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ORIGINAL ARTICLE

Effects of therapy with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate on endocrine function

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Abstract
Purpose Peptide receptor radionuclide therapy (PRRT) with radiolabelled somatostatin analogues is a novel therapy for patients with somatostatin receptor-positive tumours. We determined the effects of PRRT with [^{177}Lu-DOTA^{0},Tyr^{3}] octreotate (^{177}Lu-octreotate) on glucose homeostasis and the pituitary-gonadal, pituitary-thyroid and pituitary-adrenal axes.
Methods Hormone levels were measured and adrenal function assessed at baseline and up to 24 months of follow-up.
Results In 35 men, mean serum inhibin B levels were decreased at 3 months post-therapy (205±16 to 25±4 ng/l, $p<0.05$) and follicle-stimulating hormone (FSH) levels increased (5.9±0.5 to 22.7±1.4 IU/l, $p<0.05$). These levels returned to near baseline levels. Total testosterone and sex hormone binding globulin (SHBG) levels decreased (15.0± 0.9 to 10.6±1.0 nmol/l, $p<0.05$ and 61.8±8.7 to 33.2± 3.7 nmol, $p<0.05$), respectively, whereas non-SHBG-bound T did not change. An increase (5.2±0.6 to 7.7±0.7 IU/l, $p<0.05$) of luteinizing hormone (LH) levels was found at 3 months of follow-up returning to baseline levels thereafter. In 21 postmenopausal women, a decrease in levels of FSH (74.4±5.6 to 62.4±7.7 IU/l, $p<0.05$) and LH (26.8±2.1 to 21.1±3.0 IU/l, $p<0.05$) was found. Of 66 patients, 2 developed persistent primary hypothyroidism. Free thyroxine (FT_4) levels decreased (17.7±0.4 to 15.6±0.6 pmol/l, $p<0.05$), whereas thyroid-stimulating hormone (TSH) and triiodothyronine (T_3) levels did not change. Reverse triiodothyronine (rT_3) levels decreased (0.38±0.03 to 0.30± 0.01 nmol/l, $p<0.05$). Before and after therapy adrenocorticotropic hormone (ACTH) stimulation tests showed an adequate response of serum cortisol (>550 nmol/l, $n=18$). Five patients developed elevated HbA_{1c} levels (>6.5%).
Conclusion In men ^{177}Lu-octreotate therapy induced transient inhibitory effects on spermatogenesis, but non-SHBG-bound T levels remained unaffected. In the long term, gonadotropin levels decreased significantly in postmenopausal women. Only a few patients developed hypothyroidism or elevated levels of HbA_{1c}. Therefore, PRRT with ^{177}Lu-octreotate can be regarded as a safe treatment modality with respect to short- and long-term endocrine function.

Keywords Tumour targeting · Peptide · Somatostatin · Therapy · Radiolabelled peptides · Antibodies · Radiopharmacy · Endocrinology · Oncology

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Introduction

Treatment with radiolabelled somatostatin analogues, or peptide receptor radionuclide therapy (PRRT), is a novel treatment modality in patients with metastasized or inoperable somatostatin receptor-positive tumours, e.g. carcinoid, paraganglioma or gastrinoma. Recent reports on the effectiveness of PRRT with the most frequently used

radioligands [^{90}Y-DOTA^0,Tyr^3]octreotide (^{90}Y-octreotide) or [^{177}Lu-DOTA^0,Tyr^3]octreotate (^{177}Lu-octreotate) in patients with gastropancreatic neuroendocrine tumours described 20–30% partial remissions [1–3].

Reported short-term side effects of PRRT included mild nausea, vomiting and abdominal pain, but occurred only in a minority of patients [4]. Furthermore, severe side effects such as renal insufficiency and the occurrence of myelodysplastic syndrome or leukemia were rare [4, 5]. So far, two cases of myelodysplastic syndrome [5] and several cases of radiation-induced renal failure [6–8] have been reported. Therefore, the bone marrow and kidneys remain the dose-limiting organs with each patient receiving amino acid co-infusion during treatment to reduce the renal radiation dose and thereby the risk of renal failure [9].

Since many endocrine organs, such as the anterior pituitary gland, endocrine pancreas, adrenal medulla and thyroid, express somatostatin receptors (SSTRs), especially the SSTR subtype 2, these organs are also potentially targeted by PRRT [10–13]. Therefore, it is not unlikely that patients treated with PRRT are at risk of developing hormone disturbances or deficiencies during their follow-up period. Until recently, however, limited data regarding the effects of PRRT on endocrine function were available. In a previous report on the therapeutic effect of ^{177}Lu-octreotate in a large group of patients with gastroenteropancreatic neuroendocrine tumours, we briefly reported on the short-term effects of PRRT on endocrine function [5]. Therefore, the objective of the present study was to assess both the short- and long-term effects of PRRT on the functions of the anterior pituitary, gonads, thyroid, endocrine pancreas and adrenal glands.

Materials and methods

Patients and study design

Seventy-nine patients who were treated with 600−800 mCi ^{177}Lu-octreotate (three to four cycles with 6- to 9-week interval) between January 2000 and December 2004 and with a follow-up period of 12−24 months were selected for analysis. Only local (Dutch) residents were analysed, because these had their follow-up at our institution. All patients had tumour uptake on SSTR scintigraphy that was at least as high as the physiological uptake in normal liver tissue on planar imaging preceding therapy. Hormone measurements were performed before each administration of ^{177}Lu-octreotate and at each follow-up visit.

Inclusion criteria were: Karnofsky performance score≥50, creatinine clearance≥40 ml/min, haemoglobin>9.7 g/dl, platelet count>75×10^9/l and WBC>2.0×10^9/l. All patients gave written informed consent before inclusion in the study, which was approved by the Medical Ethics Committee of the hospital. ^{177}Lu-octreotate preparation and administration of therapy were performed as described earlier [5].

Hormone measurements

Blood samples were processed within 2 h after withdrawal. Serum was stored at −20°C until assayed.

Gonadotropins, gonadal hormones and cortisol

Serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), sex hormone binding globulin (SHBG) and cortisol were measured using luminescence-based immunometric or immunoassays (Immulite 2000, Diagnostic Products Corp., Los Angeles, CA, USA). Serum estradiol (E_2) and total testosterone (TT) levels were measured using a no-extraction coated tube radioimmunoassay (RIA) (Coat-a-Count, Diagnostic Products Corp., Los Angeles, CA, USA). Sensitivities of the assays were 0.1 IU/l for FSH and LH, 0.1 nmol/l for SHBG, 28 nmol/l for cortisol, 10 pmol/l for E_2 and 0.1 nmol/l for TT. Interassay coefficients of variation for LH and FSH were<7%, for SHBG<5%, for cortisol<5%, for E_2<10% and for TT<9%. Non-SHBG-bound T levels were calculated by using the mass action equation as described by Södergård et al. [14]. The affinity constants used for the binding of testosterone to SHBG and albumin were 5.97×10^8 l/mol and 4.06×10^4 l/mol, respectively. Dimeric inhibin B levels were assessed using an immunoenzymometric assay (Oxford BioInnovation, Oxford, UK), The detection limit of the assay was 10 ng/l. Interassay coefficients of variation were <15% and<21% at concentrations of 215 and 19 ng/l, respectively.

Thyroid hormones

Serum free thyroxine (FT_4) and triiodothyronine (T_3) were measured by chemiluminescence assays (Vitros ECi Immunodiagnostic System, Ortho-Clinical-Diagnostics Inc., Rochester, NY, USA). Serum levels of thyroid-stimulating hormone (TSH) were measured using the Immulite 2000 system. Reverse T_3 (rT_3) was measured by RIA as previously described [15]. Interassay coefficients of variation amounted to 4% for TSH, 5% for FT_4, 3.3% for T_3 and 10% for rT_3.

HbA_{1c}

Glycated haemoglobin, measured as HbA_{1c}, was obtained with the use of the HPLC method (Menarini 8160, Menarini Diagnostics, Valkenswaard, The Netherlands). The running between-day coefficient of variation was 1% for both control levels (5.8 and 10.9%) [16].

Hypothalamic-pituitary-adrenal (HPA) axis assessment

The 1 μg (low-dose) adrenocorticotropic hormone (ACTH) stimulation test (LDST) was used to test the integrity of the HPA axis. The LDST was performed in 39 patients before therapy. Eighteen patients also had an LDST 12–18 months after therapy. Cortisol was measured 0, 20, 30 and 60 min after the injection of 1 μg tetracosactrin (Synacthen, Novartis Pharma) intravenously.

The solution of 1 μg ACTH/ml was used immediately after preparation. The intravenous line used was flushed with saline after the administration and after each time a blood sample was taken. A stimulated peak cortisol concentration of at least 550 nmol/l was considered to be an adequate response.

Statistical analyses

All results are expressed as mean concentrations ± standard error of the mean (SEM). Hormone levels were analysed using repeated measures analysis of variance (ANOVA) with Bonferroni correction for multiple comparisons. For the HPA axis analysis a paired Student's *t* test was used; p values <0.05 (two-tailed) were considered significant.

Results

The patients' characteristics are listed in Table 1. Data from 35 men were available for analysis. Three were excluded at baseline: one had severe chemotherapy-induced hypogonadism, one had testicular atrophy and one had high levels of FSH and LH suggestive of a co-existing gonadotropin-secreting pituitary adenoma, which was not further analysed.

At baseline, one patient had combined low TT (<8.1 nmol/l) and inhibin B (<150 ng/l) levels, two patients had isolated low TT levels, two other patients had low non-SHBG-bound T (<5.9 nmol/l) and another ten patients had isolated low inhibin B levels.

Table 1 Baseline patient characteristics

	No. of patients	Mean (range)	%
Total	79		
Gender			
Male	38		48
Age		58.4 (30–83)	
Female	41		52
Age		54.8 (20–74)	
Weight (kg)		74.3 (43–142)	
BMI (kg/m^2)		25.0 (15.6–45.1)	
Height (cm)		172 (152–196)	
Karnofsky Performance Score		89.4 (50–100)	
Diagnosis			
Carcinoid	49		62
NET of unknown origin	8		10
NET pancreas	15		20
Gastrinoma	1		1
Insulinoma	1		1
Hürthle cell thyroid carcinoma	3		4
Medullary thyroid carcinoma	1		1
Paraganglioma	1		1
Metastases			
Liver	66		84
Bone	18		23
Prior therapy			
Surgery	36		46
Chemotherapy	6		8
External beam radiotherapy	3		4
Somatostatin analogue therapy	36		46

BMI body mass index, *NET* neuroendocrine tumour

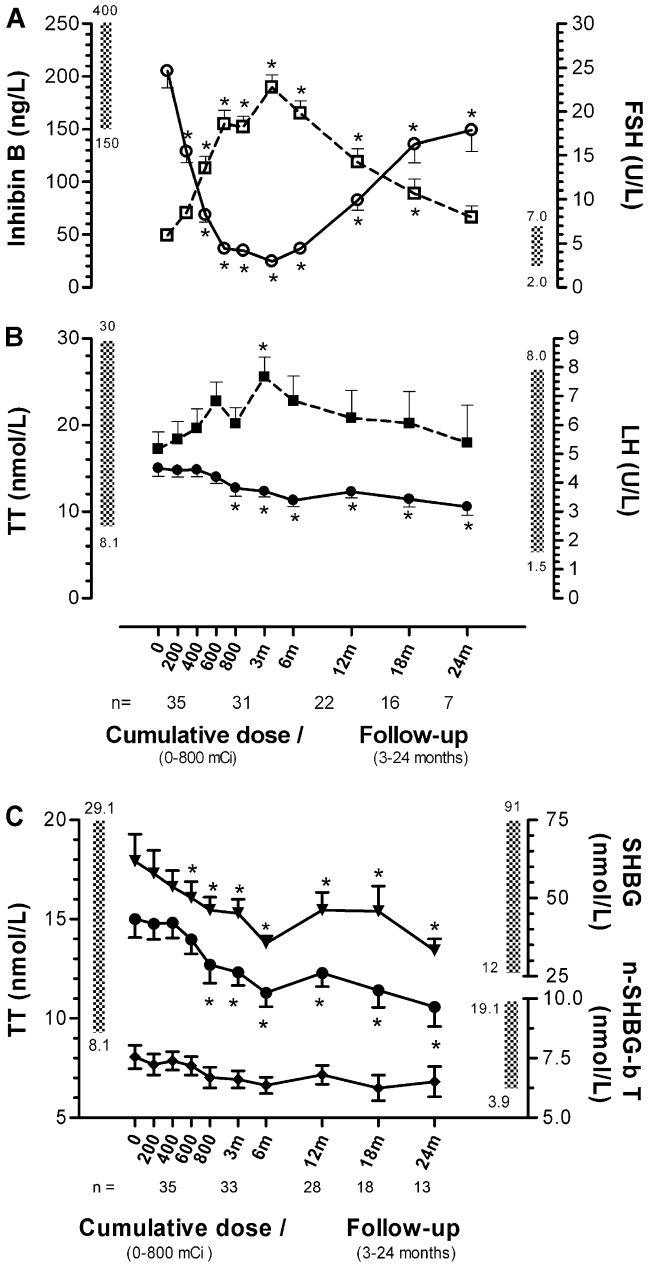

Fig. 1 **a**, **b** Longitudinal analyses of mean (± SEM) serum levels of FSH (*dotted line with open squares*), inhibin B (*black line with open circles*), LH (*dotted line with filled squares*) and TT (*black line with filled circles*) in 35 men with SSTR-positive tumours before, during and up to 24 months after 600–800 mCi ^{177}Lu-octreotate therapy. *Bars* along both y-axes represent the reference range (4 SD) values, *$p<0.05$. **c** Longitudinal analyses of mean (± SEM) serum levels of TT (*black line with filled circles*), SHBG (*black line with filled triangles*) and non-SHBG-bound testosterone (n-SHBG-bound T, *black line with filled diamonds*) in 35 men with SSTR-positive tumours before, during and up to 24 months after 600–800 mCi ^{177}Lu-octreotate therapy. *Bars* along both y-axes represent the reference range (4 SD) values, *$p<0.05$

The mean inhibin B level decreased significantly from 205±16 ng/l to a nadir level of 25±4 ng/l at 3 months after ^{177}Lu-octreotate therapy ($p<0.05$) and returned to near pre-treatment levels in the follow-up period thereafter. At 24 months post-therapy, although marginal, the inhibin B level was still significantly decreased (Fig. 1a). Mean FSH levels had a mirrored course with a transient increase from 5.9±0.5 IU/l to a maximum of 22.7±1.4 IU/l 3 months after the last therapy. Twenty-four months after the last therapy, the mean FSH level was not significantly different from baseline. The mean TT level decreased significantly from 15.0±0.9 nmol/l at baseline to 12.3±0.7 nmol/l at 3 months ($p<0.05$) with a further decline to 10.6±1.0 nmol/l at 24 months after therapy (Fig. 1b). The mean LH level increased from 5.2±0.6 IU/l to 7.7±0.7 IU/l at 3 months of follow-up ($p<0.05$) and returned to levels not significantly different from baseline at 6 months.

Concomitant with the decrease of TT, the mean SHBG level decreased significantly from a baseline level of 61.8± 8.7 nmol/l to a nadir of 33.2±3.7 nmol/l at 24 months after the last therapy ($p<0.05$). The calculated levels of non-SHBG-bound T did not change significantly (Fig. 1c).

Based on the levels of FSH, LH, inhibin B and E_2, and age before therapy, three groups of women (41 patients in total) could be distinguished. Eight women had hormonal changes during follow-up which were suggestive of menopausal transition and were therefore excluded. Since no menstrual data were available from six premenopausal women, these women were also excluded from analysis.

Gonadotropin analysis was performed in 21 postmenopausal women. Five women were excluded because of hormonal changes due to concomitant disease ($n=3$), previous cranial external beam radiation because of meningeoma ($n=1$) and temporary use of high-dose opioid medication ($n=1$). One 39-year-old woman was excluded because of bilateral oophorectomy, followed by hormone replacement therapy.

In the postmenopausal women, both mean inhibin B and E_2 were at low levels, <10 ng/l and <50 pmol/l, respectively, at baseline and did not change significantly thereafter. Before therapy, the mean FSH concentration was 74.4±5.6 IU/l. During follow-up it decreased significantly to 62.4±7.7 IU/l at 24 months of follow-up. The mean LH concentration, which was 26.8±2.1 IU/l before therapy, decreased significantly to 21.1±3.0 IU/l at 24 months ($p<0.05$). (Fig. 2).

Sixty-six patients were included for analysis of thyroid hormone status. Excluded were ten patients with thyroid-associated conditions before therapy including primary hypothyroidism ($n=4$), TSH suppressive therapy for thyroid carcinoma ($n=4$), hyperthyroidism ($n=1$) and combined neck surgery and external beam radiotherapy ($n=1$). Furthermore, three patients were excluded because they had either undetected hypothyroidism ($n=1$) or subclinical hypothyroidism ($n=2$) before ^{177}Lu-octreotate therapy and were subsequently started on thyroxine therapy. After the third cycle of therapy one patient developed anti-TPO antibody-positive hypothyroidism. Another patient gradually

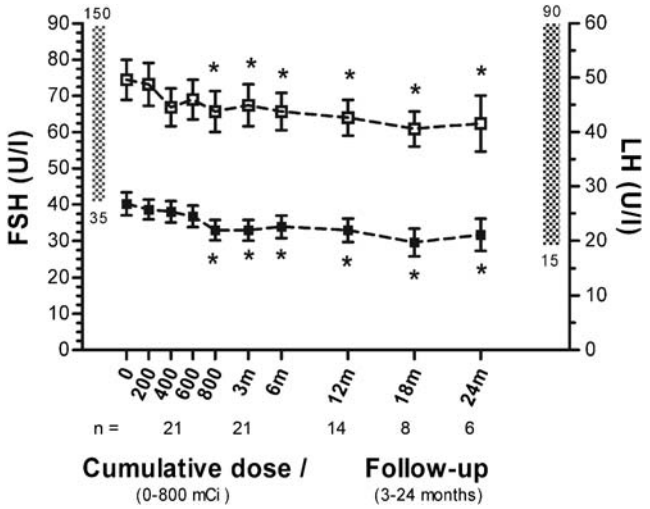

Fig. 2 Longitudinal analysis of mean (± SEM) serum levels of FSH (*dotted line with open squares*) and LH (*dotted line with filled squares*) in 21 postmenopausal women with SSTR-positive tumours before, during and up to 24 months after 600–800 mCi ^{177}Lu-octreotate therapy. The mean inhibin B and E_2 levels are not shown as these were at normal low postmenopausal levels (<10 ng/l and< 50 pmol/l, respectively). *Bars* along both y-axes represent the reference range (4 SD) values, *$p<0.05$

developed primary hypothyroidism after therapy and was eventually started on substitution therapy 3.5 years after ^{177}Lu-octreotate therapy. Thyroid hormone levels from these patients were included in the analyses until hypothyroidism was evident.

The course of the mean thyroid hormone levels of the included patients is shown in Fig. 3. The mean FT_4 decreased significantly from 17.7±0.4 to 15.6±0.6 pmol/l (reference range: 11−25 pmol/l, $p<0.05$); TSH and T_3 levels did not change significantly. The mean rT_3 concentration of 0.38±0.03 nmol/l was above the reference range (0.14–0.34 nmol/l) before therapy. During therapy a significant 18% decrease of mean rT_3 levels with a nadir of 0.30±0.01 nmol/l after a cumulative dose of 400 mCi was found ($p<0.05$). Thereafter the mean rT_3 level increased slowly to 0.32±0.03 nmol/l 24 months after therapy. The ratio of T_3 over rT_3 (T_3/rT_3), with a T_3/rT_3 of 6.24±0.03 at baseline, was significantly elevated with a maximum of 7.54±0.33 after a cumulative dose of 400 mCi ($p<0.05$) after which it returned to levels not significantly different from baseline. In a subanalysis, in which three groups of patients were analysed according to their outcome of tumour assessment at 3 months of follow-up (progressive disease, PD; stable disease, SD; minor or partial remission, MR or PR) a significant decrease of mean rT_3 level during therapy ($p<0.05$) was demonstrated in the groups with SD and MR or PR whereas in the PD group no significant change was observed (Fig. 4).

An LDST was performed before therapy in 39 patients, which showed stimulated cortisol values higher than the cut-off value of 550 nmol/l in all patients. The mean peak level after the LDST was 822±28 nmol/l. The LDST was repeated 12–18 months after the last therapy in 18 patients (8 men, 10 women). All patients again had stimulated cortisol values higher than 550 nmol/l after ^{177}Lu-octreotate therapy. The mean peak cortisol response before therapy was significantly higher than after therapy in these patients (909±57 nmol/l vs 822±35 nmol/l, $p<0.001$, $n=18$) (Fig. 5).

Of 79 patients, 9 had diabetes mellitus diagnosed before treatment and were either on subcutaneous insulin therapy ($n=4$) or oral anti-glycaemic agents ($n=5$). Furthermore, one patient had an insulinoma and another patient had an abnormal haemoglobin pattern and therefore the serum was

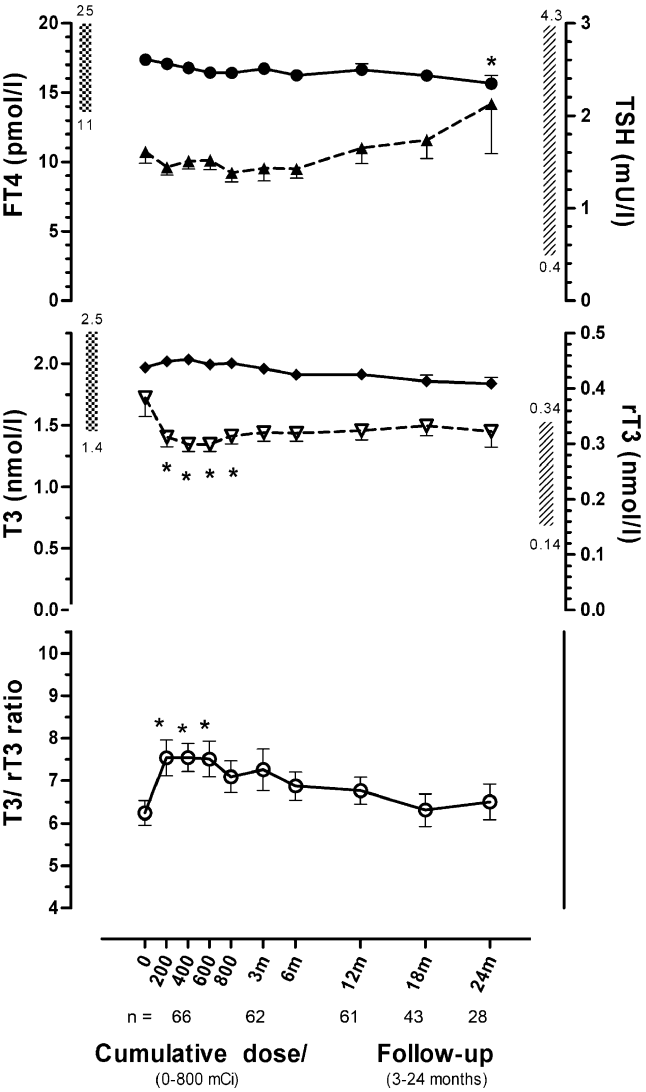

Fig. 3 Longitudinal analysis of mean (± SEM) serum levels of TSH (*dotted line with filled triangles*), FT_4 (*black line with filled circles*), T_3 (*black line with filled diamonds*), rT_3 (*dotted line with open triangles*) and T_3/ rT_3 ratio (*line with open circles*) of 66 patients with SSTR-positive tumours before, during and up to 24 months after 600–800 mCi ^{177}Lu-octreotate therapy. *Bars* along both y-axes represent the reference range (4 SD) values, *$p<0.05$

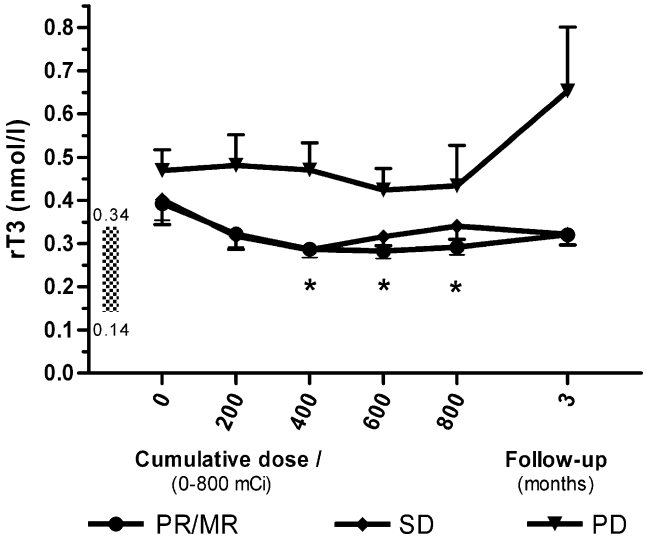

Fig. 4 Longitudinal analysis of mean (± SEM) serum levels of rT_3 in patients with SSTR-positive tumours before, during and at 3 months of follow-up after 600–800 mCi ^{177}Lu-octreotate therapy grouped according to their therapy outcome (minor remission and partial remission, MR & PR, *filled circles*; stable disease, SD, *filled diamonds*; progressive disease, PD, *filled triangles*) at 3 months of follow-up. *Bars* along the y-axis represent the reference range values, *$p<0.05$

unfit for HbA_{1c} measurement. Five patients had elevated HbA_{1c} (>6.5%) before ^{177}Lu-octreotate therapy three of whom were started on oral anti-glycaemic drugs during or after ^{177}Lu-octreotate therapy. Six patients developed high levels of HbA_{1c} after PRRT. In one patient this occurred after pancreatic surgery. In the other five patients, elevated HbA_{1c} levels occurred after 2–30 months from study inclusion (Table 2). Analysis in 69 patients demonstrated a decrease of HbA_{1c} from 5.7±0.1 to 5.5±0.1% ($p<0.05$) during therapy, but an increase to 6.0±0.1% ($p<0.05$) thereafter.

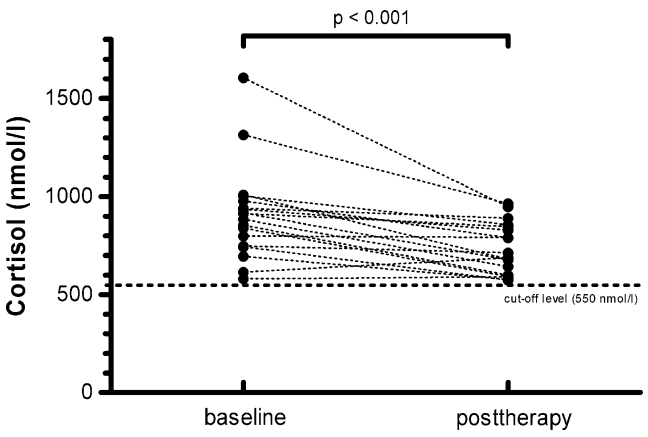

Fig. 5 Mean peak cortisol responses with the low-dose (1 μg) ACTH stimulation test in 18 patients before and 12–18 months after ^{177}Lu-octreotate therapy are shown. Each *dotted line* connects one individual patient

Table 2 Number of patients who were evaluable for HbA_{1c} percentages based on their HbA_{1c} % at baseline and after PRRT. Patients excluded at baseline were medically treated patients with diabetes ($n=9$), one patient who had an insulinoma and one patient who had with an abnormal haemoglobin pattern

		Post-therapy		
	HbA_{1c} (in %)	>6.5	≤6.5	Total
Baseline	>6.5	5 (100%)	0 (0%)	5
	≤6.5	6* (10%)	57* (90%)	63
	Total	11	57	68

*One patient developed elevated levels of HbA_{1c} after Whipple surgery

Discussion

Besides the currently known complications and adverse effects due to the non-specific radiation absorbed dose to the bone marrow and kidneys, specific receptor-related effects on non-tumourous tissue by PRRT have not been studied in detail. SSTRs are expressed in most hormone-secreting organs, such as pituitary gland, pancreas, thyroid and adrenals, as evidenced by in vitro studies as well as by the physiological uptake in vivo during somatostatin receptor scintigraphy [10, 17–20]. Although the receptor density of SSTRs in normal, non-pathological hormone-secreting organs is not as high as observed in neuroendocrine tumours, the presence of SSTRs implicates the possibility of specific receptor-mediated targeting by radiolabelled somatostatin analogues. Furthermore, as the radiopharmaceuticals used in PRRT are systemically administered, all organs will receive an additional non-specific dose, including those organs that are known to be radiosensitive (e.g. the gonads).

Of our 35 male patients, 15 (43%) had evidence of hypogonadism prior to PRRT. Gonadal dysfunction in patients with disseminated cancer prior to chemotherapeutic treatment has been reported by Chlebowski et al. [21]. A relationship between markedly decreased gonadal function and weight loss was also observed. Furthermore, other factors, including age, history of alcohol intake and liver disease, have been reported to have effects on the TT levels in male patients [22]. As there are many factors that may cause decreased TT levels, a specific or common cause of the high percentage of hypogonadism within our group of patients before PRRT is difficult to point out. Because of the very similar patterns of hormonal changes observed after PRRT in men with normal or low levels of TT before therapy (data not shown), it is likely that these additional factors did not contribute to the observed change in hormone levels in our study.

The decrease of mean TT level coincided with a decrease of SHBG level, whereas the mean non-SHBG-bound T remained stable after PRRT. These observations

are in line with findings of de Ronde et al. [23] who demonstrated a strong positive relationship between SHBG and TT levels and no or only a weak positive association between SHBG and circulating non-SHBG-bound T levels. Because SHBG correlates negatively with body mass index (BMI) [24], a possible explanation for the decrease of SHBG is the significant increase of BMI in our patients from 24.0±0.7 kg m^{-2} to a maximum of 25.3±0.8 kg m^{-2} at 12 months of follow-up. Furthermore, we found a weak positive, but significant correlation (Spearman's rho=0.29, p=0.01) between FT_4 and SHBG (data not shown). A correlation between FT_4 and SHBG was demonstrated during thyroid hormone replacement therapy in hypothyroid men by Cavaliere et al. [25]. However, whether the relatively small increase of mean BMI or the limited decline in mean FT_4 level observed in our study is responsible for the marked decline of SHBG is questionable. In theory, impaired liver function after therapy can also cause decreased SHBG levels. This is unlikely, however, because of unchanged albumin levels and stable or decreased serum levels of γ-GT, alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase throughout the whole study period (data not shown).

Our data indicate that transient impairment of spermatogenesis occurs following PRRT. A significant decrease of mean serum inhibin B levels with a concomitant increase in FSH levels was observed, with recovery to almost pre-treatment levels after 24 months. This is in line with several studies in patients with differentiated thyroid carcinoma who received radioiodine therapy [26–29]. Inhibin B is produced in the Sertoli cells of the testis and is the major feedback regulator of FSH [30, 31]. It has been demonstrated that serum inhibin B levels are positively correlated with spermatogenic status and sperm count [32, 33]. Therefore, although we did not perform semen analyses, our results likely indicate temporarily impaired spermatogenesis.

Both the gonadal and pituitary gland function are potentially at risk after PRRT. Effects on gonadotroph levels after ^{177}Lu-octreotate therapy was demonstrated in postmenopausal women. A significant decrease in both FSH and LH was found. The observed decrease in mean FSH and LH level of approximately 12.5 and 8.2% per year, respectively, was higher than could be expected because of ageing as such. In a study of 680 postmenopausal women, the decrease of gonadotropin levels between the ages of 55 and 75 years was less than 1% per year [34].

Of 66 patients, 2 (3%) developed primary hypothyroidism after treatment. One patient had hypothyroidism with the development of anti-TPO antibodies suggesting autoimmune-induced hypothyroidism. The other patient had slowly progressive primary hypothyroidism and was put on substitution therapy 3.5 years after ^{177}Lu-octreotate therapy. Thyroid hormone analyses of the total group demonstrated a significant decrease of FT_4 at the end of the study period. This is in line with the significant decrease of FT_4 levels we reported earlier [5]. The decline of FT_4 was not accompanied by a significant increase of TSH or T_3, though trends towards an increase and decrease, respectively, were noticed. Of interest, analysis excluding the two hypothyroid patients revealed no significant change in FT_4, TSH or T_3. Since chronicity and severity of disease might have an impact on the thyroid hormone status and even can induce non-thyroidal illness (NTI), the observed changes of thyroid hormones in the long term could reflect the development of NTI rather than the effect of PRRT. Signs of NTI were observed at baseline with an increased mean level of rT_3. Specific changes in thyroid hormone levels were reported to correlate with the severity of illness or even to be prognostic for survival in critically ill patients [35]. Directly after the first cycle of PRRT, rT_3 returned to reference range values. Thereafter, rT_3 slowly increased but remained within the normal reference range. The active over inactive thyroid hormone (T_3/rT_3) ratio had a similar, but inverse pattern. These changes suggest a rapid change to a more favourable disease state directly after initiation of PRRT, which persists during follow-up. A subanalysis of patients according to therapy outcome indicated that patients who had PD had a non-significant change in rT_3 level, whereas the other patients had a significant decrease, returning to the normal range during therapy. Therefore, in our group of patients, the change in rT_3 and T_3/rT_3 ratio probably reflected changes in the disease status.

The HPA axis is not affected by PRRT in terms of intact adrenal reserve. All patients had adequate responses with the LDST before therapy. Additionally, adequate responses in 18 patients after therapy indicated no apparent primary or secondary adrenal insufficiency. In a recent meta-analysis on the diagnosis of adrenal insufficiency, it was concluded that a cut-off value between 500 and 600 nmol/l cortisol is necessary to achieve reasonable sensitivity for the detection of both primary and secondary adrenal insufficiency [36]. Furthermore, the LDST is a valid replacement for the commonly used short Synacthen test and the insulin tolerance test (ITT), of which the latter is widely regarded as the gold standard test for the integrity of the HPA axis [37]. Unfortunately, the ITT is not completely safe and is costly and difficult to perform in an outpatient setting, thus hampering its clinical use.

Interestingly, the mean peak cortisol level after PRRT was significantly lower than before therapy. Whether this subtle difference in LDST response after therapy reflects radiation-induced partial adrenal insufficiency or simply a less stressful state of the patients is not clear. However, Schmiegelow et al. reported similar findings in 73 patients treated with radiotherapy and chemotherapy for childhood brain tumours with a mean follow-up of 15 years [38].

Nineteen percent of the patients had insufficiency of the HPA axis, whereas the remainder of patients, even though with an adequate response to an ACTH test or ITT, had lower peak cortisol levels compared with controls. The external beam radiotherapy, not chemotherapy, was regarded as the main factor that had contributed to the observed adrenal insufficiency. It was concluded that this group might be potentially at risk of becoming HPA axis insufficient in the future. Lifelong follow-up was recommended in these patients. Although it is difficult to compare ^{177}Lu-octreotate therapy with external beam radiation therapy in terms of dose tempo, exposure area and period of follow-up, these studies indicate that despite the adequate LDST responses found in our patients, awareness of a radiation-induced disturbance of the HPA axis is important in the long-term follow-up.

Of 62 patients, 5 (8%) developed increased levels of HbA_{1c} after ^{177}Lu-octreotate therapy without any obvious cause, such as subsequent pancreatic surgery. Pancreatic islets express somatostatin receptors, especially the subtype SSTR2a [39]. However, 46% of our patients used somatostatin analogues, such as octreotide, during and/or after therapy. Therefore, besides the possibility of a direct radiation effect as the cause of the observed subtle, but significant increase of mean HbA_{1c} after therapy, long-term treatment with somatostatin analogues could have contributed as well.

Summarizing, in men ^{177}Lu-octreotate therapy induced transient inhibitory effects on spermatogenesis, but non-SHBG-bound T levels remained unaffected. In the long term, gonadotropin levels decreased significantly in postmenopausal women. Only a small number of patients developed hypothyroidism or elevated levels of HbA_{1c}. No clinically apparent relevant effect was observed on pituitary-adrenal function. Despite temporary and minor hormonal changes, PRRT with ^{177}Lu-octreotate can be regarded as a safe treatment modality with respect to the short- and long-term endocrine function.

We conclude that patients who are treated with ^{177}Lu-octreotate therapy may develop radiation-induced hormone disturbances, some of which have been proven to be temporary and which are in general mild. No severe hormone imbalance was observed and, therefore, ^{177}Lu-octreotate therapy, in terms of endocrine sequelae, can be regarded as safe. However, awareness of the possibility of changes in, and thereby surveillance of, the endocrine status, is important and implicates the necessity of future studies.

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Conflicts of interest None.

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