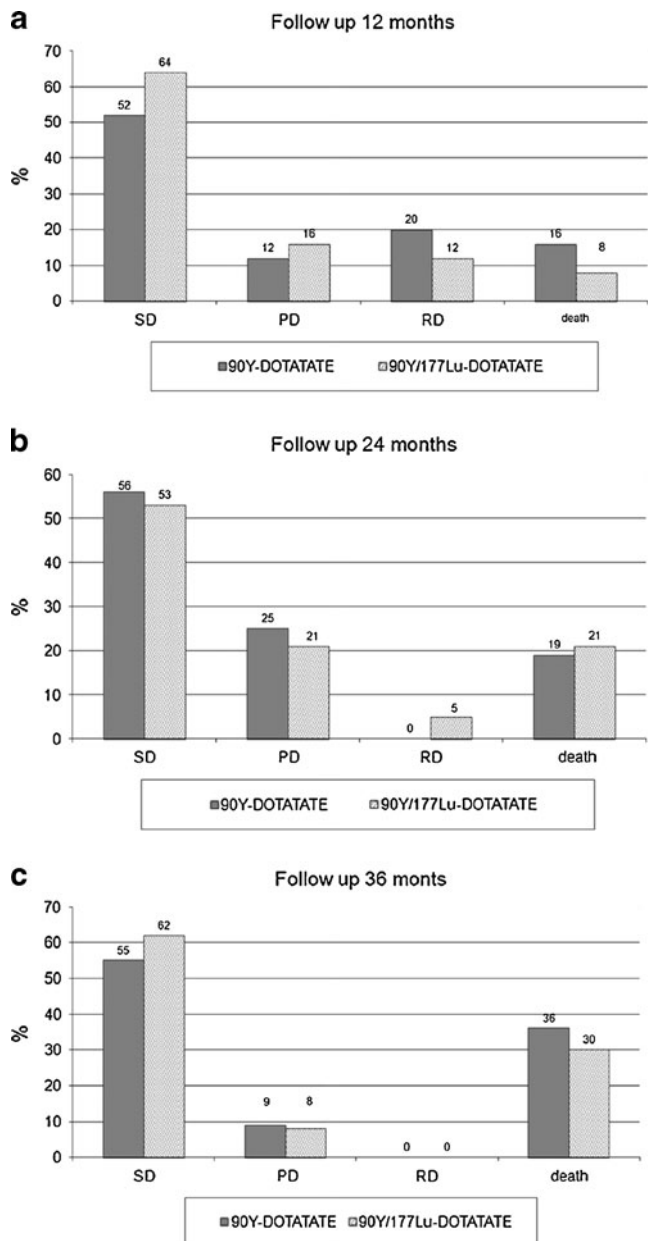


Fig. 5 Comparison of the PRRT results (SD, RD, PD and patients who died): **a** 12 months, **b** 24 months, **c** 36 months follow-up

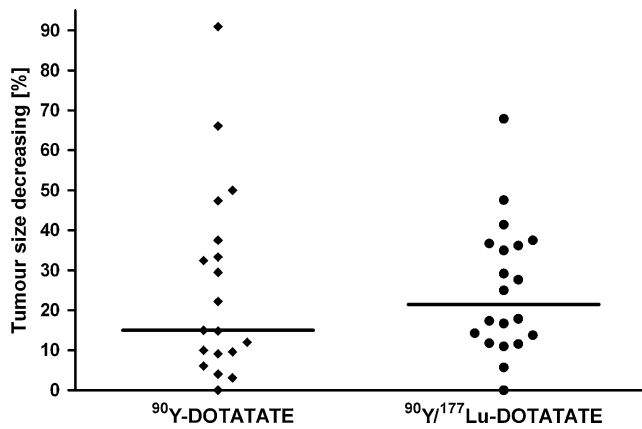


Fig. 6 Changes on CT in the size of the biggest tumours 3–6 months after completed therapy. The *line* represents median reduction of tumour size in % for both groups

log-rank test ($p < 0.027$) demonstrate that the OS in the group treated with $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE was statistically significantly longer ($p < 0.027$) (Fig. 3). The calculated probability of 24-month survival was 62% in the group treated with ^{90}Y -DOTATATE and 89% in those treated with $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE.

Median EFS in the ^{90}Y -DOTATATE and $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE groups was 21.4 and 29.4 months, respectively; the difference in EFS was not statistically significant (Fig. 4). The probability of 24-month PFS was 44 and 57%, respectively.

At the 12-month follow-up in the ^{90}Y -DOTATATE group vs the $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE group, the following was

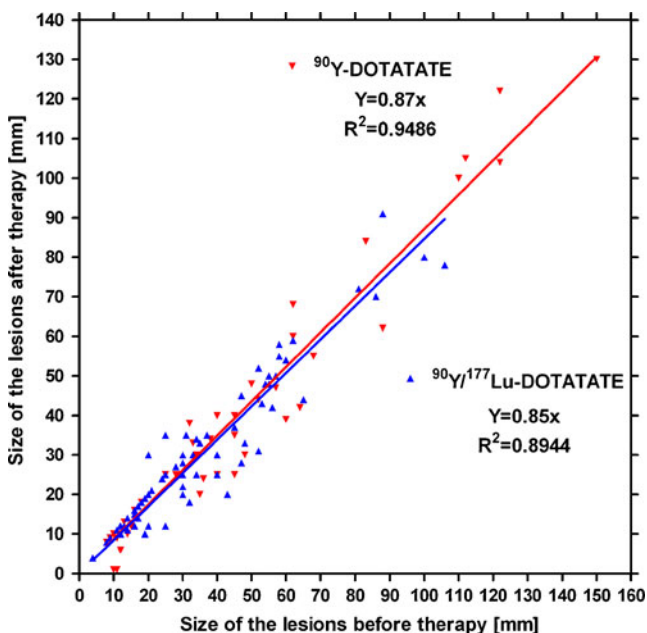


Fig. 7 Correlation between tumour size and type of therapy before and 3–6 months after therapy

observed: SD in 13 vs 16 patients, disease regression (RD) in 5 vs 3 patients, and PD in 3 vs 4 patients; 4 and 2 patients died, respectively (Fig. 5a).

At the 24-month follow-up: SD was observed in nine vs ten patients, RD in patients in the group treated with $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE and progression in four patients in both groups; five and four patients died, respectively (Fig. 5b).

At the 36-month follow-up, SD was noted in six vs eight patients and PD in one patients in both groups; four and four patients died, respectively (Fig. 5c).

CT showed regression in size of the biggest lesions in the group treated with ^{90}Y -DOTATATE from median 50 to 44 mm and in the group treated with $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE from 47 to 33 mm (Fig. 6). The changes in both groups are not statistically significant. Correlation between tumour size before and after therapy is shown in Fig. 7.

The patients in our study were not randomized to either group A or B but were treated first with ^{90}Y -DOTATATE (group A) and patients who presented later were treated with $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE. For this reason we used the Cox analysis to evaluate the effects of the relevant prognostic factors on the survival times in each group of patients and the independence of these variables.

In the proportional hazards regression model for OS the radionuclides used, age of patients, sex, CgA level, number of lesions and size of maximal lesion were included. The model for OS was stratified by number of lesions due to a violated proportional hazards assumption.

Treatment is statistically significantly associated with OS, but not with EFS (Tables 2 and 3). Statistical analysis led to lower probability of death in the group treated with tandem $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE than with ^{90}Y -DOTATATE alone [hazard ratio (HR)=5.74, 95% confidence interval (CI) 1.63–20.2, $p=0.006$] (Table 2). Effects of treatment on SRS are shown in Fig. 8.

Side effects of treatment with ^{90}Y -DOTATATE and $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE

The treatment was well tolerated. No severe adverse events occurred. Nausea and vomiting during administration of

Table 2 Cox proportional hazards regression model of OS

OS	HR (95% CI)	<i>p</i>
$^{177}\text{Lu}/^{90}\text{Y}$ vs ^{90}Y	5.74 (1.63–20.2)	0.006
Age ≥ 56 vs < 56		>0.1
Sex M vs F		>0.1
Size of lesion \geq median vs $<$ median		>0.1
Number of lesions $>$ median vs $<$ median		>0.1
CgA $>$ median vs $<$ median		>0.1

Table 3 Cox proportional hazards regression model of EFS

EFS	HR (95% CI)	<i>p</i>
$^{177}\text{Lu}/^{90}\text{Y}$ vs ^{90}Y		>0.1
Age ≥ 56 vs < 56		>0.1
Sex M vs F		>0.1
Size of lesion \geq median vs < median		>0.1
Number of lesions > median vs < median	7.2 (1.76–29.4)	0.006
CgA > median vs < median		>0.1

treatment and amino acids were observed in 20 of 50 patients (40%) with the same frequency in both groups. All cases of nausea and vomiting were successfully treated with ondansetron. Mild pain (no treatment required) at the site of the tumour was observed in 4 of 25 patients (16%) treated with ^{90}Y -DOTATATE within the first 48 h post-treatment and in 3 of 25 patients (12%) treated with $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE within the first 72 h after treatment. In 2 of 50 patients (4%) chest pain immediately after administration was observed (1 patient treated with ^{90}Y -DOTATATE and 1 patient treated with $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE). Liver tests were stable. According to WHO haematological toxicity criteria, haematological toxicity grade 3 was seen only in one patient treated with ^{90}Y -DOTATATE (patient received chemotherapy before PRRT). Toxicity grades 1 and 2 were seen with nearly the same frequency in both groups (grade 1 in six patients in the group treated with ^{90}Y -DOTATATE

vs seven patients in the group treated with $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE and grade 2 in three patients vs four patients, respectively) and without clinical symptoms. The decrease of WBC, RBC and PLT after therapy was similar in both groups. During treatment CrCl was stable in 15 patients treated with ^{90}Y -DOTATATE and in 13 patients treated with $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE. Deterioration in kidney function was observed in three patients in each group, measured by creatinine level and calculated CrCl (the maximum observed changes in CrCl in the group treated with ^{90}Y -DOTATATE was from 111 ml/min prior to therapy which declined to 54 ml/min at the 36-month follow-up and in the group treated with $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE from 106 ml/min prior to therapy to 67 ml/min at the 36-month follow-up). These patients received chemotherapy (etoposide+cisplatin) prior to PRRT. In two patients treated with $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE transient deterioration in kidney function was observed.

Totally, for all patients at the 36-month follow-up the mean creatinine level increase was 0.07 mg/dl per year and CrCl decrease 5.1 ml/min per year.

Discussion

PRRT using radiolabelled somatostatin analogues is a promising new treatment option for patients with metastatic or inoperable somatostatin receptor-positive NETs. Clinical trials and radiochemistry examinations have demonstrated

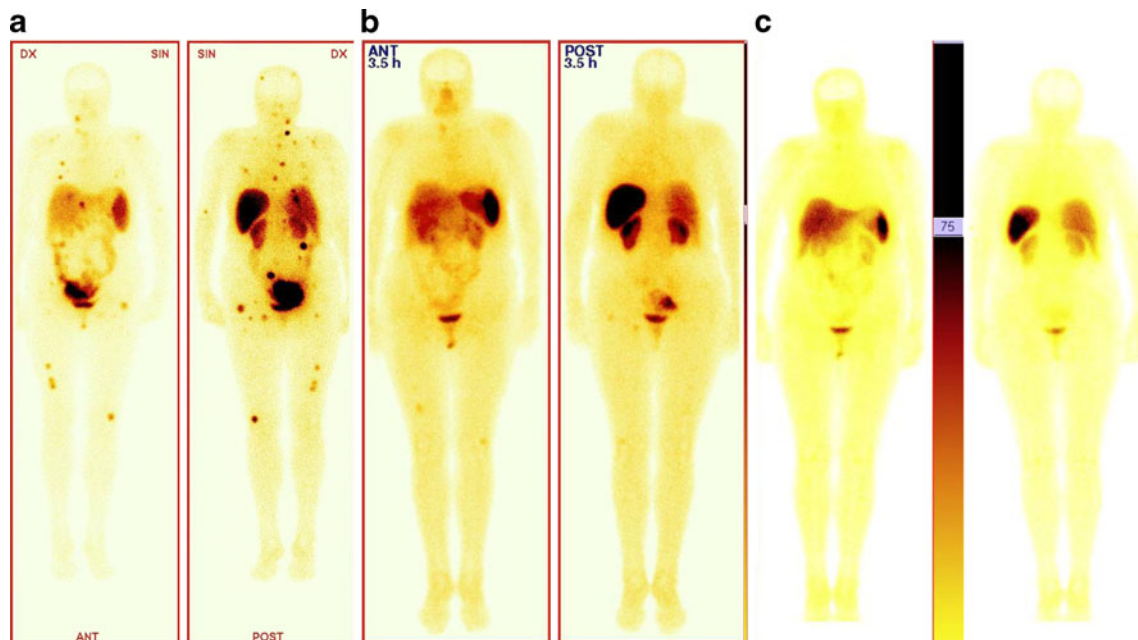


Fig. 8 A 62-year-old woman with multiple bone and liver metastases of pancreas neuroendocrine carcinoma without hormonal activity. **a** SRS with $^{99\text{m}}\text{Tc}$ -HYNIC-TATE before treatment with uptake in

metastatic lesions in bone and liver. **b** 12-month follow-up shows reduced number of metastases, with only a few visible in bone. **c** 24-month follow-up shows nearly complete response to treatment

that both ^{177}Lu and ^{90}Y are suitable beta-emitting radionuclides for PRRT. It is speculated in the literature that ^{90}Y emits beta particles with longer path lengths and higher energies which may be preferable for larger tumours, while ^{177}Lu with shorter beta particle range and longer half-life may be preferable for small tumours. In our study we did not observe an influence of beta particle energy on size response of tumours (Figs. 6 and 7). Based on the fact that ^{177}Lu has a longer half-life, it will take longer to deliver the same dose as ^{90}Y . Therefore, in patients with tumours of various sizes and non-homogeneous receptor distribution, a possible solution might be the use of a combination of radionuclides [19, 23, 24].

Another option is a sequential administration of these analogues, e.g. initial administration of ^{90}Y -labelled analogue to treat the larger tumours, followed by ^{177}Lu -labelled analogue in the next treatment cycle(s) for treatment of smaller metastases.

In our study we used OS and EFS as primary end points to assess the effect of ^{90}Y -DOTATATE only in comparison to combined $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE therapy. As we know, this the first study in the literature that evaluated the role of combined PRRT in disseminated NETs. The OS after treatment in our patients was longer in the patients treated with $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE in comparison to treatment with ^{90}Y -DOTATATE only and longer than has previously been reported in the literature [25].

We observed longer EFS in the group treated with $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE compared to treatment with ^{90}Y -DOTATATE alone, but this was not statistically significant. This difference might be significant if the period of follow-up is longer. In addition, patients were not randomized, as group A was treated first and then group B at a later date.

A study by Kwekkeboom et al. about treatment with ^{177}Lu -DOTATATE [26] reported that median PFS was 33 months and median OS was 46 months. This may be related to a longer period of follow-up.

No serious adverse events occurred after treatment with either $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE or ^{90}Y -DOTATATE. The toxicity as assessed according to the WHO criteria was limited and without clinical manifestations in both groups of patients. Therefore, we conclude that treatment with $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE in disseminated or inoperable patients with NETs is feasible and safe. Clinical improvement could be observed and most patients have benefited from the treatment. We have demonstrated that this therapy is superior to ^{90}Y -DOTATATE alone with a longer period of OS.

In addition the labelling and administration of DOTATATE in combined therapy was straightforward, and its application was safe.

The major limitation of this analysis, like other published PRRT studies, is the lack of randomization. CT treatment response is limited to anatomical changes

and it is not sensitive enough to depict functional changes. That is why, for better inclusion and evaluation of therapy response, positron emission tomography (PET)/CT techniques with ^{68}Ga -DOTATATE should be used, which was not available in our department during the study.

Conclusion

The results indicate that therapy with tandem radioisotopes ($^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE) provides longer OS than with a single radioisotope (^{90}Y -DOTATATE) and the safety of both methods is comparable. It seems that OS time and EFS time rather than WHO criteria for determining tumour burden should be used to assess the response to therapy.

However, more extensive studies with a larger number of patients are required both to establish the proportion of each isotope to be used in this dual therapy and to evaluate EFS over a longer period of follow-up.

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Conflicts of interest None.

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