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ORIGINAL ARTICLE

Somatostatin-based radiopeptide therapy with [^{177}Lu-DOTA]-TOC versus [^{90}Y-DOTA]-TOC in neuroendocrine tumours

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Abstract
Purpose Somatostatin-based radiopeptide treatment is generally performed using the β-emitting radionuclides ^{90}Y or ^{177}Lu. The present study aimed at comparing benefits and harms of both therapeutic approaches.
Methods In a comparative cohort study, patients with advanced neuroendocrine tumours underwent repeated cycles of [^{90}Y-DOTA]-TOC or [^{177}Lu-DOTA]-TOC until progression of disease or permanent adverse events. Multivariable Cox regression and competing risks regression were employed to examine predictors of survival and adverse events for both treatment groups.
Results Overall, 910 patients underwent 1,804 cycles of [^{90}Y-DOTA]-TOC and 141 patients underwent 259 cycles of [^{177}Lu-DOTA]-TOC. The median survival after [^{177}Lu-DOTA]-TOC and after [^{90}Y-DOTA]-TOC was comparable (45.5 months versus 35.9 months, hazard ratio 0.91, 95 % confidence interval 0.63–1.30, $p=0.49$). Subgroup analyses revealed a significantly longer survival for [^{177}Lu-DOTA]-TOC over [^{90}Y-DOTA]-TOC in patients with low tumour uptake, solitary lesions and extra-hepatic lesions. The rate of severe transient haematotoxicities was lower after [^{177}Lu-DOTA]-TOC treatment (1.4 vs 10.1 %, $p=0.001$), while the rate of severe permanent renal toxicities was similar in both treatment groups (9.2 vs 7.8 %, $p=0.32$).
Conclusion The present results revealed no difference in median overall survival after [^{177}Lu-DOTA]-TOC and [^{90}Y-DOTA]-TOC. Furthermore, [^{177}Lu-DOTA]-TOC was less haematotoxic than [^{90}Y-DOTA]-TOC.

A. Romer and D. Seiler contributed equally to this work.

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Keywords Yttrium · Lutetium · Somatostatin · Survival · Neuroendocrine tumour

Introduction

Neuroendocrine tumours are neoplasms arising from cells of the endocrine and nervous systems [1]. For differentiated neuroendocrine tumours, the therapeutic options include the multi-targeted tyrosine kinase inhibitor sunitinib [2] and the mTOR inhibitor everolimus [3]. For dedifferentiated tumours, the options include chemotherapy with streptozotocin, 5-fluorouracil and doxorubicin [4]. Importantly, most neuroendocrine tumours harbour subtypes of the somatostatin receptor family [5], which permits treatment with the somatostatin analogue octreotide [6, 7], imaging with radioactively labelled somatostatin analogues [8] and somatostatin receptor targeted radiopeptide treatment.

Somatostatin receptor targeted radiopeptide treatment with DOTA-TOC (tetraazacyclododecane tetraacetic acid modified Tyr^3-octreotide, Fig. 1a) was developed and brought into clinical use by our group in 1997 [9, 10]. Subsequently, it was established as an effective therapeutic option for the treatment of advanced neuroendocrine tumours [11]. DOTA-TOC is applied intravenously, is internalized into the tumour cell via the somatostatin receptor and irradiates the tumour with the β emission of the coupled radioisotope.

The radioisotopes commonly used for radiopeptide therapy are ^{90}Y and ^{177}Lu. ^{90}Y is a high-energy β emitter that can deliver high target doses. Its long emission range can penetrate to tissues further away from the target tissue. On the contrary, ^{177}Lu is a low-energy β emitter that transfers lower target doses. Its short emission range causes less irradiation of tissues further away from the target tissue. The availability of different radioisotopes potentially allows tailoring radiopeptide therapy to the individual patient.

The present study aimed to compare the efficacy and toxicity of somatostatin-based radiopeptide therapy with [^{90}Y-DOTA]-TOC versus [^{177}Lu-DOTA]-TOC in patients with progressive neuroendocrine tumours.

Materials and methods

Patients

Patients were included in the case of histologically confirmed neuroendocrine tumours, metastasized disease, progression within 1 year before enrolment and detectable tracer accumulation in the tumour in a somatostatin receptor scan. Patients were excluded in the case of concurrent anti-tumour treatment other than somatostatin treatment. Furthermore, patients were excluded in the case of pregnancy, breastfeeding, incontinence, haematological toxicities grade 3 or 4, or severe concomitant illness. Patients from Europe, Asia, North America and South America were enrolled. The study was designed and carried out according to good clinical practice, Swiss drug regulations and the Declaration of Helsinki. It was approved by the Basel Ethics Committee (Study number M120/97) and registered (Clinical Trials identifier: NCT00978211). Written informed consent was obtained from all patients.

Intervention

DOTA-TOC was synthesized and radiolabelled according to Good Laboratory Practice (GLP) as previously described [12, 13]. [^{90}Y-DOTA]-TOC was introduced at the University Hospital Basel in October 1997, and [^{177}Lu-DOTA]-TOC became available after February 2001. The present study

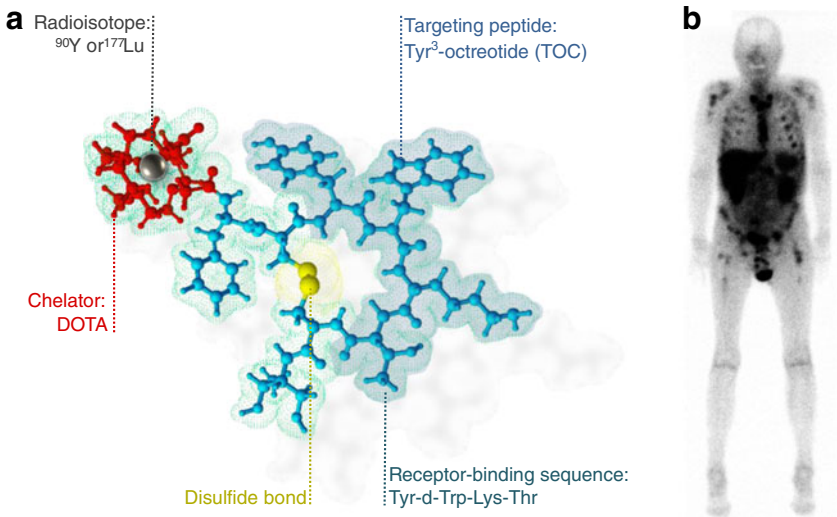


Fig. 1 Structure of the ^{90}Y- or ^{177}Lu-labelled cyclic radiopeptide DOTA-TOC (**a**). A whole-body scan 24 h after injection of 7.4 GBq [^{177}Lu-DOTA]-TOC showing tumour uptake in a patient with extensive liver and bone metastases from a small bowel carcinoid (**b**)

compares the outcome after [^{177}Lu-DOTA]-TOC and [^{90}Y-DOTA]-TOC in patients with metastasized neuroendocrine tumours from the time both tracers were available. There were no strict criteria for allocating patients to both treatment forms; however, [^{177}Lu-DOTA]-TOC was predominantly used in patients with low tumour burden (≤3 lesions), small lesions (diameter <3 cm) or low kidney function with increased creatinine level (>90 μmol/L). Lysine- and arginine-containing amino acid solutions were applied before and after [^{177}Lu-DOTA]-TOC and [^{90}Y-DOTA]-TOC injection to inhibit tubular reabsorption of the radiopeptide [11, 14, 15].

Long-acting somatostatin analogues were withheld at least 6 weeks and short-acting somatostatin analogues were withheld at least 3 days before radiopeptide therapy. All treatment cycles were performed on an inpatient basis.

Based on the findings of our pilot study [14], therapeutic cycles were repeated at an interval of at least 6 weeks in the presence of at least one of the following criteria: (1) stabilization or reduction in the summation of the longest widths of all pre-therapeutically identified lesions, (2) improvement in at least one of the five main symptoms: flush, diarrhoea, pain, fatigue and weight loss or (3) a detectable post-therapy marker decrease after a pre-therapy marker increase. The following markers were employed: hydroxyindoleacetic acid, angiotensin-converting enzyme, adrenocorticotropic hormone, alphafetoprotein, CA-125, CA-19.9, parathormone, calcitonin, carcinoembryonic antigen, chromogranin A, dopamine, gastrin, glucagon, noradrenaline, neuron-specific enolase, pancreatic polypeptide, proinsulin, serotonin and vasoactive intestinal peptide.

Intratherapeutic imaging

The biodistribution of DOTA-TOC was evaluated with planar whole-body scanning as previously described [11, 13, 16, 17] (Fig. 1b). The maximum tracer accumulation in the tumour (*tumour score*) and the kidneys (*kidney score*) was visually scored by three board-certified nuclear medicine physicians blinded to the patient's baseline and follow-up data using a four-point scale: no tracer accumulation (*score 0*), tracer accumulation lower than in the liver (*score 1*), tracer accumulation similar to that in the liver (*score 2*) and tracer accumulation higher than that in the liver (*score 3*).

Follow-up

All patients were monitored prior to and for 3 days after injection of DOTA-TOC, and adverse events were continually logged. Following discharge, serum chemistry and haematological parameters were assessed biweekly for 10 weeks or until normalization of any pathological findings. The initial post-therapy morphological imaging was planned 6–8 weeks after treatment.

Additional DOTA-TOC cycles were suspended in the case of progression, permanent toxicity or loss of the ability or the willingness to travel to the treatment centre. At this time, follow-up was aimed at gathering data on survival and adverse events, including renal toxicity, until the patient's death. Follow-up information was gathered from the referring centres; family physicians and patients were contacted if further follow-up information was required. All follow-up information was centrally gathered and all individual cases were reviewed and checked for completeness at the study centre.

All toxicities were categorized in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) v. 3.0 of the National Cancer Institute. Renal function was evaluated with the Modification of Diet in Renal Disease (MDRD) formula [18]; renal adverse events were categorized in accordance with the guidelines of the National Kidney Foundation.

Statistical analysis

Primary endpoints were survival and severe renal toxicity. Severe renal toxicity was defined as toxicity grade 4 or 5 (glomerular filtration rate <30 or <15 ml/min per 1.73 m^2). Survival was evaluated from time of enrolment to death.

Survival predictors were evaluated using multivariable Cox regression with the subsequent pre-specified prognostic variables: gender, age, histology, duration of disease, prior surgery, prior chemotherapy, prior radiation, single lesion vs multiple lesions, liver lesions vs no liver lesions, bone lesions vs no bone lesions, tumour uptake score and treatment with [^{177}Lu-DOTA]-TOC vs treatment with [^{90}Y-DOTA]-TOC.

Pre-specified subgroup analyses were performed to investigate survival effects in subgroups with low vs high tumour accumulation, solitary vs multiple lesions, liver lesions vs no liver lesions and bone lesions vs no bone lesions. Based on previous results from an animal model [19], we hypothesized that [^{177}Lu-DOTA]-TOC would be advantageous in terms of a survival benefit in patients with limited tumour burden, e.g. solitary metastases, which in our cohort are common in extrahepatic disease, and small metastases, which in planar scintigraphy often show low tumour uptake. Furthermore, both drugs might have different effects in patients with bone metastases as free ^{177}Lu and ^{90}Y are incorporated into the bone. We added each of these baseline variables in turn to our statistical model together with the corresponding interaction term with treatment group. In the case of any statistically significant interactions, we simultaneously added the significant interaction terms to the model in order to identify any independent interactions. Effect estimates were reported using hazard ratios (HR) with 95 % confidence intervals (CI).

The haematotoxicity rates for [^{177}Lu-DOTA]-TOC and [^{90}Y-DOTA]-TOC were compared employing logistic regression using the same set of co-variables as specified for the survival analyses.

In order to correctly identify predictors of renal adverse events the competing risk of death prior to renal adverse events was included into all analyses. Cumulative incidence functions were employed to identify the percentage of patients with renal adverse events or the competing event of death [20] and a Fine and Gray regression model for the subdistribution hazard [21] was established. The subsequent pre-specified cofactors were used for these calculations: gender, age, glomerular filtration rate at time of enrolment and allocation to [^{177}Lu-DOTA]-TOC or [^{90}Y-DOTA]-TOC.

Response evaluation using RECIST was established in 2000, 36 months after enrolment of the first patient [22], and was not an a priori study outcome. In a supplementary analysis, all CT and MRI imaging results were revised to include all patients, in whom RECIST was applicable.

Further sensitivity analyses were performed to identify the effect of the year of treatment and the effect of all pre-specified co-variables on the 1-, 2- and 5-year survival, respectively. A two-sided p value of <0.05 was considered to indicate statistical significance.

Results

Patients

From February 2001 to February 2010, 1,744 patients were screened for eligibility. Of these patients, 103 (5.9 %) were not eligible and 590 patients (33.8 %) were eligible but not stratified for either [^{177}Lu-DOTA]-TOC or [^{90}Y-DOTA]-TOC (Fig. 2). The remaining 1,051 patients (60.3 %) were enrolled either for [^{177}Lu-DOTA]-TOC or for [^{90}Y-DOTA]-TOC. These patients were referred from more than 100 institutions in 27 countries (Switzerland: 291 patients; Germany: 270; USA: 150; Israel: 95; Denmark: 78; France: 74; Hungary: 51; Spain: 7; Luxembourg: 6; Turkey: 4; Arabic Emirates, Brazil, Croatia, Italy, Japan, Netherlands, Portugal, Ukraine: 2 patients each; Austria, Belgium, Latvia, Mexico, Pakistan, Slovakia, Slovenia, South Africa, UK: 1 patient each); their baseline data are presented in Table 1.

Treatment

Overall, 141 patients underwent 259 cycles of [^{177}Lu-DOTA]-TOC (median number of cycles 2, range 1–5) with a mean cumulative activity of 13.5±6.5 GBq. Re-treatment was performed due to clinical improvement (36 patients, 25.5 %), post-therapeutic tumour marker decrease (23 patients, 16.3 %; median marker decrease 54.1 %, interquartile range 43.3–75.1 %) and/or stabilization or decrease in the sum of diameters of the detected tumour lesions (34 patients, 24.1 %). RECIST could be applied in 16 of those 34 patients (47.0 %), with partial response in 7 (5.0 %) and stable disease in 9 patients (6.4 %).

A total of 910 patients underwent 1,804 cycles of [^{90}Y-DOTA]-TOC (median number of cycles 2, range 1–6) with a mean cumulative activity of 13.1±4.7 GBq. Re-treatment was performed due to clinical improvement (230 patients, 25.3 %), post-therapeutic tumour marker decrease (147 patients, 16.2 %; median marker decrease 56.8 %, interquartile range 40.7–73.1 %) and/or stabilization or decrease in the sum of diameters of the detected tumour lesions (331 patients, 36.4 %). RECIST could be applied in 142 of those 331 patients (42.9 %), with partial response in 62 (6.8 %), stable disease in 75 (8.2 %) and complete remission in 5 patients (0.5 %). Their median progression-free interval was 12.7 months (range 2.1–21.2 months).

No significant differences in response rates were found in the subgroups of patients with low vs high tumour accumulation, solitary vs multiple lesions, liver lesions vs no liver lesions and bone lesions vs no bone lesions.

Survival

In the [^{177}Lu-DOTA]-TOC group, 48 patients (34.0 %) died and 93 (66.0 %) survived throughout a median follow-up of 9.0 months (1.0–80.1 months). In the [^{90}Y-DOTA]-TOC group, 360 patients (39.6 %) had died and 545 patients (59.9 %) had survived during a median follow-up of 11.0 months (1.0–100.7 months); 5 patients (0.5 %) were not available for follow-up.

The overall median survival of the [^{177}Lu-DOTA]-TOC group and the [^{90}Y-DOTA]-TOC group was comparable (45.5 vs 35.9 months, HR 0.91, 95 % CI 0.63–1.30, p = 0.49, Fig. 3a). The subgroup analyses revealed statistically significant interactions suggesting longer survival with [^{177}Lu-DOTA]-TOC in patients with low tumour accumulation (Fig. 3b), solitary lesions (Fig. 3c) and extra-hepatic lesions (Fig. 3d) when compared with [^{90}Y-DOTA]-TOC in a multivariable regression (Fig. 4). No significant differences in effects were found in the subgroup of patients with bone lesions vs no bone lesions (Fig. 3e). When all three significant interaction terms were simultaneously added to the statistical model, only the low tumour uptake effect remained close to statistical significance (p = 0.09).

Sensitivity analyses found no significant differences in survival after [^{177}Lu-DOTA]-TOC and [^{90}Y-DOTA]-TOC in patients with carcinoids (n = 402, p = 0.39), pancreatic

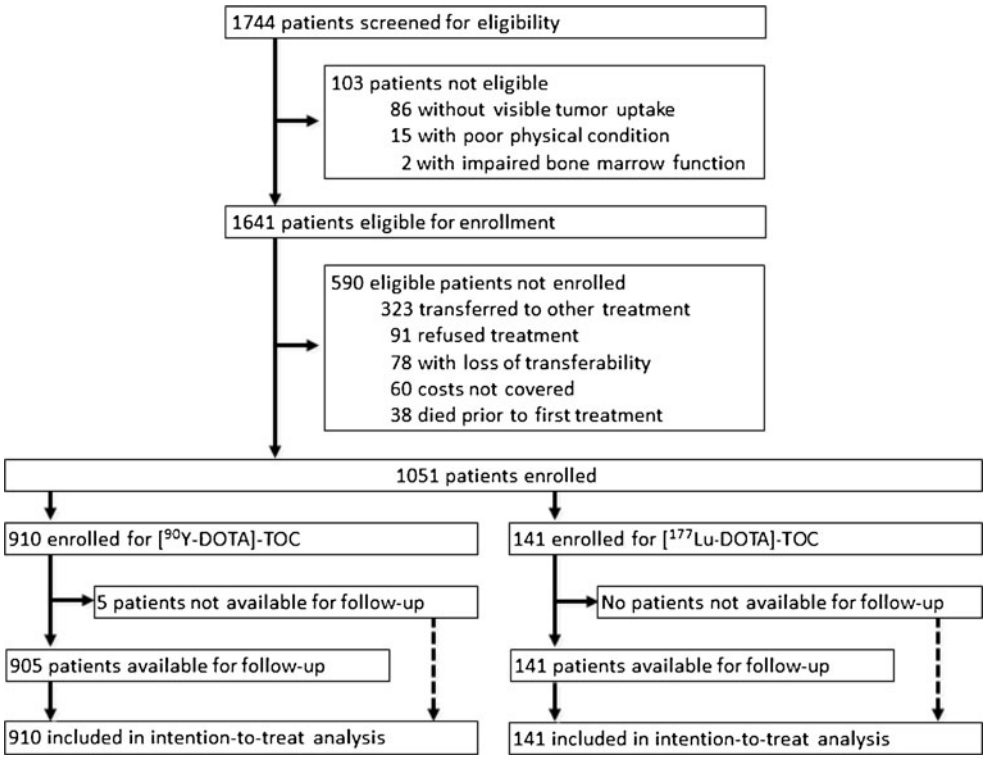


Fig. 2 Patient flow. "Loss of transferability" refers to the loss of the patient's ability to travel to the treatment centre to receive radiopeptide therapy

Table 1 Baseline patient characteristics

Characteristic		[^{90}Y-DOTA]-TOC (n=910)	[^{177}Lu-DOTA]-TOC (n=141)
Gender	Female	400 (44.0 %)	59 (41.8 %)
	Male	510 (56.0 %)	82 (58.2 %)
Age (years)	Median	59.6	62.4
	Range	11.2–91.1	14.8–83.4
Disease duration (years)	Median	1.9	1.4
	Range	0.1–37.8	0.1–30.8
Pretreatment	Surgery	500 (54.9 %)	79 (56 %)
	Chemotherapy	274 (30.1 %)	17 (12.1 %)
	Radiation	97 (10.7 %)	46 (32.6 %)
Extent	Single lesion	87 (9.6 %)	43 (30.5 %)
	Liver metastases	748 (82.2 %)	71 (50.4 %)
	Bone metastases	163 (17.9 %)	22 (15.6 %)
Creatinine (μmol/L)	Median	70	95
	Range	27–434	26–585
Tumour uptake	Score 1	48 (5.3 %)	45 (39.1 %)
	Score 2	51 (5.6 %)	22 (15.6 %)
	Score 3	811 (89.1 %)	74 (52.5 %)
Kidney uptake	Score 0	49 (5.4 %)	7 (5.0 %)
	Score 1	114 (12.5 %)	9 (6.4 %)
	Score 2	218 (24.0 %)	23 (16.3)
	Score 3	524 (57.6 %)	102 (72.3 %)
Histology	Carcinoid	402 (44.2 %)	61 (43.3 %)
	PNET	277 (30.4 %)	26 (18.4 %)
	Rare NET	68 (7.5 %)	24 (17.0 %)
	Unknown primary	163 (17.9 %)	30 (21.3 %)

PNET pancreatic neuroendocrine tumours, *NET* neuroendocrine tumours, *Rare NET* comprise medullary thyroid cancers, neuroblastomas, phaeochromocytomas, paragangliomas, small cell lung cancers and Merkel cell tumours

neuroendocrine tumours ($n=277$, $p=0.93$), rare neuroendocrine tumours ($n=68$, $p=0.90$) and neuroendocrine tumours of unknown origin ($n=163$, $p=0.78$). The HR for the main co-variables did not vary over the observed interval. All predictors of the 1-, 2- and 5-year survival are presented in the Supplementary Table A.

Toxicities

In the [^{177}Lu-DOTA]-TOC group, two cases (1.4 %) of transitory grade 3/4 haematotoxicity occurred (both cases with thrombocytopenia). Myeloproliferative disorders did not occur after [^{177}Lu-DOTA]-TOC. In 13 patients (9.2 %) severe permanent renal toxicity occurred (8 cases of grade 4 and 5 cases of grade 5). At the time of enrolment, 42 of 141 patients receiving [^{177}Lu-DOTA]-TOC had a glomerular filtration rate of >90 ml/min per 1.73 m^2. In two (4.8 %) of these patients severe permanent renal toxicity (no cases of grade 4 and two cases of grade 5) occurred.

In the [^{90}Y-DOTA]-TOC group, 92 cases (10.1 %, $p=0.001$ compared to [^{177}Lu-DOTA]-TOC group) of transitory grade 3/4 haematotoxicity occurred (leucopenia 59 patients, anaemia 10 patients, thrombocytopenia 57 patients). In 71 patients (7.8 %, $p=0.39$ compared to [^{177}Lu-DOTA]-TOC group) severe permanent renal toxicity occurred (53 cases of grade 4 and 18 cases of grade 5). At the time of enrolment, 510 of 910 patients receiving [^{90}Y-DOTA]-TOC had a glomerular filtration rate of >90 ml/min per 1.73 m^2. In 24 (4.7 %) of these severe permanent renal toxicity (16 cases of grade 4 and 8 cases of grade 5) occurred.

At the time of enrolment, 20 patients had a glomerular filtration rate below 30 ml/min per 1.73 m^2; the other 1,031 patients were included in the competing risks analyses to identify predictors of renal adverse events. These analyses found no difference in the risk for renal adverse events after [^{177}Lu-DOTA]-TOC or [^{90}Y-DOTA]-TOC. The main risk factor for renal adverse events was a reduced glomerular filtration rate at the time of enrolment (Table 2 and Fig. 3f).

Discussion

This study in 1,051 neuroendocrine tumour patients showed no difference in overall survival between patients undergoing [^{177}Lu-DOTA]-TOC and patients undergoing [^{90}Y-DOTA]-TOC treatment. However, subgroup analyses found evidence for differential effects of both drugs. Patients with low tumour accumulation, solitary lesions and extra-hepatic lesions survived longer on [^{177}Lu-DOTA]-TOC, while patients with higher tumour accumulation, multiple lesions and liver lesions may benefit from [^{90}Y-DOTA]-TOC. Significantly fewer patients experienced haematotoxicity after [^{177}Lu-DOTA]-TOC therapy than after [^{90}Y-DOTA]-TOC therapy.

Fig. 3 Survival and renal adverse events. Covariate-adjusted Kaplan-Meier estimates of overall survival are shown for [^{177}Lu-DOTA]-TOC versus [^{90}Y-DOTA]-TOC treatment (**a**). **b** Cumulative incidence functions displaying the proportion of patients with renal adverse events for [^{177}Lu-DOTA]-TOC and [^{90}Y-DOTA]-TOC and the competing event of death (*dotted line*). Furthermore, covariate-adjusted Kaplan-Meier estimates of survival after [^{177}Lu-DOTA]-TOC versus [^{90}Y-DOTA]-TOC treatment are shown for patients with low tumour uptake (tumour score = 1, **c**), solitary metastases (**d**), extra-hepatic metastases (**e**) and bone metastases (**f**)

The observed differences of therapeutic efficacy in several patient subgroups may derive from the properties of both radioisotopes. The high-energy β emitter ^{90}Y is able to induce high target doses. With its maximum range of 12 mm, it can deposit about 87 % of its energy in a 3-cm lesion; however, it can only deposit 63 % in a 1-cm lesion [23]. Conversely, the lower-energy β emitter ^{177}Lu induces lower target doses. Nevertheless, with its emission range of 2.1 mm, it can deposit about 81 % of its energy in a 1-cm lesion [23]. The advantage of using ^{90}Y for larger lesions and ^{177}Lu in smaller lesions had formerly been suggested based on animal studies [19]. The present data support the hypothesis and indicate beneficial effects of [^{177}Lu-DOTA]-TOC over [^{90}Y-DOTA]-TOC in early stages with solitary metastases.

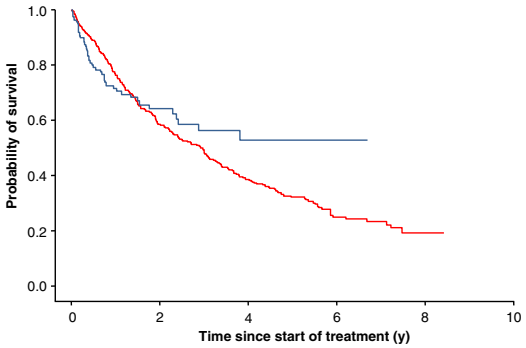
The described subgroup effects meet the criteria for credible subgroup analyses [24]. Only a small number of a priori defined hypotheses were tested. All hypotheses were derived from a rationale developed in an animal model [19]. All subgroup variables are characteristics measured at baseline. The directions of the subgroup effects were defined a priori and assessed within one study. Large and significant effect sizes were found. As especially small solitary extra-hepatic metastases show low tumour uptake in the planar whole-body scan, a correlation of subgroup effects was found when simultaneously adding all significant interaction terms to the model.

Haematotoxicity is an acute toxicity that can be due to irradiation from [^{90}Y-DOTA]-TOC or [^{177}Lu-DOTA]-TOC circulating through the body or binding to somatostatin receptors on bone marrow cells [25] or due to the small fraction of free ^{90}Y and ^{177}Lu that is administered during treatment cycles and that integrates into the bone matrix [26]. The present study found higher rates of haematotoxicity after [^{90}Y-DOTA]-TOC as compared to [^{177}Lu-DOTA]-TOC. [^{177}Lu-DOTA]-TOC might be preferable in patients with a reduced bone marrow function.

Until now, only inter-study comparisons of renal toxicity after ^{90}Y- and ^{177}Lu-based radiopeptide therapy were available [11, 16, 17, 27]. There are several reasons why these studies commonly found lower kidney toxicity rates than reported in the present study. First, we allowed patients with reduced kidney function very close to severe renal toxicity who per se have a high likelihood of developing severe renal toxicity to be included. Second, the long follow-up period in

a Overall survival

	No. of patients	No. of deaths	Median survival	Hazard ratio	P value
[177Lu-DOTA]-TOC	141	48	3.79 years	0.91 vs. [90Y-DOTA]-TOC	0.49
[90Y-DOTA]-TOC	910	360	2.99 years		

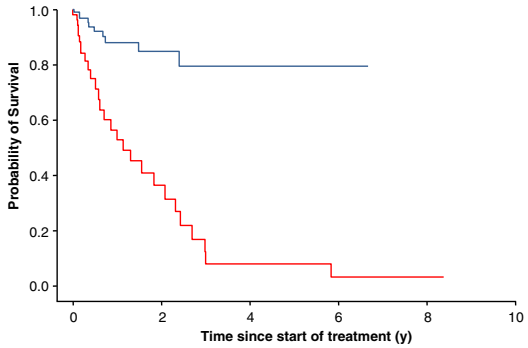


No. at risk

Total	1051	328	134	42	7	0
[90Y-DOTA]-TOC	910	296	125	40	7	0
[177Lu-DOTA]-TOC	141	32	9	2	0	0

b Survival of patients with low tumor uptake

	No. of patients	No. of deaths	Median survival	Hazard ratio	P value
[177Lu-DOTA]-TOC	45	10	4.83 years	0.15 vs.[90Y-DOTA]-TOC	<0.001
[90Y-DOTA]-TOC	47	28	2.48 years		

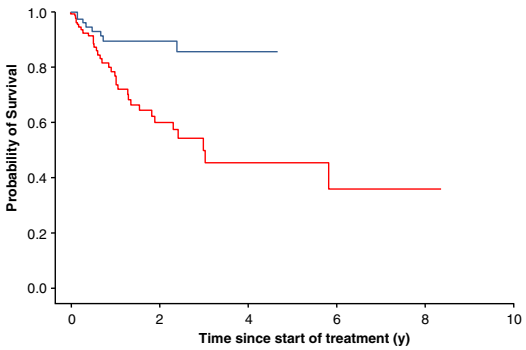


No. at risk

Total	92	26	9	5	1	0
[90Y-DOTA]-TOC	47	11	4	3	1	0
[177Lu-DOTA]-TOC	45	15	5	2	0	0

c Survival of patients with solitary metastases

	No. of patients	No. of deaths	Median survival	Hazard ratio	P value
[177Lu-DOTA]-TOC	43	8	4.66 years	0.30 vs.[90Y-DOTA]-TOC	0.02
[90Y-DOTA]-TOC	86	34	3.94 years		

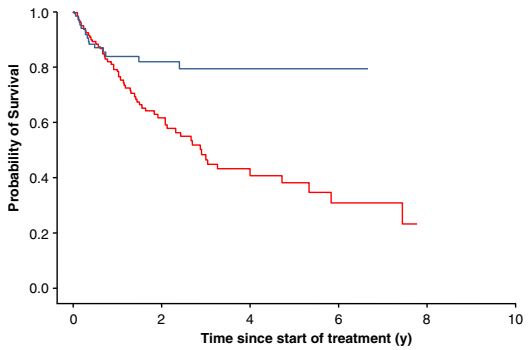


No. at risk

Total	129	37	13	4	1	0
[90Y-DOTA]-TOC	86	24	10	4	1	0
[177Lu-DOTA]-TOC	43	13	3	0	0	0

d Survival of patients with extra-hepatic metastases

	No. of patients	No. of deaths	Median survival	Hazard ratio	P value
[177Lu-DOTA]-TOC	59	16	4.43 years	0.42 vs.[90Y-DOTA]-TOC	0.012
[90Y-DOTA]-TOC	160	62	3.77 years		

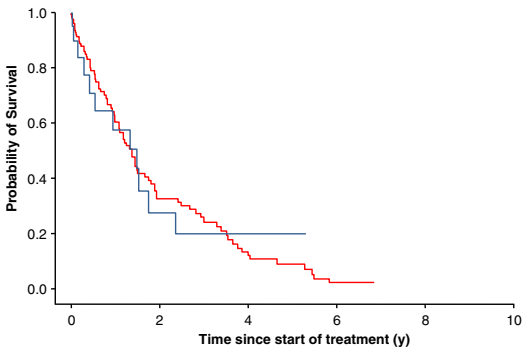


No. at risk

Total	219	71	27	10	0	0
[90Y-DOTA]-TOC	160	52	19	8	0	0
[177Lu-DOTA]-TOC	59	19	8	2	0	0

e Survival of patients with bone metastases

	No. of patients	No. of deaths	Median survival	Hazard ratio	P value
[177Lu-DOTA]-TOC	22	12	2.13 years	1.07vs. [90Y-DOTA]-TOC	0.87
[90Y-DOTA]-TOC	161	82	2.47 years		

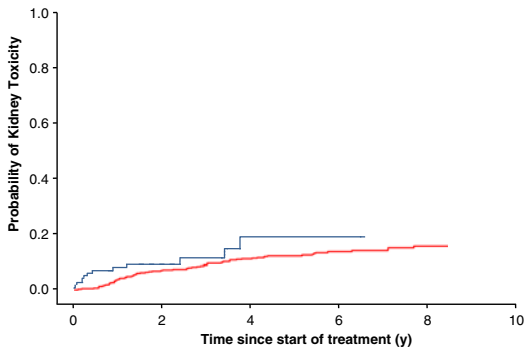


No. at risk

Total	183	41	15	2	0	0
[90Y-DOTA]-TOC	161	37	13	2	0	0
[177Lu-DOTA]-TOC	22	4	2	0	0	0

f Overall incidence of kidney toxicities

	No. of patients	No. of deaths	Hazard ratio	P value
[177Lu-DOTA]-TOC	133	13	1.39 vs.[90Y-DOTA]-TOC	0.32
[90Y-DOTA]-TOC	898	71		



No. at risk

Total	1031	326	133	42	7	0
[90Y-DOTA]-TOC	898	296	126	40	7	0
[177Lu-DOTA]-TOC	133	30	7	2	0	0

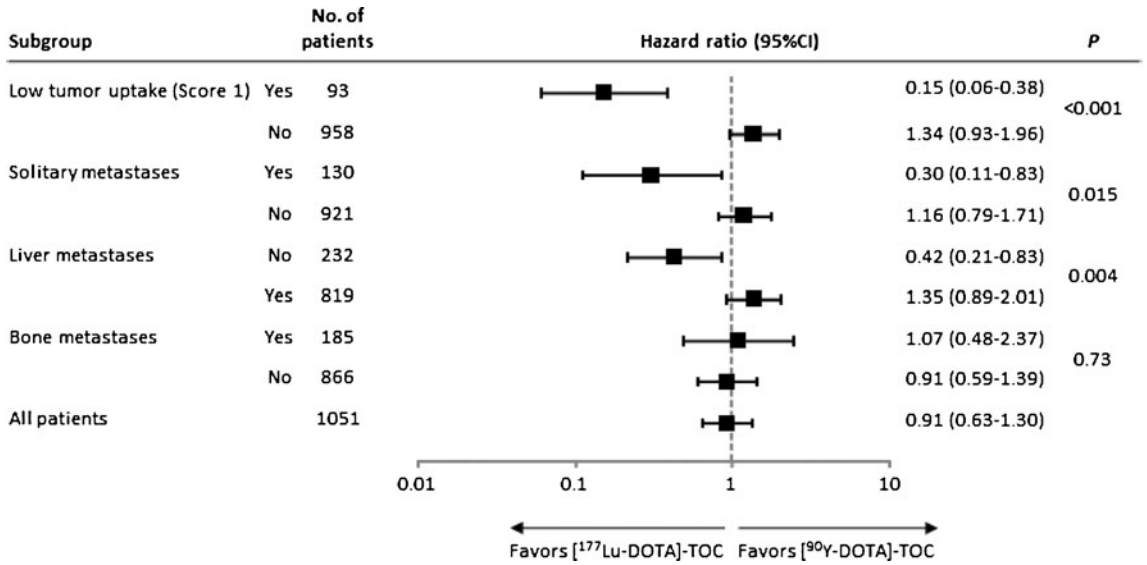


Fig. 4 Subgroup analyses. HR for mortality from multivariable Cox regression models investigating [^{177}Lu-DOTA]-TOC versus [^{90}Y-DOTA]-TOC are shown for pre-specified patient subgroups

many patients implicates an additional natural decrease in kidney function and a high possibility of nephrotoxic interventions after DOTA-TOC therapy. Third, our thorough follow-up until the patients' death was predisposed to detect decreased renal function. However, the cause for differences in renal toxicities found between each different study will remain widely unapparent. These differences, however, highlight the importance of increased comparative effectiveness research in radiopeptide therapy. In the present comparative study both treatment groups were followed up equally and the duration of follow-up was adequate to identify kidney toxicities that occur months after [^{177}Lu-DOTA]-TOC and [^{90}Y-DOTA]-TOC therapy. As patients with pre-existing low baseline renal function were enrolled, the baseline renal function in both treatment groups, and especially in the [^{177}Lu-DOTA]-TOC group, was lower than in the reports of other groups. When correcting for the baseline kidney function, however, no significant difference was detected in the renal toxicity of [^{90}Y-DOTA]-TOC as compared to [^{177}Lu-DOTA]-TOC. Further comparative studies are warranted to assess potential differences in renal toxicity after ^{90}Y- and ^{177}Lu-based radiopeptide therapy.

Table 2 Survival analyses and competing risks analyses

Cofactor	HR (95 % CI)[a]	*p* value
Survival		
Gender (male vs females)	0.94 (0.77–1.14)	0.53
Age (per 10 years)	1.18 (1.09–1.29)	<0.001
Disease duration (per year)	0.99 (0.96–1.01)	0.38
Prior surgery (vs no surgery)	0.75 (0.60–0.94)	0.012
Prior chemotherapy (vs no chemotherapy)	1.87 (1.52–2.30)	<0.001
Prior radiation (vs no radiation)	0.94 (0.68–1.29)	0.68
Single lesions (vs multiple metastases)	0.78 (0.50–1.23)	0.29
Liver lesions (vs no liver metastases)	1.31 (0.93–1.83)	0.12
Bone lesions (vs no bone metastases)	1.87 (1.45–2.40)	<0.001
Tumour uptake score 2 (vs uptake score 1)	0.77 (0.43–1.39)	0.38
Tumour uptake score 3 (vs uptake score 1)	0.45 (0.26–0.78)	0.004
[^{177}Lu-DOTA]-TOC (vs [^{90}Y-DOTA]-TOC)	0.91 (0.63–1.30)	0.49
Severe kidney toxicity		
Gender (male vs female)	0.80 (0.51–1.23)	0.30
Age (per 10 years)	1.21 (0.98–1.49)	0.07
Baseline glomerular filtration rate (per 10 ml/min per 1.73 m^2)	0.57 (0.48–0.67)	<0.001
[^{177}Lu-DOTA]-TOC (vs [^{90}Y-DOTA]-TOC)	1.39 (0.72–2.68)	0.32

[a] Estimates for all co-variables have been adjusted for histology as a categorical co-variable and for all further co-variables above

Strengths of the present study include the recruitment of 1,051 patients, allowing for powerful analyses, while the limited number of pre-specified co-variables in the regression model and the limited number of pre-specified subgroup analyses allowed the risk of overfitting and data-driven associations to be minimized. The single-centre design provided homogeneity of intervention among all patients. Advances in supportive care during the enrolment period of 9 years might have influenced the individual patient survival; however, no significant influence of the enrolment date on any of the described effects was found. Especially, the longer survival of [^{177}Lu-DOTA]-TOC over [^{90}Y-DOTA]-TOC in the patient subgroups with low tumour accumulation, solitary lesions and extra-hepatic lesions was independent from the patients' time of recruitment. Nevertheless, allocation to the treatment arms was done in a non-randomized fashion. All analyses were

adjusted for the relevant known prognostic co-variables, but unidentified factors might have been unbalanced between the treatment groups. Finally, although the present analysis meets current criteria for credible subgroup effects, our finding should be interpreted cautiously and confirmatory evidence is warranted.

In conclusion, this study compares survival and long-term toxicities of therapeutic regimens using the two most widely employed radioisotopes for radiopeptide therapy. Its results indicate longer survival for [^{177}Lu-DOTA]-TOC over [^{90}Y-DOTA]-TOC in patients with low tumour accumulation, solitary lesions and extra-hepatic lesions, while patients with higher tumour accumulation, multiple lesions and liver lesions may benefit from [^{90}Y-DOTA]-TOC. Furthermore, the present results indicate lower haematotoxicity of [^{177}Lu-DOTA]-TOC treatment in comparison to [^{90}Y-DOTA]-TOC treatment. These results may represent a step towards individual tailoring of somatostatin-based radiopeptide therapy.

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Conflicts of interest None.

References

1. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008;26(18):3063–72.
2. Raymond E, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 2011;364(6):501–13.
3. Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 2011;364(6):514–23.
4. Oberg K. Chemotherapy and biotherapy in the treatment of neuroendocrine tumours. Ann Oncol 2001;12 Suppl 2:S111–4.
5. Reubi JC. Peptide receptors as molecular targets for cancer diagnosis and therapy. Endocr Rev 2003;24(4):389–427.
6. Oberg K. Cancer: antitumor effects of octreotide LAR, a somatostatin analog. Nat Rev Endocrinol 2010;6(4):188–9.
7. Rinke A, Müller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol 2009;27(28):4656–63.
8. Krenning EP, Bakker WH, Breeman WA, Koper JW, Kooij PP, Ausema L, et al. Localisation of endocrine-related tumours with radioiodinated analogue of somatostatin. Lancet 1989;1(8632):242–4.
9. Otte A, Mueller-Brand J, Dellas S, Nitzsche EU, Herrmann R, Maecke HR. Yttrium-90-labelled somatostatin-analogue for cancer treatment. Lancet 1998;351(9100):417–8.
10. Marincek N, Jörg AC, Brunner P, Schindler C, Koller MT, Rochlitz C, et al. Somatostatin-based radiotherapy with [90Y-DOTA]-TOC in neuroendocrine tumors: long-term outcome of a phase I dose escalation study. J Transl Med 2013;11:17.
11. Imhof A, Brunner P, Marincek N, Briel M, Schindler C, Rasch H, et al. Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [90Y-DOTA]-TOC in metastasized neuroendocrine cancers. J Clin Oncol 2011;29(17):2416–23.
12. Otte A, Jermann E, Behe M, Goetze M, Bucher HC, Roser HW, et al. DOTATOC: a powerful new tool for receptor-mediated radionuclide therapy. Eur J Nucl Med 1997;24(7):792–5.
13. Villard L, Romer A, Marincek N, Brunner P, Koller MT, Schindler C, et al. Cohort study of somatostatin-based radiopeptide therapy with [(90)Y-DOTA]-TOC versus [(90)Y-DOTA]-TOC plus [(177)Lu-DOTA]-TOC in neuroendocrine cancers. J Clin Oncol 2012;30(10):1100–6.
14. Otte A, Herrmann R, Heppeler A, Behe M, Jermann E, Powell P, et al. Yttrium-90 DOTATOC: first clinical results. Eur J Nucl Med 1999;26(11):1439–47.
15. Waldherr C, Pless M, Maecke HR, Haldemann A, Mueller-Brand J. The clinical value of [90Y-DOTA]-D-Phe1-Tyr3-octreotide (90Y-DOTATOC) in the treatment of neuroendocrine tumours: a clinical phase II study. Ann Oncol 2001;12(7):941–5.
16. Iten F, Müller B, Schindler C, Rochlitz C, Oertli D, Mäcke HR, et al. Response to [90Yttrium-DOTA]-TOC treatment is associated with long-term survival benefit in metastasized medullary thyroid cancer: a phase II clinical trial. Clin Cancer Res 2007;13(22 Pt 1):6696–702.
17. Iten F, Muller B, Schindler C, Rasch H, Rochlitz C, Oertli D, et al. [(90)Yttrium-DOTA]-TOC response is associated with survival benefit in iodine-refractory thyroid cancer: long-term results of a phase 2 clinical trial. Cancer 2009;115(10):2052–62.
18. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. N Engl J Med 1994;330(13):877–84.
19. de Jong M, Breeman WA, Valkema R, Bernard BF, Krenning EP. Combination radionuclide therapy using 177Lu- and 90Y-labeled somatostatin analogs. J Nucl Med 2005;46 Suppl 1:13S–7S.
20. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med 2007;26(11):2389–430.
21. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509.
22. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92(3):205–16.
23. Siegel JA, Stabin MG. Absorbed fractions for electrons and beta particles in spheres of various sizes. J Nucl Med 1994;35(1):152–6.
24. Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ 2010;340:c117.
25. Walrand S, Barone R, Pauwels S, Jamar F. Experimental facts supporting a red marrow uptake due to radiometal transchelation in 90Y-DOTATOC therapy and relationship to the decrease of platelet counts. Eur J Nucl Med Mol Imaging 2011;38(7):1270–80.
26. Chen PS, Terepka AR, Hodge HC. The pharmacology and toxicology of the bone seekers. Annu Rev Pharmacol 1961;1(1):369–96.
27. Kwekkeboom DJ, de Herder WW, Kam BL, van Eijck CH, van Essen M, Kooij PP, et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0, Tyr3]octreotate: toxicity, efficacy, and survival. J Clin Oncol 2008;26(13):2124–30.