Pituitary Function after High-Dose ^{177}Lu -DOTATATE Therapy and Long-Term Follow-Up

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Keywords

^{177}Lu -DOTATATE · Peptide receptor radionuclide therapy · Pituitary · Radiotherapy · Neuroendocrine tumor

Abstract

Introduction: The pituitary gland has a high expression of somatostatin receptors and is therefore a potential organ at risk for radiation-induced toxicity after ^{177}Lu -DOTATATE treatment. **Objective:** To study changes in pituitary function in patients with neuroendocrine tumors (NETs) treated with dosimetry-based ^{177}Lu -DOTATATE to detect possible late toxicity. **Methods:** 68 patients from a phase II clinical trial of dosimetry-based, individualized ^{177}Lu -DOTATATE therapy were included in this analysis. Patients had received a median of 5 (range 3–9) treatment cycles of 7.4 GBq/cycle. Median follow-up was 30 months (range 11–89). The GH/IGF-1 axis, gonadotropins, and adrenal and thyroid axes were analyzed at baseline and on a yearly basis thereafter. Percent changes in hormonal levels over time were analyzed statistically using a linear mixed model and described graphically using box plots. The absorbed radiation dose to the pituitary was estimated based on post-therapeutic imaging, and the results analyzed versus percent change in IGF-1 levels over

time. **Results:** A statistically significant decrease in IGF-1 levels was found ($p < 0.005$), which correlated with the number of treatment cycles ($p = 0.008$) and the absorbed radiation dose ($p = 0.03$). A similar decrease, although non-significant, was seen in gonadotropins in postmenopausal women, while in men there was an increase during the first years after therapy, after which the levels returned to baseline. No change was observed in the adrenal or thyroid axes. **Conclusions:** No signs of severe endocrine disorders were detected, although a significant decrease in the GH/IGF-1 axis was found, where dosimetric analyses indicated radiation-induced damage to the pituitary gland as a probable cause.

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Introduction

Peptide receptor radionuclide therapy (PRRT) with ^{177}Lu -DOTATATE is an approved treatment for metastatic neuroendocrine tumors (NET) of gastroenteropancreatic origin based on the positive results of the NETTER-1 trial [1] and previously published single-center experiences [2, 3]. The molecular basis for PRRT is the

Fig. 1. Images of the head-and-neck region of an NET patient from pre-therapeutic ^{68}Ga -DOTATATE PET/CT illustrating the distinct tracer uptake in the pituitary gland (arrows) indicating a high expression of somatostatin receptors in this endocrine organ.

Fig. 2. Three-planar, post-therapeutic, scintigraphic images of the head-and-neck region of the same patient as in Figure 1 after receiving PRRT with ^{177}Lu -DOTATATE. The images correspond to 24, 96, and 168 h after injection, respectively, with arrows indicating the uptake in the pituitary region.

generally high expression of the somatostatin receptor (SSTR) on the cell membrane of NET cells [4]. These receptors are the binding site of the somatostatin analogue (SSA) that constitutes the peptide ligand of ^{177}Lu -DOTATATE, leading to a targeted internal radiotherapy of the tumors. SSTRs are also expressed on normal cells throughout the body, especially in endocrine organs and neuroendocrine epithelial cells of several organs including the respiratory and gastrointestinal tracts. The pituitary gland has a high physiological expression of SSTR, readily identifiable on ^{68}Ga -DOTATATE-PET/CT (Fig. 1). Such areas may receive a significant absorbed dose (AD) of radiation during ^{177}Lu -DOTATATE therapy (Fig. 2), which could potentially lead to toxicity in the form of reduced physiological function in the short- or long-term after therapy.

Pituitary function after PRRT is an area that has received little attention in the trials that have been conducted so far, with the exception of the study by Teunissen et al. [5], who published their results of PRRT on endocrine function, although not specifically pituitary function, in patients followed up to 2 years. The conclusion of the authors was that PRRT may lead to mild radiation-induced endocrine toxicity, and therefore PRRT was deemed safe with respect to short- and long-term endocrine function. A larger body of evidence comes from external beam radiotherapy (EBRT), indicating that hypopituitarism after cranial irradiation is dose and time dependent: the higher

the AD and the longer the follow-up, the higher the rates of hypopituitarism [6]. The hormones produced in the pituitary gland are specific to certain cell types. The different cell types have different radiation sensitivity, with isolated GH deficiency being the first sign of pituitary dysfunction while radiosensitivity is less pronounced for gonadotropins (LH and FSH), adrenal (ACTH) and thyroid (TSH) cell populations, in that order [6]. In EBRT, a mean AD ≤ 45 Gy is advised to prevent panhypopituitarism, while a mean AD ≤ 20 Gy is recommended to avoid GH deficiency [7].

Physiological control of hormone levels is an intricate system of feedback loops between the hypothalamus, pituitary gland, and the respective end organs. When pituitary hormonal excretion decreases, the result is a decrease in the end-organ hormone, which in turn leads to stimulation of pituitary hormone excretion through a biochemical feedback loop. The levels of the pituitary hormone can thus be maintained as long as the inflicted damage on the pituitary gland is not severe, while the end-organ hormone will be in the low or low-normal range. This makes the pituitary hormones a suboptimal parameter for evaluating early-stage gland dysfunction. The best way to screen for pituitary dysfunction is therefore to analyze end-organ hormones, i.e., IGF-1, thyroxine, cortisol, or testosterone, for example. The exception to this rule is gonadotropin function in postmenopausal women, since the near complete loss of end-organ hor-

mone production (estrogen) maintains the levels of LH and FSH at continuous maximal stimulation making even early signs of decreasing function readily detectable. The confirmation of a suspected pituitary dysfunction affecting one or several axes entails the use of different stimulatory tests to analyze the response capacity of the corresponding pituitary hormones.

From 2012 to 2018, all patients eligible for PRRT at two university hospitals in Sweden were offered inclusion in a clinical trial. The primary objective of the trial was to study the efficacy and safety of individualized PRRT based on kidney dosimetry. The treatment scheme resulted in 75% of the cases having received more than 4 cycles of 7.4 GBq ^{177}Lu -DOTATATE at the interim analysis [8]. The aim of this treatment scheme was to improve disease control by reaching higher cumulative ADs within the tumor lesions. However, this also leads to an increased AD to the organs at risk with potential short- and long-term toxicity.

The aim of the present analysis was to determine whether PRRT, when given at a higher-than-standard cumulative activity, affects pituitary function in the long term.

Patients and Methods

Trial Design

From 2012 to 2018, 103 patients were treated with ^{177}Lu -DOTATATE in the phase II clinical trial Iluminet (EudraCT 2011-000240-16). Eligible patients had histologically confirmed, progressive, grade 1–2 NET, with SSTR expression in tumors higher than the basal liver uptake on planar ^{111}In -octreotide images. All patients received dosimetry-based, individualized treatment as previously described [8]. Treatment was given with an activity of 7.4 GBq/cycle, at 10 ± 2 -week intervals, and continued until reaching the targeted renal biologically effective radiation dose of 27 ± 2 Gy (for patients with risk factors for nephropathy and/or bone marrow toxicity) or 40 ± 2 Gy (for patients without risk factors) [9]. In case of tumor progression or unacceptable toxicity during the treatment phase, PRRT was terminated, and the patient offered alternative treatment or active follow-up, respectively. Further details on study design can be accessed at www.clinicaltrials.gov (NCT01456078). The last patient was included in September 2017. All patients gave their written informed consent prior to inclusion in the trial.

Patients

Of the 103 patients that were included in the trial, 3 had missing baseline data on pituitary function, and 25 had a follow-up <10 months due to progression of disease, death, or loss to follow-up and were therefore not evaluable. Seven patients had received PRRT as part of their treatment prior to entering the trial, and they were also excluded from this analysis. The results are based on the remaining 68 patients.

Baseline data of the patients included in this analysis are summarized in Table 1. Median age at inclusion was 66 years, 31 of the

Table 1. Baseline characteristics of the 68 patients with pituitary function followed up >10 months

	Patients	Median	Range
Total evaluable patients, <i>n</i>	68		
Female	31 (46%)		
Postmenopausal	25 (81%)		
Male	37 (54%)		
Age, years		66	41–80
BMI		24.9	17.3–37.1
On SSA treatment	55 (81%)		
Previous systemic treatment			
Chemotherapy	8 (12%)		
1 line of chemotherapy	4 (6%)		
2 lines of chemotherapy	2 (3%)		
3 lines of chemotherapy	2 (3%)		
Biologics	10 (15%)		
MIBG	1 (1%)		
Liver-directed therapy	27 (40%)		
Presence of liver metastases	62 (91%)		
Primary tumor origin			
Small intestine	40 (59%)		
Pancreas	14 (21%)		
Lung	5 (7%)		
Other	9 (13%)		
Treatment cycles		5	2–9
1–3	9		
4	12		
5	19		
6	18		
7–9	10		
Accumulated injected activity, GBq		37.0	14.8–66.6

The term “biologics” refers to treatment with everolimus, sunitinib, or interferon. Liver-directed therapy includes bland embolization, radioembolization, and radiofrequency ablation.

68 patients (46%) were female, and 25 (81%) of them were postmenopausal at the time of inclusion; 55 patients (81%) had a stable dose of SSA treatment at baseline and continued with the same dose all through treatment and follow-up according to the protocol. The remaining 13 patients did not have any SSA treatment at study entry, nor did they initiate such treatment during the therapy or follow-up phase of the trial. Median follow-up from inclusion was 30 months (range 11–89). Median cumulative injected activity was 37 GBq (14.8–66.6), median number of treatment cycles received was 5 [3–9], and 47 patients (69%) had >4 treatment cycles. Patients with concomitant treatment with drugs known to alter the levels of the measured hormones were excluded from the analysis of the respective axis, as specified below.

Evaluation of Pituitary Function

Laboratory values of pituitary function were continuously assessed from baseline and on a yearly basis thereafter for as long as the patient was followed up. Pituitary function was evaluated through a screening approach by analyzing plasma levels of TSH, fT4, testosterone, and SHBG (males only), FSH, LH, ACTH, corti-

sol, and IGF-1. The analytical methods used varied to some extent between both sites and changed in some cases during follow-up, but were all standard methods performed by accredited hospital laboratories. In some cases, the use of different analytical methods also meant different reference ranges for normal values. For this reason, all values have been normalized to the baseline value, and follow-up values are described as percent change from baseline.

For the evaluation of the GH axis, IGF-1 was analyzed. No specific concomitant drugs were considered to exclude subjects from this analysis. However, we found it to be of interest to evaluate the hepatic function by analyzing albumin levels in parallel with IGF-1. The reasons for this were the following: (1) >75% of all circulating IGF-1 is produced in the liver [10, 11], (2) most patients studied in the present trial had liver metastases, and (3) uptake of ¹⁷⁷Lu-DOTATATE in the liver metastases leads to radiation exposure of normal liver parenchyma. In order to elucidate whether any possible decrease in IGF-1 levels was due to a decrease in hepatic function, we analyzed albumin levels in the whole patient cohort (68 patients), since albumin is another protein produced in the liver and often used to evaluate the synthetic capacity of the liver.

For the evaluation of the gonadotropin axis, LH and FSH were analyzed. Separate analyses were performed for males and females, and only postmenopausal women were included. Postmenopausal status was defined as (1) age over 55 and/or (2) FSH >25 IU/L [12, 13]. Female patients treated with tamoxifen, aromatase inhibitors, and estrogen replacement were excluded from the analysis. In males, LH, FSH, testosterone, and SHBG as well as the testosterone/SHBG ratio were analyzed, and patients receiving antiandrogens or testosterone were excluded from the analysis.

For the evaluation of the adrenal axis, ACTH and early morning plasma cortisol levels were analyzed. Patients on steroid treatment were excluded from the analysis.

For the evaluation of the thyroid axis, TSH and fT4 were analyzed in all included subjects except those who initiated levothyroxine treatment, or had a change in levothyroxine dose, during the follow-up period (7 patients).

Dosimetry and Dose-Response Analysis

To explore the possible existence of a dose-response relationship in patients receiving PRRT, we developed a method for estimating the AD to the pituitary gland based on post-therapeutic images. Briefly, a region of interest corresponding to the pituitary gland was delineated in each of 4 anterior planar images acquired during the first week after therapy in all cycles for all patients. The pituitary gland was readily identifiable in a majority of the patients since there is little focal, physiological uptake in the head-and-neck region (Fig. 2). The exceptions to this rule were those patients with uptake in skull metastases and sometimes diffuse uptake in the nasal mucosa. Patients in whom it was deemed difficult to distinguish pituitary uptake from adjacent pathological or physiological uptake were excluded from dosimetric analysis. For all evaluable patients, activity uptake was quantified from the image region of interest at each imaging time point, and AD was estimated as a function of the effective half-life of the radiopharmaceutical (data from images), the area under the time-activity curve, and the pituitary mass. As the pituitary mass could not be determined on an individual basis, a standard mass of 0.6 g was used, based on data from the literature [14]. A detailed description of the dosimetry method will be published separately.

In order to be able to compare the estimated ADs with data from EBRT, they were converted into the equivalent dose in 2-Gy

fractions (EQD2). This is a quantity used to compare radiotherapy given with different dose rates and fractionation schemes, to the standard situation in EBRT with 2-Gy fractions (linear-quadratic model parameters of $\alpha/\beta = 2$ Gy and a repair half-time of 1.5 h were assumed for this calculation). The results from the dosimetric calculations for all evaluable patients and cycles were thus used to estimate a median per cycle AD and EQD2 to the pituitary gland. Given the difficulties in delineating the pituitary uptake for some patients, and that the uncertainties of the patient- and cycle-specific dose estimates were high, we used the per-cycle median dose values to calculate the total AD and EQD2 for each patient (number of cycles $\times$ median dose/cycle). The relationship between the radiation dose and change in IGF-1 levels was analyzed both as number of treatment cycles (1–3, 4, 5, 6, and 7–9) versus percent change in IGF-1, and EQD2 versus percent change in IGF-1. The EQD2 categories were set to <20, 20–45, and >45 Gy, according to the empirical limits for GH deficiency and panhypopituitarism as described in the Introduction. Only patients with at least 6 months of follow-up after the last treatment cycle were included in the dose-response analyses in order to ensure that the effect of the whole treatment period was taken into account.

Statistical Analysis

To take the longitudinal character of the data into account, with a large variation in follow-up time (11–89 months) and some missing data, linear mixed models were employed to determine the significance of the changes observed over time. A value of $p < 0.05$ was considered statistically significant. Box plots were used to describe the results graphically. The time intervals were adjusted to 6 or 12 months in such a way that the resulting number of patients in each group was similar. The intervals were the same in all analyses except gonadotropins (by sex), where the total number of individuals was so small that the intervals had to be increased to get a reasonable number of patients in each group. The time intervals were the same for the mixed model and for the box plots for each hormone analyzed.

The dose-response analyses were also performed using a linear mixed model, looking both at the number of cycles received and the EQD2 as explanatory variables. In the absence of a control group (0 cycles), the group having received 1–3 cycles and the patients having received <20 Gy served as reference in the respective analysis.

All statistical analyses were performed using IBM SPSS statistics version 25.

Results

The results of the analyses of the different hormonal axes are presented graphically in Figure 3 and here described in descending order of radiosensitivity.

GH/IGF-1 Axis

Sixty-five patients were evaluable. Follow-up was ≥ 25 months for 34 patients. The mixed model analysis indicated a statistically significant decrease of IGF-1 during the follow-up period ($p < 0.005$). The decrease was –15%

a

(Figure continued on next page.)

Fig. 3. Box plots illustrating the development of hormone levels over time. The p values are from the mixed model analysis. The median value is indicated by a black horizontal line, and the 25th and 75th percentiles define the limits of the box. The whiskers indicate the minimum and maximum values found within 1.5 interquartile ranges from these percentiles, and values beyond that range are considered outliers. The scales on the y-axes have been

adjusted for improved readability, in some cases leaving out outlier values. **a** IGF1-, gonadotropin, and albumin values. **b** Adrenal and thyroid axis values. BL, baseline; TSH, thyroid-stimulating hormone; ft4, free thyroxine; SHBG, steroid hormone binding globulin; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; FSH, follicle-stimulating hormone.

(95% CI -8 to -23%) at 19–24 months of follow-up, and -30% (95% CI -21 to -39%) at follow-up >48 months. The box plots also demonstrated a progressive decline with increasing follow-up.

Gonadotropin Axis

For LH and FSH, males and females were analyzed separately.

There were 20 evaluable postmenopausal women, with 10 followed up ≥ 25 months. The box plots indicate a decrease in median LH and FSH, which increased with longer follow-up. These changes were not significant in the mixed model analysis.

There were 34 and 33 evaluable males for LH and FSH, respectively, and follow-up was ≥ 25 months for 18 patients. The mixed model analysis indicated a statistically significant and large initial increase in both LH and FSH, with values returning to baseline levels again with further follow-up. For the patients with the longest follow-up (>48 months), LH and FSH values increased again ($p = 0.10$ and 0.05 , respectively) at the same time as the testosterone/SHBG ratio reached its lowest values. The box plots show the same trends as the results from the mixed model analysis.

Thirty-one males were evaluable for the testosterone/SHBG ratio, and 32 for testosterone. Follow-up was ≥ 25 months for 15 patients. Neither of both analyses reached

Fig. 4. Box plot illustrating the relationship between percent change in IGF-1 from baseline and the number of treatment cycles received. $p = 0.008$ (mixed model analysis). IGF-1, insulin-like growth factor 1.

statistical significance (testosterone/SHBG ratio: $p = 0.325$, testosterone: $p = 0.680$). For the median testosterone/SHBG ratio, the box plots indicated a progressive decline, with the deviation from baseline increasing with longer follow-up.

Adrenal Axis

Sixty patients were evaluable for plasma cortisol, of which 30 had a follow-up of at least 25 months; 63 patients were evaluable for ACTH, of which 33 had a follow-up of at least 25 months. The cortisol levels did not change significantly during the observation period ($p = 0.771$), and box plots showed stable levels over time. ACTH levels increased significantly during the first year of follow-up (+58%, 95% CI 26–90%) according to the mixed model analysis, after which they returned to baseline levels. This increase was not evident in the box plots, where median ACTH levels appeared to remain stable all through treatment and follow-up.

Thyroid Axis

Sixty-four and 61 patients were evaluable for TSH and fT4, respectively, with follow-up ≥ 25 months for 32 and 28 patients. No statistically significant changes in hormone levels were found (TSH: $p = 0.127$; fT4: $p = 0.429$), and box plots showed stable levels over time.

Dosimetry and Dose-Response Analysis

Of the 68 patients with clinical follow-up, 63 patients and 209 cycles were evaluable for dosimetry based on the criteria of having a clearly distinguishable uptake in the pituitary gland. The median AD/cycle to the pituitary

gland over all patients and all cycles was 6.6 Gy (range 3.4–13.6) and an EQD2/cycle of 3.5 Gy (1.7–7.7). For a patient who had received 6 cycles, this meant an estimated total AD of 39.3 Gy, corresponding to 20.9 Gy had it been given in 2-Gy fractions.

Fifty-five patients with a follow-up longer than 6 months after the last treatment cycle were evaluable for dose-response analysis. Among these, there was a highly significant effect of the number of treatment cycles on the IGF1-levels ($p = 0.008$; Fig. 4) when adjusted for follow-up time. The significance level increased with increasing number of treatment cycles, with $p = 0.05$ for patients that had received 4 cycles, $p = 0.015$ for 5 cycles, $p = 0.029$ for 6 cycles, and $p = 0.0002$ for those that had received 7–9 cycles. In the EQD2 analysis, 31 patients had received less than 20 Gy, and 24 patients had received the equivalent of 20–45 Gy. No patient exceeded an EQD2 of 45 Gy. There was a significant effect of EQD2 on the decrease in IGF-1 for those patients that had received 20–45 Gy as compared to those who had received <20 Gy ($p = 0.03$).

Discussion

In the current analysis, we study the effect of an individualized, dosimetry-based PRRT strategy on pituitary function. We do not find any signs of serious endocrine disorders, although there was a significant decrease in the GH/IGF-1 axis, which seems to be an early sign of radiation-induced toxicity. The strength of these results is the combination of a long follow-up of a population that has received a higher-than-standard dose of ^{177}Lu -DOTATATE coupled with the first documented dose-response analysis for pituitary function and PRRT.

IGF-1 was the hormone most clearly affected in our patients during follow-up, which may be secondary to GH deficiency on the pituitary level. Alternative explanations are conditions affecting the capacity of the liver to produce IGF-1 or a physiological decline in pituitary function with age. To evaluate the synthetic function of the liver, albumin was analyzed in parallel with IGF-1. The results showed no change in albumin levels during the observation period, neither in mixed model analysis nor in box plots of the median values (Fig. 3a), making it unlikely that the decrease in IGF-1 was a result of liver damage.

One can speculate whether the high proportion of SSA-treated patients has contributed to our results since somatostatin is known to inhibit GH secretion [10]. The inclusion/exclusion criteria for the trial demanded that patients on SSA should have had a stable dose prior to

inclusion during at least 3 months. This dose was not changed during treatment or follow-up unless signs of clinical or radiological progression were present, in which case follow-up within the trial was terminated. In a prospective clinical trial including 23 patients with advanced NET, the effect of long-acting SSA on IGF-1 levels was followed and analyzed at 3 time points: 4.5, 18, and 48 months after treatment initiation. The results showed an initial mean decrease of 26% at the first time point, after which IGF-1 levels remained stable [15]. These results make it unlikely that SSA treatment per se would explain the significant decrease in IGF-1 seen in our analysis.

A relative GH deficiency is part of the normal aging process, with a 15% decrease per decade occurring after the third decade of life [16, 17]. A parallel process is seen for IGF-1 with a linear, progressive decline from the third decade and onward in the range of 15–20% per decade [11, 18]. In our trial population, the decrease in IGF-1 was >20% over a 5-year period, and can thus not be attributed solely to normal aging. If the observed changes were secondary to a decrease in GH secretion in the pituitary gland, it would be classified as pathological adult GH deficiency. This is a condition associated with a gradual increase in body fat, decreased muscle mass and bone density, as well as psychosocial problems. GH-deficient adults also have an increased mortality rate compared to age-matched controls, which seems to be due primarily to cardio- and cerebrovascular disease. GH replacement therapy significantly improves these symptoms with manageable side effects [10]. Concurrent active malignant disease is however a contraindication to GH replacement therapy and would therefore not be an option for this patient group [19].

In the analysis of the gonadotropin axis, results differed between male and female patients. In postmenopausal women, the mixed model analysis did not show any statistically significant change in LH or FSH, while the box plots show a progressive decline in the median levels of these hormones. Normal aging has been found to result in a progressive decline in LH and FSH of approximately 40% over a period of 20–35 years in healthy, postmenopausal women [20]. We observed a decrease in the order of 30–40% over a 5-year period, which is too large to be explained by normal aging alone. The small number of evaluable patients in this analysis may have affected the level of significance, which makes it impossible to draw firm conclusions regarding whether or not the observed changes are true. The results are however coherent with earlier findings by Teunissen et al. [5].

In the male patients, the gonadal axis was evaluated by measuring LH, FSH, testosterone, and the testosterone/

SHBG ratio. A very distinct initial increase in LH and FSH was seen, but there was no change in testosterone or the testosterone/SHBG ratio. This is similar to the results previously published by Teunissen et al. [5] and may be explained by an earlier decrease in testosterone, secondary to off-target irradiation of the spermatocytes during the therapy period, which has then led to a stimulation of gonadotropin release from the pituitary gland. At the time of measurement, this process seems to have achieved a normalization of testosterone levels again, which would indicate that the initial damage to the testes was reversible. The later, non-significant decrease in the testosterone/SHBG ratio, which is coupled to a significant increase in FSH and LH, is more difficult to explain. If true, it would indicate an effect on the peripheral tissues rather than on the pituitary gland. A possible explanation could be an additive effect of late radiation damage on the normal aging-related decline in testosterone production by the testes.

A similar effect was observed for the adrenal axis, where the mixed model analysis of ACTH levels showed an initial significant increase with unchanged plasma cortisol levels. ACTH levels returned to normal with further follow-up and remained so. A possible explanation for these findings is that the adrenal medulla is neuroendocrine tissue, with a specific uptake of ^{68}Ga -DOTATATE on PET imaging [21]. There may therefore have been a specific uptake also of ^{177}Lu -DOTATATE leading to a radiation-induced decline in cortisol from the adjacent adrenal cortex during therapy, which would then have stimulated ACTH until cortisol levels normalized again.

As for clinical significance, the fact that we see signs of GH deficiency in this patient population with a median age of 66 years is of little consequence. Only if PRRT, in the future, were to be used in a different setting where patients have a longer life expectancy, i.e., as neo-adjuvant/adjuvant therapy, or in younger patients, would radiation-induced hypopituitarism be a possible side effect to consider in long-term follow-ups.

Our results are coherent with what is seen in patients treated with EBRT to the pituitary gland: the first axis to be affected is the GH axis, followed by the gonadotropins, and adrenal and thyroid axes in that order [6]. It is also analogous in the sense that an increased cumulative radiation dose and increased follow-up increases the incidence of pituitary dysfunction.

Although our objective is similar to that of Teunissen et al. [5], there are some significant differences. In terms of the patient population, our patients had received higher cumulative activity (median 37 GBq vs. maximum 29.6 GBq), a majority of our patients had been simultaneous

SSA therapy (81 vs. 46%), and the follow-up in our trial was considerably longer (11–89 vs. 12–24 months). In terms of endocrine function analysis, our approach was to perform screening of signs of pituitary dysfunction, while Teunissen et al. [5] performed a somewhat more general endocrine analysis including, for example, HbA_{1c}, spermatogenesis, and ACTH stimulation testing. On the other hand, they did not include the GH/IGF-1 axis, which is known to be the first axis to reflect radiation effects on the pituitary gland. These differences are likely the explanation for the slightly different conclusions we reach regarding the effect of PRRT on pituitary function.

One weakness in our analysis is that we were not able to work with absolute values of the hormonal levels due to the differences in analytical methods and reference intervals used in different laboratories. In some cases, the analytical method changed during the observation period, which complicates interpretation further. To compensate for these issues, we have worked with normalized values and percent changes, and thereby relevant conclusions could be drawn at group level. When applying our results to specific patients, however, the absolute values and reference ranges should guide patient management. If some degree of pituitary dysfunction is suspected, complementary testing needs to be performed in order to confirm the diagnosis.

The dosimetric analysis harbors both strengths and weaknesses. It is a strength that we have been able to perform dosimetry, but the small size of the pituitary gland and the poor spatial resolution in the planar images leads to a relatively large uncertainty in the dosimetric estimates at individual level. In particular, individual estimates of the pituitary gland mass were not available. To compensate for this, to some extent, we refrained from presenting patient-specific AD data so as to respect the limited conclusions that can be drawn at individual level. Since it is the first attempt at all to perform such an analysis, it did seem of interest to present the results at group level.

Conclusions

We found no signs of serious endocrine disorders in this population of patients with metastatic NET who had received dosimetry-based PRRT. A statistically significant decrease in IGF-1 levels was observed, which was significantly correlated with the number of cycles of ¹⁷⁷Lu-DOTATATE received as well as to the radiation dose. These findings indicate a probable radiation-induced damage to the pituitary gland, in accordance with published data on similar effects after EBRT. We do not con-

sider our data to support any change in the current use or follow-up of PRRT, but caution is advised if PRRT is used in settings where patients have a longer overall survival or receive potentially higher ADs to the pituitary gland.

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Statement of Ethics

The clinical trial within which this analysis was performed was conducted in accordance with the Declaration of Helsinki and the ICH guidelines for Good Clinical Practice. The trial was approved by the Swedish Medical Products Agency and the Institutional Ethics Board (Regionala Etikprövningsnämnden Lund, ref. No. 2011/287). All patients gave their written informed consent prior to study inclusion.

Disclosure Statement

Anna Sundlöv has acted as a consultant/lecturer/advisory board member for Ipsen, Novartis, Sam Nordic, and Spago Nanomedical. The other authors have no conflicts of interest to declare.

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Author Contributions

Oncologist A.S. participated in the design of the clinical trial, recruitment and treatment of the patients, data analysis and interpretation, and manuscript preparation. Physicist K.S.-G. participated in the design of the dosimetric method and calculations, data analysis and interpretation, and manuscript preparation. Oncologist J.T. participated in the design of the clinical trial, recruitment and treatment of patients, interpretation of data, and manuscript preparation. Oncologist L.D. participated in data analysis and interpretation. Oncologist J.S. contributed to the design of the trial, recruitment and treatment of the patients, and interpretation of the results. Statistician A.Å. gave statistical advice. Physicist P.B. participated in the design of the dosimetric method used in the trial. Endocrinologist O.L. participated in the analysis and interpretation of data as well as manuscript preparation. All authors read and approved the final manuscript. All coauthors participated in the critical review of the manuscript.

References

- 1 Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al.; NETTER-1 Trial Investigators. Phase 3 Trial of ^{177}Lu -Dotatate for Midgut Neuroendocrine Tumors. *N Engl J Med*. 2017 Jan;376(2):125–35.
- 2 Kim SJ, Pak K, Koo PJ, Kwak JJ, Chang S. The efficacy of (^{177}Lu)-labelled peptide receptor radionuclide therapy in patients with neuroendocrine tumours: a meta-analysis. *Eur J Nucl Med Mol Imaging*. 2015 Dec;42(13):1964–70.
- 3 Garske-Román U, Sandström M, Fröss Baron K, Lundin L, Hellman P, Welin S, et al. Prospective observational study of ^{177}Lu -DOTA-octreotate therapy in 200 patients with advanced metastasized neuroendocrine tumours (NETs): feasibility and impact of a dosimetry-guided study protocol on outcome and toxicity. *Eur J Nucl Med Mol Imaging*. 2018 Jun;45(6):970–88.
- 4 Reubi JC. Peptide receptor expression in GEP-NET. *Virchows Arch*. 2007 Aug;451(S1 Suppl 1):S47–50.
- 5 Teunissen JJ, Krenning EP, de Jong FH, de Rijke YB, Feelders RA, van Aken MO, et al. Effects of therapy with [^{177}Lu -DOTA 0,Tyr 3] octreotate on endocrine function. *Eur J Nucl Med Mol Imaging*. 2009 Nov;36(11):1758–66.
- 6 Darzy KH, Shalet SM. Hypopituitarism following radiotherapy. *Pituitary*. 2009;12(1):40–50.
- 7 Lambrecht M, Eekers DB, Alapetite C, Burnet NG, Calugaru V, Coremans IE, et al.; work package 1 of the taskforce “European Particle Therapy Network” of ESTRO. Radiation dose constraints for organs at risk in neuro-oncology; the European Particle Therapy Network consensus. *Radiother Oncol*. 2018 Jul;128(1):26–36.
- 8 Sundlöv A, Sjögreen-Gleisner K, Svensson J, Ljungberg M, Olsson T, Bernhardt P, et al. Individualised ^{177}Lu -DOTATATE treatment of neuroendocrine tumours based on kidney dosimetry. *Eur J Nucl Med Mol Imaging*. 2017 Aug;44(9):1480–9.
- 9 Bodei L, Cremonesi M, Ferrari M, Pacifici M, Grana CM, Bartolomei M, et al. Long-term evaluation of renal toxicity after peptide receptor radionuclide therapy with ^{90}Y -DOTATOC and ^{177}Lu -DOTATATE: the role of associated risk factors. *Eur J Nucl Med Mol Imaging*. 2008 Oct;35(10):1847–56.
- 10 Hersch EC, Merriam GR. Growth hormone (GH)-releasing hormone and GH secretagogues in normal aging: Fountain of Youth or Pool of Tantalus? *Clin Interv Aging*. 2008; 3(1):121–9.
- 11 Olarescu NC, Gunawardane K, Hansen TK, Möller N, Lunde Jørgensen JO. Normal physiology of growth hormone in adults. In: Feingold KR, Bradley A, Boyce A, Chrousos G, Dungan K, Grossman A, et al, editors. *Endotext* [Internet]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK279056/>.
- 12 Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, et al.; STRAW + 10 Collaborative Group. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. *J Clin Endocrinol Metab*. 2012 Apr;97(4):1159–68.
- 13 Luoto R, Kaprio J, Uutela A. Age at natural menopause and sociodemographic status in Finland. *Am J Epidemiol*. 1994 Jan;139(1):64–76.
- 14 Valentin J. Basic Anatomical and Physiological Data for Use in Radiological Protection: Reference Values: ICRP Publication 89. Ann ICRP. 2002 Sep;32(3-4):1-277.
- 15 Ronchi CL, Peracchi M, Corbetta S, Massironi S, Ciafardini C, Conte D, et al. Evaluation of IGF-I levels during long-term somatostatin analogs treatment in patients with gastroenteropancreatic endocrine tumors. *J Endocrinol Invest*. 2007 Mar;30(3):241–6.
- 16 Zadik Z, Chalew SA, McCarter RJ Jr, Meistas M, Kowarski AA. The influence of age on the 24-hour integrated concentration of growth hormone in normal individuals. *J Clin Endocrinol Metab*. 1985 Mar;60(3):513–6.
- 17 Garcia JM, Merriam GR, Kargi AY. Growth hormone in aging. In: Feingold KR, Bradley A, Boyce A, Chrousos G, Dungan K, Grossman A, et al, editors. *Endotext* [Internet]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK279163/>.
- 18 Juul A, Bang P, Hertel NT, Main K, Dalgaard P, Jørgensen K, et al. Serum insulin-like growth factor-I in 1030 healthy children, adolescents, and adults: relation to age, sex, stage of puberty, testicular size, and body mass index. *J Clin Endocrinol Metab*. 1994 Mar; 78(3):744–52.
- 19 EMEA Summary of Product Characteristics Somatropin. 2003.
- 20 Hall JE, Lavoie HB, Marsh EE, Martin KA. Decrease in gonadotropin-releasing hormone (GnRH) pulse frequency with aging in postmenopausal women. *J Clin Endocrinol Metab*. 2000 May;85(5):1794–800.
- 21 Kuyumcu S, Özkan ZG, Sanli Y, Yilmaz E, Mudun A, Adalet I, et al. Physiological and tumoral uptake of (^{68}Ga)-DOTATATE: standardized uptake values and challenges in interpretation. *Ann Nucl Med*. 2013 Jul;27(6):538–45.