Pre- and postoperative $^{68}$Ga-DOTATOC positron emission tomography for hormone-secreting pituitary neuroendocrine tumours

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Abstract

Objectives: Somatostatin receptors (SSTRs) are potential targets for detecting pituitary neuroendocrine tumours (PitNETs) that can be visualized effectively with $^{68}$Ga-labelled PET tracers. With this study, we have evaluated the diagnostic properties of such a tracer, $^{68}$Ga-DOTATOC, in patients with hormone-producing PitNETs before and after surgery.

Design/Methods: This prospective case-control study presents preoperative positron emission tomography (PET) and histopathological data in 18 patients with somatotroph ($n = 8$), corticotroph ($n = 7$) and thyrotroph ($n = 3$) PitNETs. Patients were scanned pre- and postoperatively with $^{68}$Ga-DOTATOC PET. For the postoperative part of the study, patients with gonadotroph tumours ($n = 7$) were also included. Fifteen pituitary healthy controls underwent the same protocol once. The maximum standard uptake value (SUV$_{max}$) was analysed in manually outlined regions around the tumour in patients and around the pituitary gland in controls. specimens were collected during surgery in subjects for assessment of adenohypophyseal tumour cell type and the SSTR expression.

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1 | INTRODUCTION

Tumours arising from hormone-producing cells in the anterior lobe of the pituitary gland are members of the neuroendocrine family, pituitary neuroendocrine tumours (PitNETs), and can be either functioning, that is hormone-producing, or nonfunctioning (NF), that is without hormone secretion. PitNETs are common, representing approximately 10% of all intracranial tumours and account for 25% of all intracranial surgical resections.

Magnetic resonance imaging (MRI) is the ‘gold standard’ for the detection of PitNETs. There are, however, limitations to this technique. MRI has low sensitivity for detection of tumours <5 mm. With the addition of contrast agent, the detection rate for smaller tumours is improved, but with low specificity, the utility of MRI for small tumours is limited. Particularly in patients with Cushing’s disease, corticotroph tumours manifest frequently as microadenomas (<10 mm) and cannot be detected by MRI in up to 40% of the cases. Another challenge with MRI is postoperative radiological assessment. Many patients with functioning PitNETs undergo surgery, resulting in altered anatomic conditions, postoperative changes and implant insertion that can cause imaging artefacts. Discrimination of tumour tissue from scar tissue is challenging and, because MRI only provides morphological information, the detection of residual tumour tissue is only possible by observing longitudinal tumour growth on repeated scans. Moreover, the relative lack of functional information limits the evaluation of nonsurgical treatment response.

Positron emission tomography (PET) using ¹⁸F-labelled somatostatin (SSTR) analogues is the molecular imaging modality of choice for the detection of neuroendocrine tumours, for which the defined characteristic is SSTR expression. Although PitNETs also express SSTR, this technique has not been properly evaluated for these tumours. Recently, we and others have reported intriguing results from small-scale pilot studies arguing for the diagnostic potential of ¹⁸F-labelled octreotide DOTATOC PET, by demonstrating meaningful differences in tracer uptake between the normal pituitary gland and NF-PitNETs (mostly gonadotroph tumours) as well as corticotroph tumours. Furthermore, SSTR PET has also found use in the imaging assessment of patients with multiple endocrine neoplasia type 1. However, these pilot studies were only targeted at a subset of PitNETs and, apart from our NF-PitNET study, the published imaging data were not accompanied by relevant histopathological data.

Our hypothesis was that SSTR expression is different in functioning PitNETs compared to normal pituitary gland and, therefore, tumours can be visualized by using ¹⁸F-DOTATOC PET. To test the hypothesis, we have conducted a prospective, case-control study, including patients with different PitNET subtypes who have been investigated with ¹⁸F-DOTATOC PET before and after surgery.

2 | MATERIALS AND METHODS

2.1 | Study design

This prospective, case-control study was conducted at the Departments of Endocrinology and Nuclear Medicine at the Sahlgrenska University Hospital, Gothenburg, Sweden between December 2015 and May 2020. Adult PitNET patients were examined with ¹⁸F-DOTATOC PET before and 6-8 months after pituitary surgery. Height and weight were measured before each PET scan. In premenopausal women, a pregnancy test was used to exclude pregnancy. After the PET scan, all subjects filled in a standardized report form to register any possible side effects within 24 h after tracer administration. Control subjects underwent the same PET protocol once.

The Regional Ethical Review Board (Gothenburg, Sweden) approved the study, which was conducted in accordance with the Declaration of Helsinki. Signed informed consent was obtained from all subjects before engaging in the study protocol, that also allowed for collection of tumour specimens during surgery, after full explanation of the purpose and nature of all procedures used.

RESULTS: Thyrotroph tumours showed higher uptake (median SUV_max 41.1; IQR 37.4-60.0) and corticotroph tumours lower uptake (SUV_max 6.8; 2.6-9.3) than normal pituitary gland (SUV_max 13.8; 12.1-15.5). The uptake in somatotroph tumours (SUV_max 15.9; 11.6-19.7) was similar to the uptake in the pituitary gland. There was a strong correlation between SUV_max and SSTR2 expression (r = .75 (P < .01)). In the postoperative evaluation, PET was able to correlate tracer uptake with biochemical cure and noncure in patients with an abnormal postoperative magnetic resonance image and a preoperative tumour uptake SUV_max > 13.8.

CONCLUSIONS: ¹⁸F-DOTATOC PET can be used to detect thyrotroph tumours in the pre- and postoperative imaging assessment. Corticotroph tumours had a significantly lower uptake compared to the pituitary gland but without a distinct increased tumour uptake the clinical postoperative value is limited.

KEYWORDS
DOTATOC PET, pituitary neuroendocrine tumour, somatostatin receptor imaging
2.2 | Subjects

Twenty-three PitNET patients (25-74 years of age at diagnosis; 10 men) were included in this study: two were NF-PitNETs of corticotroph cell origin from a previous publication and the remaining 21 were somatotroph \((n = 9)\), corticotroph \((n = 8)\) and thyrotroph \((n = 4)\) tumours at clinical presentation. For the postoperative part of the study, seven patients with clinical NF-PitNETs of gonadotroph cell origin were included for their postoperative PET evaluation, where the preoperative PET scan data are presented in a previous pilot study. The patients, all recruited from university hospitals in Sweden and referred for pituitary surgery, were diagnosed in a routine clinical setting based on MRI evidence of a pituitary tumour, biochemical analyses and clinical presentation that met the criteria for ICD-10 code pituitary tumour (D35.2) in combination with acromegaly (E22.0), Cushing’s disease (E24.0) or thyroid-stimulating hormone (TSH) hypersecretion (E05.8). Biochemical analyses performed pre- and postoperatively include, but are not restricted to, S-TSH, S-FT3, S-FT4, S-ACTH, S-cortisol, S-IGF-1, S-LH, S-FSH, S-testosterone, S-estradiol and depending on hormonal presentation oral glucose suppression test, TRH test, T3-suppression test and/or dexametason suppression test are added. Patients with lactotroph tumours were not included, as they rarely undergo pituitary surgery. In all cases but one, the tumour was seen on the pituitary MRI. Patients without clinical or biochemical signs of pituitary hormone overproduction were deemed as NF-PitNET. For patients with corticotroph tumours < 7 mm or without a detectable tumour on MRI, the diagnosis was confirmed by using inferior sinus petrosus catheterization sampling. Patients ≥ 18 years of age with a treatment-naive tumour (including surgery, somatostatin analogues or dopamine agonists) waiting surgical treatment were recruited for this study.

Sixteen controls (37-79 years of age; 9 men) were included, comprising two groups. The first group included 13 healthy volunteers who were randomly selected from the population registry in Gothenburg, Sweden. Exclusion criteria included any pituitary disease and/or ongoing treatment with somatostatin analogues or dopamine agonists. To be included in the evaluation as a control, the MRI had to be negative for incidentalomas in the pituitary. The second group included three controls with thyroid-associated ophthalmopathy (TAO) who were participating in another study (http://www.clinicaltrials.gov; identifier NCT02378298), where \(^{68}\)Ga-DOTATOC PET was performed using the same scanning protocol as in our patients to evaluate eye-muscle inflammation. Inclusion criteria for that study were euthyroid men or women ages 18-70 years with TAO necessitating intravenous glucocorticoid treatment. All controls except two were presented in our previous publication. \(^{68}\)Ga-DOTATOC PET was performed before any glucocorticoid treatment was administered. Exclusion criteria for TAO controls were the same as those for healthy controls.

Two patients discontinued participation in the study before the first PET scan. One had to undergo pituitary surgery rapidly before the PET scan could be performed and the other chose to withdraw further participation. Two patients with hypercortisolism and a suspected corticotroph tumour, respectively, were excluded from analyses as explorative surgery was unable to confirm any tumour finding. One patient with clinical hyperthyroidism of central origin declined surgical treatment and was excluded after the first PET scan and is not included in the preoperative analyses. Two patients (#15 and #17; Table 1) with preoperative PET scan and resected tumour specimen for immunohistochemical (IHC) analysis dropped out before postoperative PET scan was performed. Moreover, the postoperative evaluations for three patients (#9, #10 and #14; Table 1) have been delayed because of the COVID-19 pandemic as clinical research visits to the hospital have not been allowed. Consequently, these patients are awaiting their postoperative evaluation. One of the control subjects had a panic attack in the MRI scanner and chose to withdraw further participation.

Thus, in this study, we present preoperative PET and histopathological data from 18 patients as well as PET data from 15 control subjects. Data from the postoperative PET scans are presented in 20 patients; 13 of 18 patients with preoperative PET and 7 patients with NF-gonadotroph tumours from a previous publication. A flowchart over the inclusion and research visits for patients and controls is presented in the appendix to help with a better overview of the process.

2.3 | MRI

MRI was performed according to the clinical protocol of the Department of Radiology, Sahlgrenska University Hospital, Gothenburg, Sweden, including a T1-weighted scan, both with and without gadolinium contrast enhancement as well as a 3D-acquired T1 sequence. T2 sequences were also used for tumour evaluation. Similar clinical protocols were undertaken at the regional hospitals for patients that were recruited from other regions. If the 3D-acquired T1 sequence was missing, a complementary MRI was carried out at the Department of Radiology, Sahlgrenska University Hospital, Gothenburg, before the PET scan. MRI scans were performed within 3 months of the \(^{68}\)Ga-DOTATOC PET. For controls, MRI scans were performed by the same protocol as for the patients but without any contrast agent.

Postoperative MRI scans were assessed by an experienced neuroradiologist (DZ) with respect to residual tumour tissue and postoperative changes.

2.4 | \(^{68}\)Ga-DOTATOC PET

Radiotracer synthesis and quality control were performed with the same scanning protocol as in our previous publication. Scanning was performed with a dynamic list mode acquisition starting at the time of injection to collect emission data over a 45-minute period. The list mode data were reconstructed into 14 frames (5 × 60, 5 × 180, 3 × 300 and 1 × 600 s). All PET images were iteratively
reconstructed (MLEM/OSEM) using five iterations and 21 subsets with time-of-flight resolution recovery (TrueX), computed tomography (CT)-based attenuation and scatter corrections, and a 3-mm Gaussian postprocessing filter.

The postsurgical PET scan was performed with the same study protocol ≥ 6 months after pituitary surgery to avoid any interference in uptake due to inflammatory activity.

2.5 | Image analysis

PMOD software v3.8 (PMOD Technologies, Ltd.) was used for image analysis. MRI and PET images were co-registered using the ‘Fuse it’ toolkit. The PET images were motion corrected by aligning all frames to a reference frame created by the mean position of the first three frames using the ‘motion correction’ function before co-registration to the MRI images. Tumour findings were outlined in transverse slices, creating a volume of interest (VOI) around the tumour area. For the control group, the VOIs were outlined around the pituitary gland.

The VOIs in the postsurgical scans were created in the same manner as the presurgical VOIs, around areas of suspected residual tumour tissue or inconclusive abnormal findings in postoperative MRI scans. Tracer uptake was analysed in the VOI with regard to maximum standardized uptake value (SUV\text{max}). Data from the 35- to 45-min frame was chosen for the statistical analysis. No measurements were performed for patients considered cured on the basis of combined biochemical and clinical factors and without any abnormal MRI findings.

2.6 | Tumour classification and immunohistochemical analyses

Tumour tissues samples were collected during surgery from the PitNET patients. Representative tumour tissue was confirmed in routine haematoxylin/eosin-stained sections from formalin-fixed, paraffin-embedded tissue blocks. Pituitary tumours were classified into histological subtypes according to the 2017 WHO classification based on the immunohistochemical expression of anterior pituitary hormones (growth hormone [GH], TSH, prolactin [PRL], adrenocorticotropic hormone [ACTH], luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) and pituitary-specific transcription factors (T-Pit, SF-1 and Pit-1). Plurihormonal tumours were categorized as to their clinical presentation.

The following antibodies used were as follows: anti-FSH (monoclonal, clone C10, DAKO, catalogue number M3504, dilution 1:300), anti-LH (monoclonal, clone 93C, DAKO, catalogue number M3502, dilution 1:400), anti-TSH (monoclonal, clone 0042, DAKO catalogue number M3503, dilution 1:100), anti-GH (polyclonal, catalogue number M3503, dilution 1:100).
number A0570, dilution 1:3000), anti-ACTH (monoclonal, clone 02A3, DAKO, catalogue number M3501, dilution 1:1200), anti-Pit-1 (Novus Biologicals, polyclonal, code no. NBPI-92273, dilution 1:500), anti-SF-1 (Thermo Fisher Scientific, monoclonal, clone N1665, dilution 1:100) and anti-T-Pit (TBX19) (monoclonal, clone CL6251, Atlas Antibodies, dilution 1:1000). Normal pituitary gland served as a positive control for immunohistochemical analyses with the antibodies toward anterior pituitary hormones and pituitary-specific transcription factors. For each tumour, proliferation index Ki67 was analysed (monoclonal antibody, clone MIB1, DAKO, catalogue number IR626/ GA626, ready to use) and assessed by counting the percentage of Ki67 immunolabelled cells among 2000 tumour cells in hot spots regions. Normal lymph gland served as a positive control for Ki67 immunostaining. All immunohistochemical staining was performed with Dako EnVision FLEX system and DAKO Autostainer.

The immunohistochemical analyses of anterior pituitary hormones, pituitary-specific transcription factors and SSTR were all performed with the same protocol, using specific monoclonal antibodies, as described in our previously published study. The immunoreactive score (IRS) was used for the quantification of SSTR expression, as the product of the proportion of immunoreactive cells (0 = 0%, 1 = <10%; 2 = 10%-50%, 3 = 51%-80% and 4 = >80%) and the staining intensity (0 = no staining, 1 = weak; 2 = moderate and 3 = strong). IRS scoring was performed by an experienced pathologist (OC-B) who was blinded to the cl

2.7 Statistical analysis

All statistical analyses were performed using Prism 8.0 (GraphPad Software, Inc). Normal distribution of data was tested with the Shapiro-Wilk test. Variables with continuous data are presented as means and standard deviations (SD), and variables not following normal distribution are presented as medians and interquartile ranges (IQR). Mann-Whitney U test was used for comparison of 68Ga-DOTATOC uptake in patients and controls. Spearman’s rank-order correlation was used for correlation analyses between SSTR expression and SUV\textsubscript{max}. For all tests, \( P < .05 \) was considered as statistically significant.

3 RESULTS

3.1 Preoperative 68Ga-DOTATOC PET in patients and controls

Uptake data are presented as median (IQR) values. SUV\textsubscript{max} was 15.9 (11.6-19.7), 6.8 (2.6-9.3) and 41.1 (37.4-60.0) for somatotroph, corticotroph and thyrotroph tumours, respectively (Figure 1) [see Table 2 for individual values]. The median uptake in all 15 control subjects was SUV\textsubscript{max} 13.8 (12.1-15.5). Compared to the normal pituitary gland, there was a significant difference in uptake in thyrotroph (Mann-Whitney U = 0; \( P < .01 \)) and corticotroph tumours (Mann-Whitney U = 11; \( P < .01 \)), but not for somatotroph tumours (Mann-Whitney U = 42; \( P = .27 \)). Representative PET and MRI images along with corresponding immunohistochemical images of SSTR expression for each type tumour are presented in Figure 2A-C. In addition, dynamic data of tracer uptake in tumour subtypes and the normal pituitary gland are presented in Figure 3A and B. Dynamic data for gonadotroph tumours were also presented in a previous publication.

3.2 Postoperative 68Ga-DOTATOC PET

Among the 20 patients who underwent postoperative PET scan, nine demonstrated unequivocal signs of complete tumour resection on postoperative MRI accompanied by corresponding clinical remission. The other 11 patients showed an abnormal postoperative MRI with findings of either a suspected residual tumour tissue or an inability to distinguish between scar tissue or residual tumour (Table 3). For tumours with preoperative uptake higher than the median uptake for controls (SUV\textsubscript{max} > 13.8), a cut-off level at 60% of the preoperative uptake could be observed, dividing the cured and noncured patients. A low uptake postoperatively (<60%
of the preoperative uptake) corresponded with clinical remission in all four cases. In these tumours with high uptake, a persistent SUV\textsubscript{max} postoperatively representing > 60% of the preoperative uptake corresponded with maintained hypersecretion in two cases. A figure illustrating these two groups can be found in the appendix.

### 3.3 | Histopathological characterization of PitNETs

In the eight patients with acromegaly, histopathological assessment demonstrated one pure somatotroph tumour, six somatolactotroph tumours and one plurihormonal tumour with GH, PRL, TSH, FSH and LH expression. Among patients with clinically thyrotroph tumours,

<table>
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<th>Patient</th>
<th>Clinical presentation</th>
<th>Tumour type(^a)</th>
<th>SUV\textsubscript{max} (^b)</th>
<th>IHC (^c)</th>
<th>SSTR1</th>
<th>SSTR2</th>
<th>SSTR3</th>
<th>SSTR5</th>
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Note: Abbreviations: ACTH, adrenocorticotropic hormone; GH, growth hormone; IHC, immunohistochemistry, IRS, immunoreactive score; PET, positron emission tomography; PRL, prolactin; SSTR, somatostatin receptor; SUV\textsubscript{max}, maximum standardized uptake value.

\(^a\) Determined by immunohistochemistry with monoclonal antibodies toward adenohypophyseal hormones and tumour-specific transcription factors.

\(^b\) PET data from the region of interest containing the tumour with SUV\textsubscript{max} measured over the 35- to 45-min frame.

\(^c\) IRS determined as the product of the proportion of immunoreactive cells (0 = 0%, 1 = < 10%; 2 = 10%-50%, 3 = 51%-80% and 4 = > 80%) and the staining intensity (0 = no staining, 1 = weak; 2 = moderate and 3 = strong). Group data presented as median IRS value.

\(^d\) Published previously.\(^13\)

\(^e\) No histopathological data.

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FIGURE 2  Preoperative images demonstrating MRI alone and co-registered PET and MRI images plus immunohistochemical images of SSTR expression for three patients. (A) Patient with a 10 × 20 × 10 mm large somatotroph pituitary tumour (blue arrow). There is incidental uptake in a dural mass in the left sigmoid sinus that was later diagnosed as a meningioma (green arrow). SSTR expression showed IRS 0, 12, 6, and 2 for SSTR1, SSTR2, SSTR3, and SSTR5, respectively. (B) Patient with a 3 × 3 × 4 mm small corticotroph tumour (blue arrow). There is evidently higher uptake in the normal pituitary to the left in the sella (green arrow) than in the tumour to the right (blue arrow). SSTR expression showed IRS 0, 2, 12 and 12 for SSTR1, SSTR2, SSTR3 and SSTR5, respectively. The MRI images are affected with imaging artefacts. (C) Patient with a 5 × 5 × 5 mm large thyrotroph tumour located in the superior part of the sella, paramedially to the right, in close proximity to the pituitary stalk (blue arrow). The scale is adjusted up SUV\textsubscript{max} 40 because of high uptake. SSTR expression showed IRS 0, 12, 2 and 1 for SSTR1, SSTR2, SSTR3 and SSTR5, respectively.
one patient had a pure thyrotroph tumour and two patients had a plurihormonal tumours with GH, PRL and TSH expression. Five patients with Cushing's disease and two patients with clinically NF-tumours had ACTH- and T-Pit-positive corticotroph tumours (Table 2).

TSH-producing tumours (two GH + PRL + TSH plurihormonal tumours and one pure thyrotroph tumour) expressed the highest degree of SSTR2 (median IRS 12) followed by moderately high expression of SSTR5 (median IRS 6) and SSTR3 (median IRS 6), but no expression of SSTR1 (median IRS 0).

In corticotroph tumours (silent corticotroph tumours included), there were low expression for SSTR1 and SSTR2 (median IRS 1 for SSTR1 and SSTR2), high expression of SSTR3 and SSTR5 (median IRS 12 for SSTR3 and SSTR5).

In patients with acromegaly (six somatolactotroph, one pure GH-producing and one plurihormonal tumour), SSTR expression was high for all receptors (median IRS 12 for SSTR2 and SSTR5, and 9 for SSTR3) except SSTR1 (median IRS 0) (Table 2).

### 3.4 Correlation between 68Ga-DOTATOC SUV<sub>max</sub> and SSTR expression

Spearman’s rank-order correlation coefficient between SUV<sub>max</sub> and SSTR expression was -0.31 for SSTR1 (P = .23), 0.75 for SSTR2 (P < .01), -0.37 for SSTR3 (P = .14) and -0.18 for SSTR5 (P = .48).

### 3.5 Adverse events and incidental findings

Reported adverse events after PET scanning were headache, diarrhoea and nausea. There were no serious adverse events during the study. One patient (#10, Table 2) had an incidental finding of a dural...
mass located in the proximity of the left sigmoid and transverse dural venous sinuses with high \( ^{68}\text{Ga-DOTATOC} \) uptake (SUV\(_{\text{max}} \) 26) (Figure 2A). Further clinical investigation later confirmed a meningioma.

### Discussion

This pilot study evaluated the diagnostic properties of the \( ^{68}\text{Ga-DOTATOC} \) tracer for hormone-secreting PitNETs with respect to their histopathological features and demonstrates its clinical value in pre- and postoperative imaging of thyrotroph tumours. SUV\(_{\text{max}} \) correlated with SSTR2 expression intensity, which was expressed to the highest degree in both thyrotroph (both pure TSH-producing and plurihormonal tumours) and somatotroph tumours. The study also found significant differences in tracer uptake between the normal pituitary gland and both thyrotroph and corticotroph tumours. This observation is of high clinical relevance as the diagnostic procedure of thyrotroph tumours is complex and time consuming. The process for confirmation of a thyrotroph tumour is based on proving autonomous TSH production through extensive endocrine testing,\(^{18}\) as NF-PitNETs are much more common than TSH-producing tumours.\(^{19}\) NF-PitNETs were previously demonstrated to have a significantly lower uptake of \( ^{68}\text{Ga-DOTATOC} \) compared to the normal pituitary gland in our previous study.\(^{13}\) Therefore, the tracer adds valuable information in that it may distinguish thyrotroph tumours from both NF-PitNETs and the normal pituitary gland.

In somatotroph tumours, SSTR2 and SSTR5 receptors were expressed to the highest degree (median IRS 12 for both), but with a similar tracer uptake to normal pituitary tissue (mean SUV\(_{\text{max}} \) 15.5 compared to 13.8 in normal pituitary gland). Interestingly, somatotroph tumours showed significantly lower tracer uptake compared to thyrotroph tumours despite both groups demonstrated equally high SSTR2 expression (median IRS of 12 for both groups). In contrast to thyrotroph tumours, somatotroph tumours demonstrated much higher expression of both SSTR3 and SSTR5, which paradoxically rendered a lower tracer uptake value. One hypothesis that could be derived from this is that a higher total number of receptors induce competitive interference at the receptor level, which results in a lower overall tracer uptake. Another explanation could be that the IRS scale is an ordinal scale and based on visual, semi-quantitative determination. Thereby, there could still be a numerical difference in number of receptors between these tumours, even though both showed a visually determined IRS score of 12.

On the contrary to thyrotroph and somatotroph tumours, tracer uptake in corticotroph tumours was generally lower in the tumour region compared to normal pituitary tissue (Figures 1 and 2B). This is in line with a previous study that evaluated smaller corticotroph tumours with \( ^{68}\text{Ga-DOTATATE} \), demonstrating a significant lower tracer uptake in these tumours (mean SUV\(_{\text{max}} \) 3.5 ± 2.1 in tumours compared to 5.9 ± 2.7 in normal pituitary tissue, \( P < .01 \)).\(^{14}\) Interestingly, we found higher median uptake in these tumours using \( ^{68}\text{Ga-DOTATOC} \) compared to the above mentioned study using \( ^{68}\text{Ga-DOTATATE} \),\(^{14}\) even though DOTATATE demonstrates higher affinity to the SSTR2 receptor.\(^{20}\) Further comparison is however precarious, since other methodological differences also may contribute. Even though both studies found significantly lower uptake in corticotroph tumours, the clinical significance is nonetheless limited, especially in the postoperative image assessment, as the lower uptake could not be inferred as a tumour-specific finding.

In total, three tumours demonstrated immunohistochemical expression of multiple hormones belonging to the Pit-1 cell lineage. According to the modified WHO 2017 classification of pituitary tumours, plurihormonal tumours are considered to be a distinct subgroup of tumours within the Pit-1-positive cell lineage apart from lactotroph, somatotroph, and thyrotroph tumour groups.\(^{21}\) However, in this study, they were classified according to their clinical presentation as in clinical practice, with two patients in the TSH hypersecretion group and one patient in the acromegaly group (Figure 1 and Table 2). These plurihormonal tumours demonstrated no significant difference in uptake from the pure TSH-producing and somatolactotroph tumours and could not be considered as outliers in their group.

\( ^{68}\text{Ga-DOTATOC} \) PET added limited value to the postsurgical evaluation generally. Only thyrotroph tumours demonstrated a significantly higher tumour uptake than the pituitary gland, distinguishing them from both scar tissue and normal pituitary tissue in the postoperative image assessment. As an illustrative case, one patient who presented with a thyrotroph tumour had an inconclusive abnormal MRI finding postoperatively. The tracer showed low uptake in the abnormal MRI finding, which corresponded with scar tissue (Figure 4). For the other tumours, there were no significant differences in uptake compared to the pituitary gland or high enough to be regarded as a tumour-specific finding. However, when comparing uptake levels between the pre- and postoperative PET in the same patients, tracer uptake level at 60% was observed to distinguish clinical and biochemical remission from noncurable tumours with a preoperative uptake above the median uptake of the normal pituitary (SUV\(_{\text{max}} \) 13.8). For patients with a preoperative uptake SUV\(_{\text{max}} > 13.8 \) but with a postoperative uptake SUV\(_{\text{max}} < 60\% \) of the preoperative uptake, the tracer correctly identified clinical remission in all cases and, conversely, patients with no biochemical remission demonstrated a postoperative SUV\(_{\text{max}} > 60\% \) in both cases (Table 3).

As a major strength of this study, uptake data of the different subgroups of PitNETs were accompanied by histopathological data on adenohypophyseal cell types based on both transcription factors and staining for adenohypophyseal hormones. Also, the degree of SSTR expression has been presented in a quantitative scale that provides a more detailed description of tumour heterogeneity regarding tracer uptake. We found a significant correlation between tracer uptake and the expression of the SSTR2 receptor, evoking the hypothesis that medical treatment with somatostatin analogues could be monitored in tumours with excess SSTR2 expression, that is in thyrotroph tumours. Analogously, tumours with high degree of SSTR3 expression, that is corticotroph and gonadotroph tumours, may be better detected and monitored by tracers such as DOTANOC, with
high affinity to this receptor. This may be within the scope for future studies.

The major limitation of our study was the small number of cases, a consequence of studying rare tumours. Although this study suggests a potential role of the $^{68}$Ga-DOTATOC tracer in pre- and postoperative image assessment in thyrotoph tumours, the limited number of patients still makes these results somewhat uncertain and further evaluation in larger cohorts is needed to confirm this. Uptake differences in somatotroph tumours and normal pituitary tissue were indicated in this study, but could not be proven with statistical significance, presumably because of the small sample size. For smaller tumours, there are several methodological limitations by using $^{68}$Ga-DOTATOC. First, the relatively high positron energy for $^{68}$Ga ($E_{\text{mean}} = 0.83$ MeV) needs to be considered, which yields a long positron range of $R_{\text{mean}} = 3.5$ mm, resulting in a limited intrinsic image resolution. Furthermore, the partial volume effect displays a confounding factor for tracer uptake, especially in assessing smaller tumours and smaller postoperative findings. SUV$_{\text{max}}$ may be impacted by several other factors than SSTR expression such as partial volume effect that, in turn, may be influenced by both size of the lesion as well as movements of the subjects. However, since validated methods for partial volume correction in PitNETs have not been published, no adjustments for this potential effect was performed. Instead, we present unmodified uptake data as it was measured, with a caveat of possible significant impact of partial volume effect in smaller lesion, in particular lesion under 1 cm. Also, the postoperative PET evaluations were relatively few, as postoperative evaluations had to be delayed because of the current COVID-19 pandemic.

However, even as a small pilot study, this study demonstrated a significant difference in uptake levels between thyrotoph and corticotroph tumours versus normal pituitary tissue and interesting postoperative results that cured patients may be discriminated from noncured patients based on PET uptake if tumours preoperatively presented with a high uptake. This study also presents interesting findings regarding SSTR expression in PitNETs, in particular the high SSTR3 expression in both corticotroph tumours, that could be the starting point for further, more focused studies.

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![Figure 4](image.png)

**FIGURE 4** Postoperative PET-MRI images for a patient with a thyrotoph tumour. MRI revealed an abnormal finding in the inferior right of the sella, which was inconclusive to determine residual tumour or scar tissue (blue arrow). Preoperative tumour uptake was SUV$_{\text{max}}$ 60. The abnormal finding in the postoperative MRI demonstrated an uptake of SUV$_{\text{max}}$ 6. In the anterior and left part of the sella, there is a homogenous uptake of SUV$_{\text{max}}$ 15, corresponding to normal pituitary gland (green arrow). The images are affected by dimming artefacts in the right part of the neck.
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CONFLICT OF INTEREST
The authors declare that they have no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

AUTHOR CONTRIBUTION
All authors contributed significantly to the work, meet the criteria for authorship, provided critical review of the manuscript and approved the final version.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon request.

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Figure A1  Figure demonstrating postoperative uptake profiles for six patients with a preoperative tumor uptake of SUV$_{max}$ > 13.8. Four patients with a postoperative uptake with < 60% of preoperative uptake corresponded with biochemical cure. Conversely, in two patients with tumor uptake > 60% of the preoperative uptake, the uptake corresponded with a persistent tumor.

1 = control subject also part of a TAO study (http://www.clinicaltrials.gov; identifier NCT02378298)

2 = preoperative data presented in a previous study. DOI: 10.1111/cen.14144