Diagnosis and treatment of prolactinomas: the patient's perspective anno 2025

Trigt, V.R. van

CHAPTER 8

Patient-Reported Outcomes in Refractory Hormone-Producing Pituitary Adenomas: An Unmet Need

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Victoria R. van Trigt[1], Iris C.M. Pelsma[1], Nienke R. Biermasz[1]

Author affiliations

1. Dept. of Medicine, Division of Endocrinology, and Center for Endocrine Tumors Leiden, Leiden University Medical Center, Leiden, the Netherlands

ABSTRACT

Purpose

To describe quality and outcomes of patient-reported outcome (PRO) measures (PROMs) used in patients with refractory hormone-producing pituitary adenomas, and to provide an overview of PROs in these challenging pituitary adenomas.

Methods

Three databases were searched for studies reporting on refractory pituitary adenomas. For the purpose of this review, refractory adenomas were defined as tumors resistant to primary therapy. General risk of bias was assessed using a component approach and the quality of PROM reporting was assessed using the International Society for Quality of Life Research (ISOQOL) criteria.

Results

20 studies reported on PROMs in refractory pituitary adenomas, using 14 different PROMs, of which 4 were disease specific (median general risk of bias score: 33.5% (range 6–50%) and ISOQOL score: 46% (range 29–62%)). SF-36/RAND-36 and AcroQoL were most frequently used. Health-related quality of life in refractory patients (measured by AcroQoL, SF-36/Rand-36, Tuebingen CD-25, and EQ-5D-5L) varied greatly across studies, and was not always impaired compared to patients in remission.

Conclusion

There is a scarcity of data on PROs in the subset of pituitary adenomas that is more difficult to treat, e.g., refractory and these patients are difficult to isolate from the total cohort. The patients' perspective on quality of life, therefore, remains largely unknown in refractory patients. Thus, PROs in refractory pituitary adenomas require adequate analysis using properly reported disease specific PROMs in large cohorts to enable appropriate interpretation for use in clinical practice.

INTRODUCTION

The definition of refractory hormone-producing pituitary adenomas is ambiguous. Moreover, 'refractory tumors' or refractoriness was not defined in the 4th edition of the World Health Organization Guidelines for Classification of Pituitary Tumors [1]. Throughout the current literature, multiple definitions have therefore been used depending on the type of pituitary adenoma: adenomas not responding to conventional doses of dopamine agonists (DAs) in prolactinomas [2,3,4], failure of pituitary tumor resection or radiotherapy (RT) in Cushing's Disease (CD) [5], and a combination of (a) Ki-67 index > 3%, (b) > 2% monthly growth, (c) resistance to current treatments and (d) recurrence ≤ 6 months after surgery for all pituitary adenomas [6].

Regardless of the exact definition, refractoriness can theoretically result in prolonged treatment, more interventions, higher disease burden, longer exposure to supraphysiological hormone levels, and a higher risk of hypopituitarism. Therefore, refractory patients might be more prone to impaired quality of life (QoL) and functional disability compared to patients with pituitary tumors who are cured by a single intervention [7, 8]. Biochemical and other clinician reported outcomes, however, might be discordant with patient-reported health-related QoL (HR-QoL), and other patient-reported outcomes (PROs) in pituitary tumors [9, 10, 11]. Thus, clinician reported outcomes and PROs should be used simultaneously [12, 13].

Various generic, and disease-specific patient-reported outcome measures (PROMs) have been developed, which are increasingly being used in the field of pituitary care and research. Moreover, PROMs are used to classify patients holistically, e.g., using SAGIT and ACRODAT in patients with acromegaly [14, 15]. Despite the increased use of PROMs, no previous systematic review has focused on PROs in refractory pituitary adenomas. In this systematic review, quality and outcomes of PROMS used in patients with refractory hormone-producing pituitary adenomas are described.

MATERIALS AND METHODS

This systematic review was performed in accordance with the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) guidelines [16].

Literature search and eligibility criteria

A literature search was conducted on 16-09-2022 (PubMed, Embase and Web of Science). The full search strategy, and in- and exclusion criteria are shown in Supplementary Table 1 and 2, respectively. In brief, articles reporting on PROMs in patients with refractory hormone-producing pituitary adenomas in English were included. Articles were excluded if no full text was available, if they reported on < 5 refractory patients per disease, or on non-original data.

Following consensus amongst the authors, for this review, refractory adenomas were defined as difficult-to-treat adenomas, meeting the following criteria: hormone-producing adenomas not responding to first-line therapy—either pituitary surgery for acromegaly, CD, thyrotrophic adenomas (TSH-oma) and gonadotropinomas, or the maximum tolerated dose of DAs for prolactinomas. Studies on prolactinomas resistant to surgical treatment, and studies on pituitary adenomas for which surgery was the primary treatment option, but not performed in all patients (due to contraindications), were also included. Consequently, due to paucity of data, the definition of refractory adenoma was highly inclusive. Notably, no PRO studies on patients with aggressive pituitary tumors were available.

Data extraction

All identified studies were imported into Endnote X9. Studies were screened by title and abstract and those of interest were reviewed by full-text screening. An overview of extracted data was shown in Supplementary Table 3. If data was only presented in figures without absolute values, numerical values were estimated.

PROMs

Questionnaires were the only type of PROMs used in the included articles, and therefore solely these results were reported. All PROMs were described briefly below and elaborately in Supplementary Table 4.

Disease-specific

The validated Acromegaly Quality of Life Questionnaire (AcroQoL) assesses four domains of HR-QoL (range 0–100, with higher scores indicating better HR-QoL) [17]. Tuebingen Cushing's Disease quality of life inventory (Tuebingen CD-25) and Cushing Quality of Life Questionnaire (CushingQoL), both validated in patients with CD, describe multiple dimensions of HR-QoL in CD (range 0–100, with higher scores indicating worse HR-QoL for Tuebingen CD-25 and better HR-QoL for CushingQoL) [18, 19]. Discomfort in acromegaly is quantified by Acromegaly Comorbidities & Complaints Questionnaire (ACCQ) (range 0–24, with higher scores indicating more discomfort) [20].

Pituitary specific

Pituitary Quality of Life Questionnaire (PIT QOL) describes HR-QoL in patients with pituitary disease (range 0–371, with higher scores indicating better HR-QoL [21]).

Generic HR-QoL

The 36-item short-form (SF-36) and Research and Development-36 (RAND-36) measure eight domains of HR-QoL and two component scales (range 0–100, with higher scores indicating better HR-QoL) [22, 23]. SF-12 is the shorter, 12-question version of this questionnaire [24]. EQ-5D-5L measures 5 health dimensions and includes a visual analogue score (VAS). Raw values can be transformed into index scores using population

specific value sets (index score range 0.446–1.00, with higher scores indicating worse HR-QoL, VAS: 0–100, with higher scores indicating better HR-QoL). 15-Dementional (15-D) measures general HR-QoL (range 0–1, with higher scores indicating better HR-QoL) [25].

Symptom specific

Beck Depression Inventory (BDI) determines signs and intensity of depression (range 0–63, with higher scores indicating worse depression). The Multidimensional Body-Self Relations Questionnaire (MBSRQ) measures body satisfaction (range 0–5, with higher scores indicating more satisfaction) [26, 27]. SCL-90-R assesses nine domains of psychopathology (range 0–100, with higher scores indicating more distress or disturbance) [28]. Cloninger's Tridimensional Personality Questionnaire (TPQ) measures novelty seeking (range 0–34), harm avoidance (range 0–34) and reward dependence (range 0–30), with higher scores indicating stronger emphasis on the behavior [29, 30]. Hospital Anxiety and Depression Scale (HADS) describes the severity of anxiety and depression in outpatient settings (range 0–21, with higher scores indicating more anxiety and depression) [31].

Risk of bias assessment

The quality of selected articles was assessed using a component approach for the general risk of bias [32], and the quality of reporting on PROs by the modified ISOQOL criteria for non-randomized studies [33, 34] (Supplementary table 5). The cut-off for sufficient quality of reporting was 69%, as previously published [34, 35].

Data analysis

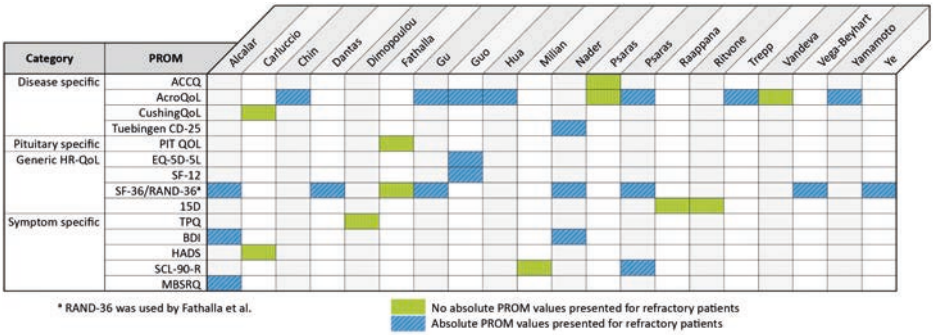
Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) was used for data collection. The primary study outcomes were PROMs. The secondary outcomes were the quality of reporting on PROMs and PRO results. Statistical analysis could not be performed, due to insufficient data to perform a meta-analysis.

RESULTS

Study selection

A total of 4554 articles were screened for eligibility, as depicted in the flowchart of article screening and inclusion in Supplementary Table 6. Twenty articles were included in the systematic review, of which 14 were cross-sectional studies, 5 were cohort studies, and 1 article reported on cross-sectional and cohort data (study characteristics: Supplementary Table 7). As some studies reported on multiple types of refractory adenomas, the number of studies reporting on patients with the included pituitary diseases were 14 for refractory acromegaly, 6 for refractory CD, and 4 for refractory prolactinoma. No studies reported on TSH-oma or gonadotropinoma. In total, 14 different PROMs reported on refractory adenomas, of which 4 were disease-specific (overview of PROMs per study: Figure 1).

Figure 1 Patient reported outcome measures for refractory patients per study



AcroQoL, Acromegaly Quality of Life Questionnaire; *ACCQ*, Acromegaly Comorbidities & Complaints Questionnaire; *BDI*, Beck Depression Inventory; *CushingQoL*, Cushing Quality of Life Questionnaire; *EQ-5D-5L*, 5-level EuroQoL-5; *HADS*, Hospital Anxiety and Depression Scale; *MBSRQ*, Multidimensional Body-Self Relations Questionnaire; *PIT QOL*, Pituitary Quality of Life; *PROM*, patient reported outcome measure; *SCL-90-R*, Symptom Checklist-90-Revised; *SF-36*, Short Form-36; *RAND-36*, Research and Development-36; *TPQ*, Cloninger's Tridimensional Personality Questionnaire; *Tuebingen CD-25*, Tuebingen Cushing's Disease Quality of Life Inventory; *15D*, 15-Dimentional.

Risk of bias assessment

Estimated risk of bias was high in all studies (median score 33.5%, range 6–50%) (Supplementary Table 8). None of the studies defined refractoriness. Two studies explicitly stated that patients with active disease were symptomatic, although none included a definition of the symptoms. Four studies reported on missing PROM data, of which only one reported < 10% missing data [36]. Quality of PROMs reporting was insufficient in all studies (median score 46%, range 29–62%) (Supplementary Table 9). Two studies included a hypothesis specifically for the used PROM [20, 37], whereas only one described the method of statistical analysis for the PROM hypothesis [37]. Solely one study described a statistical approach for missing PRO data [38].

PROMs

AcroQoL and SF-36 were most frequently used. In 8/20 studies, absolute PRO results were not reported, with only conclusions being reported on whether refractory patients scored higher or lower than patients in remission or healthy controls [20, 36, 37, 39,40,41,42,43].

Disease-specific HR-QoL

AcroQoL

AcroQoL was used in nine studies (Figure 1), of which seven reported absolute values. In these seven studies, scores of refractory acromegaly patients compared to patients in remission varied substantially, described as either comparable in the two patient groups in four studies [44,45,46,47], decreased in one study [38], or decreased except for the domain personal relations in another study [48] (Table 1). One study compared

refractory acromegaly patients to healthy controls, finding lower scores in all domains for refractory patients [49]. By contrast, two studies did not present absolute values, of which one reported comparable scores in refractory patients compared to patients in remission [20], and the other reported that AcroQoL scores improved less after treatment (TSS/RT/DA) in refractory patients compared to patients in remission [43] (mean follow-up time: 29.6 ± 19.7 months and 29.3 ± 18.8, respectively).

ACCQ

One study reported on the ACCQ in refractory acromegaly, albeit without presenting absolute values, and concluded the scores were comparable to patients in remission [20].

Tuebingen CD-25

Tuebingen CD-25 scores of refractory CD patients were reported in one study, showing no difference with CD patients in remission [50] (Supplementary Table 10).

CushingQoL

The only study reporting on the CushingQoL reported lower (i.e., worse) CushingQoL scores in refractory CD patients compared to patients in remission [39]. Absolute values were not presented.

PIT QOL

PIT QOL scores, solely reported in one study and without presenting absolute values, were comparable in refractory acromegaly patients and patients in remission [40].

Table 1 AcroQoL. AcroQoL scores for refractory patients with acromegaly per study

	Chin [47]	Gu [44]	Guo [38]	Hua [46]		Psaras [49]	Trepp [48]	Yamamoto [45][f]	
Baseline	**Mean (range) N=36**	**Median [IQR] N=44**	**Mean ± SD N=154**	**Mean ± SD N=11**	**Mean ± SD N=11**	**Mean ± SD N=14**	**Mean ± SD N=6**	**Median [IQR] N=20**	**Median [IQR] N=18**
	Before SMS	**preoperative**		**SMS (+)[a]**	**SMS (-)**			**< 65 years-old**	**≥65 years-old**
Physical	67.5 (30.0-97.5) = [c]		41.3 ± 25.5 ↓	55.1 ± 30.4 • [d]	42.3 ± 33.2 • [d]	67.7 ± 22.4 • [e]	42 ± 32 ↓	70 [31-82] =	52 [32-80] =
Psychological	74.3 (27.1-91.4) = [c]		40.1 ± 22.9 ↓	55.7 ± 24.8 • [d]	56.4 ± 29.4 • [d]	62.5 ± 20.2 • [e]	44 ± 23 ↓	61 [50-76] =	67 [50-85] =
Appearance [b]	65.7 (22.9-88.6) = [c]		33.9 ± 21.5 ↓	47.4 ± 26.2 • [d]	43.8 ± 34.5 • [d]	51.8 ± 25.3 • [e]	30 ± 21 ↓		
Personal relations [b]	82.9 (31.4-100.0) = [c]		46.3 ± 26.9 ↓	65.9 ± 24.2 • [d]	69.2 ± 28.7 • [d]	77.3 ± 17.6 • [e]	52 ± 24 =		
Total	74.6 (33.6-93.6) = [c]	64.1 [51.8-71.8] =	40.5 ± 22.9 ↓	56.1 ± 26.4 • [d]	51.3 ± 28.6 • [d]	64.9 ± 17.8 • [e]	43 ± 25 ↓	67 [42-78] =	61 [43-85] =
First follow-up	**12 weeks After starting SMS [g]**	**6 months postoperative**							
Physical	71.3 (40.0-97.5) = [c]								
Psychological	78.6 (27.1-97.1) = [c]								
Appearance [b]	72.3 (22.9-94.3) = [c]								
Personal relations [b]	80.0 (31.4-100.0) = [c]								
Total	74.1 (32.7-99.5) = [c]	82.7 [74.1- 88.6] =							
Second Follow-up	**24 weeks After starting SMS [g]**								
Physical	71.3 (42.5-97.5) = [c]								
Psychological	78.6 (27.1-97.1) = [c]								
Appearance [b]	77.1 (22.9-97.1) = [c]								
Personal relations [b]	85.7 (21.4-100.0) = [c]								
Total	77.3 (32.7-95.5) = [c]								

AcroQoL, Acromegaly Quality of Life Questionnaire; *IQR*, interquartile range; *SMS(+)*, on somatostatin analogue treatment; *SMS(-)*, not on somatostatin analogue treatment; ↓ significantly lower compared to acromegaly patients in remission; ↑ significantly higher compared to acromegaly patients in remission; • no P-value reported; = tested and no significant difference compared to controlled disease.

[a] Patients received octreotide LAR every two weeks (dose not reported).

[b] Psychological subscales.

[c] AcroQoL scores did not differ between refractory patients and patients in remission at 24 weeks .

[d] No significant difference between all refractory patients (SMS+/-) and patients compared to patients in remission. No subgroup analysis performed for SMS(+) and SMS(-) separately.

[e] Refractory patients scored significantly lower than healthy controls.

[f] Values estimated based on figure, absolute values were not presented.

[g] Patients received weekly intramuscular injections of octreotide LAR 20mg. At 12 weeks a dose escalation to octreotide LAR 30mg was permitted in case GH > 2.5 ug/L and/or IGF1 above upper limit of normal for age, but this was not obligatory.

Generic HR-QoL

SF 12/36 and RAND-36

SF-12/36 and RAND-36 were reported in nine studies (Table 2), of which eight presented absolute values. The results were inconsistent across studies and between diseases. In acromegaly patients, one study reported comparable results between refractory acromegaly patients and patients in remission [44], one reported lower scores in refractory patients except for physical functioning and general health [38] and another reported lower scores in refractory acromegaly only in the role physical, bodily pain and vitality domains [51]. The study that did not report absolute values found no difference in RAND-36 scores between refractory acromegaly and patients in remission [40].

In CD patients, one study reported comparable scores in refractory CD compared to patients in remission [50], and one reported lower scores except for the general health and vitality domains [52]. Furthermore, one study concluded no postoperative trend of improvement over time (mean 7.4 months) was observed in refractory CD patients, whereas CD patients in remission did improve postoperatively [53]. Two studies compared refractory CD patients to healthy controls, of which one found lower scores in refractory patients only for physical functioning, bodily pain and general health [54], and the other found lower scores for general health, mental health, social functioning and role emotional [49].

One study reported on SF-36 in refractory prolactinomas, finding lower scores compared to patients in remission except for the bodily pain domain [52].

EQ-5D-5L

EQ-5D-5L scales, reported in solely one study, for pain/discomfort and anxiety/depression were worse in refractory acromegaly patients compared to acromegaly patients in remission [38]. Mean EQ-5D VAS scores were 62.8 ± 21.6 in refractory acromegaly, which was similar compared to acromegaly in remission [38] (Supplementary Table 11).

15D

Two studies reported on 15D without presenting absolute values, of which one on refractory acromegaly, CD and prolactinoma patients (without performing a subgroup analysis per disease) [36], and the other reported on refractory prolactinomas and acromegaly [42]. Both studies found comparable results in refractory patients compared to patients in remission.

Table 2 SF-12 and SF-36 scores for refractory patients with acromegaly, Cushing's Disease and prolactinoma per study.

First Author, year of publication	Dantas [51]	Gu [44]	Guo [38] SF-12	Psaras [49]	Alcalar [54]
Disease	**AC**	**AC**	**AC**	**AC**	**CD**
Baseline	**Mean N=14** [a]	**Median [IQR] N=44**	**Mean ± SD N=154**	**Mean ± SD N=14**	**Mean ± SD N=8**
Physical functioning	54.09 =		49.1 ± 9.3 =	51.0 ± 25.8 •	18.63 ± 5.61 •[c]
Role physical	50.00 ↓		40.9 ± 11.4 ↓	43.2 ± 29.0 •	5.63 ± 1.99 •
Bodily pain	43.64 ↓		36.7 ± 11.7 ↓	35.7 ± 20.6 •	6.81 ± 3.52 •[c]
General health	63.36 =		32.0 ± 10.7 =	39.9 ± 29.7 •[b]	11.88 ± 3.68 •[c]
Social functioning	60.00 =		38.3 ± 12.1 ↓	43.4 ± 34.7 •	7.00 ± 2.14 •
Role emotional	45.27 =		35.1 ± 12.8 ↓	39.7 ± 31.3 •[b]	4.25 ± 1.28 •
Mental health	66.91 =		37.2 ± 5.6 ↓	38.2 ± 37.2 •[b]	20.00 ± 5.90 •
Vitality	45.45 ↓		44.7 ± 10.6 ↓	33.8 ± 29.4 •[b]	13.63 ± 5.15 •
MCS			38.9 ± 8.0 ↓		
PCS			39.6 ± 8.8 ↓		
Total		65.4 [63.2- 67.7] =			
First follow-up		**6 mos postop**			
Physical functioning					
Role physical					
Bodily pain					
General health					
Social functioning					
Role emotional					
Mental health					
Vitality					
Total		75.3 [70.1- 82.3] =			
Second follow-up					
Physical functioning					
Role physical					
Bodily pain					
General health					
Social functioning					
Role emotional					
Mental health					
Vitality					

AC, acromegaly; *CD*, Cushing's Disease; *IQR*, interquartile range; *MCS*, mental component summary; *mos*, months; *PCS*, physical component summary; *postop*, postoperative; *PRL*, prolactinoma; *SD*, standard deviation; ↓ significantly lower compared to acromegaly patients in remission; ↑ significantly higher compared to acromegaly patients in remission; • no P-value reported; = tested and no significant difference compared to controlled disease.

	Nader [50][d]	Psaras [49]	Vega-Beyhart [52]	Ye [53][d]	Vega-Beyhart [52]
	CD	CD	CD	CD	PRL
	Unclear[e] N=8	Mean ± SD N=5	Median [IQR] N=7	Unclear[g] N=7	Median [IQR] N=28
	75 =[f]	37.6 ± 32.4 •	45 [20-85]↓	55 [52-60] •	82 [48-95] ↓
	75 =[f]	25.0 ± 23.1 •	25 [0-50] ↓	29 [23-32] •	50 [0-100] ↓
	25 =[f]	44.6 ± 24.2 •	45 [25-67] ↓	58 [54-62] •	78 [45-90] =
	38 =[f]	39.7 ± 37.8 •[b]	40 [20-45] =	34 [30-39] •	48 [26-65] ↓
	62 =[f]	31.6 ± 32.9 •[b]	50 [37-62] ↓	50 [45-55] •	62 [40-75] ↓
	62 =[f]	26.0 ± 29.3 •[b]	0 [0-0] ↓	38 [32-41] •	50 [0-100] ↓
	62 =[f]	43.8 ± 42.7 •[b]	44 [16-68] ↓	56 [50-60] •	56 [36-68] ↓
	50 =[f]	47.2 ± 38.0 •	45 [10-60] =	32 [28-35] •	45 [35-67] ↓
			29 [22-53] ↓		57 [31-69] ↓
			44 [16-70] ↓		66 [36-81] ↓
				Mean 2.35 mos postop, N=6[h]	
				49 [42-52] •	
				23 [19-30] •	
				65 [60-70] •	
				28 [22-34] •	
				53 [50-69] •	
				45 [40-50] •	
				51 [45-59] •	
				25 [20-30] •	
				Mean 7.4 mos postop, N=4[h]	
				50 [45-54] •	
				30 [27-34] •	
				60 [66-64] •	
				42 [40-47] •	
				61 [58-65] •	
				58 [52-61] •	
				55 [50-60] •	
				39 [35-42] •	

[a] Number of patients not reported in article. Author provided information upon request.
[b] Refractory patients scored significantly lower than healthy controls.
[c] Refractory patients scored significantly lower than healthy controls and patients in remission (no post-hoc analysis was performed).
[d] Values estimated based on figure, absolute values were not presented.
[e] Unclear whether reported numbers concern mean or median values.
[f] All SF-36 scores were worse in refractory patients compared to patients in remission, however not significant.
[g] Unclear what the values indicate. Figure does not include a legenda.
[h] Missing data was not reported in article. Author provided information upon request.

Symptom-specific

BDI

BDI was reported in two studies, using different cut-off values. In refractory acromegaly, mean BDI scores were 18.9 ± 10.9 (Alcalar et al. used a score of > 17 points to indicate presence of depression) [54] (Supplementary Table 12). In refractory CD, 2/8 patients scored ≥ 18 points (Nader et al. described a score of ≥ 18 points as a severe depression) [50].

SCL-90-R

Two studies reported on SCL-90-R. One found higher hostility scores in refractory AC and CD than in healthy controls, and psychoticism in refractory CD [49] (Supplementary Table 13). The other, without presenting absolute values, reported higher obsessive–compulsive scores in refractory acromegaly patients compared to patients in remission 3 months after surgery, whereas no differences were observed at 12 months [41].

MBSRQ

Refractory CD patients had significantly lower MBSRQ scores for fitness and health evaluation, body areas satisfaction and mean item score compared to those in remission and healthy controls [54] (Supplementary Table 14).

HADS

The only study reporting on HADS found higher anxiety scores in refractory CD patients compared to patients in remission [39]. Absolute values were not presented.

TPQ

TPQ, reported by only one study, without presenting absolute values, found higher fear of uncertainty, fatigability and asthenia, leading to a higher total harm avoidance score in refractory CD patients compared to CD patients in remission [37].

DISCUSSION

An unequivocal definition of refractory is lacking, and data, including patient-reported outcomes, on difficult-to-treat (e.g., refractory) patients is scarce. A plethora of PROMs were used in research and care of pituitary adenomas, of which few were disease specific. The quality of reporting in the available studies was low, with a high risk of bias, leading to inconsistent PROs. Due to the paucity of data, no conclusions on HR-QoL and the contributing factors in refractory patients could be made.

Currently, no consensus on the definition of refractory is available in the literature, resulting in the application of the present definition (i.e., tumors not responding to primary therapy) for data selection. Using this definition, it should be noted that the status of refractoriness is not only dependent on tumor characteristics, but also on the

surgical experience within the treating center, as more experienced surgeons may have somewhat better outcomes. However, from a patient's perspective, this definition might implicitly reflect the impact of the disease, due to prolonged absence of disease remission and the need for secondary treatment. Furthermore, the scarcity of data influenced the present, inclusive definition, as studies reporting on PROs in the most challenging patients (persistent disease despite multimodality treatment and aggressive tumors) were lacking. Consequently, these most challenging cases could not be identified at present, and therefore warrant future in-depth systematic investigation.

Nevertheless, there were some studies reported on PROs in patients with persistent disease after primary treatment—the present definition of refractory patients—to address our clinical question. The next challenge was the use of plethora of PROMs, which were mostly generic and sometimes disease-specific. Disease-specific PROMs focus on quality-of-life domains specifically impaired in the disease of interest, allowing identification of more subtle impairments than generic questionnaires [17, 55, 56].

Despite their better sensitivity, results of the disease specific questionnaires (ACCQ, AcroQoL, Tuebingen-CD25, CushingQoL) were equally ambiguous compared to those of the less sensitive, pituitary-specific (PIT QOL), and generic HQ-QoL questionnaires (EQ-5D-5L, SF12/36, RAND-36, 15D). Surprisingly, independent of the type of questionnaire used, results of refractory patients compared to patients in remission were inconsistent; being lower in some, yet comparable in other studies. A possible explanation may lie in the fact that patients in remission report ongoing impaired quality of life.

Furthermore, there was no clear difference in outcomes between the types of adenomas. HR-QoL measured by SF-12/36 and RAND-36 varied greatly between the studies within same type of adenomas. Previous literature reported the worst HR-QoL in active CD compared to other pituitary adenomas [57], improving partially after remission [11, 58]. However, HR-QoL in refractory CD (measured by SF-12/36 or RAND-36) was not evidently lower than in other adenomas and not always worse compared to CD in remission. The symptom specific PROMS (HADS, TPQ, SCLR-90) found worse scores in varying—mostly psychological—domains, albeit inconsistent across studies. Similarly, in refractory acromegaly, subscales such as bodily pain and physical functioning (SF-12/36, RAND-36) and appearance (AcroQoL), expected to be most affected [7, 59], were not always worse compared to patients in remission. As expected, prolactinomas were the most understudied type of adenoma, with only one study reporting absolute values, thereby impeding proper comparison. Thus, overall results were inconsistent and inconclusive, regardless of questionnaire and adenoma type.

The well-known Wilson and Cleary model (WCM) [60] states that general wellbeing results from a complex interplay of physiological, clinical and social aspects. According to this model, HR-QoL can be influenced, either directly or indirectly, by six factors:

biological and psychological factors, symptom status, functional status, general health perceptions and characteristics of the environment and of the individual. In patients with pituitary adenoma, irrespective of whether they are refractory, all these factors might be affected due to prolonged supraphysiological hormone levels, leading to severe symptomatology, decreased functional status, and impaired general health perceptions. Therefore, impaired HR-QoL may be anticipated in all patients with a pituitary tumor and the impact of having a more refractory status may be difficult to distillate from other factors influencing HR-QoL.

In agreement with the WCM, we found HR-QoL in refractory acromegaly and CD was not always worse than in patients in remission. This may be caused by ongoing symptoms in patients in biochemical remission, resulting from permanent complications (e.g., arthropathy in acromegaly and osteoporotic fractures and chronic depression in CD [61,62,63,64]) leading to persistently impaired HR-QoL. Contrarily, surgery could have improved symptomatology and functional status, thereby increasing HR-QoL, without achievement of biochemical remission in refractory patients [49]. However, true differences in HR-QoL may have been concealed by biased results, use of small sample sizes and generic questionnaires in the included studies. Furthermore, questionnaires cannot grasp all aspects of life.

The importance of the use of PROs in addition to clinician-reported outcomes is well recognized in care for pituitary disease, as well as other diseases [12, 13]. Ideally, PROs should focus on issues relevant to the specific (refractory) tumor, using a combination of generic, disease-specific and symptom-specific PROMs. Although consensus on which combination of PROMs to use is lacking, our group has gained some experience in selecting PROMs, according to the three-tier Value Based Health Care approach, at each relevant timepoint within the care trajectory [65]. This approach enables individualization of care trajectories. For this purpose, we developed the Leiden Bother and Needs Questionnaire, which is currently used in clinical practice to assess patients' bother related to consequences of the disease and their need for support [66]. An example of prospective PRO research including potentially difficult-to-treat (i.e., refractory) cases is the prolactinoma research project (PRolaCT) [67]. In the future, these care and research strategies should be used in patients with refractory adenomas.

An important limitation to this systematic review was the high risk of bias and low quality of PRO reporting, limiting proper interpretation and comparability. Secondly, isolating the patients who met our definition of refractory was challenging, as information on treatment was not always presented. This led to an inhomogeneous population. Due to the quality of data, no conclusions could be drawn about HR-QoL in refractory patients, compared to those in remission. Lastly, comparison of PROs with biochemical outcomes lay beyond the scope of this review, which would be interesting to place the PROs in perspective. To adequately treat and support refractory patients,

future studies using disease-specific PROMs in large cohorts of patients with pituitary adenomas should be performed, with subgroup analyses for patients who are not in remission after primary therapy.

CONCLUSION

The current systematic review demonstrated a scarcity of high-quality data on PROs in the subset of refractory pituitary adenomas—defined as adenomas being difficult to treat. Additionally, in the current literature, data from refractory patients was difficult to isolate from the rest of the cohort, and the patients' perspective on quality of life therefore remains largely unknown in refractory patients. Thus, PROs in patients with refractory hormone-producing pituitary adenomas require adequate analysis using properly reported disease-specific PROMs in large cohorts to enable appropriate interpretation and use for clinical practice.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1 Search strategy per database

a. PubMed
("Pituitary Neoplasms"[MeSH] OR "Pituitary Neoplasm*"[tiab] OR "Hyperprolactinemia"[MeSH] OR "Hyperprolactinemia"[tiab] OR "Hyperprolactinaemia"[tiab] OR "pituitary adenoma*"[tiab] OR "Prolactinoma"[MeSH] OR "Prolactinoma*"[tiab] OR "Microprolactinoma*"[tiab] OR "Macroprolactinoma*"[tiab] OR "Giant prolactinoma*"[tiab] OR "Pituitary Tumor*"[tiab] OR "hyperpituitarism"[MeSH] OR "acromegaly"[MeSH] OR "Acromegal*"[tiab] OR "gigantism"[MeSH] OR "Gigantism"[tiab] OR "growth hormone-secreting pituitary adenoma"[MeSH] OR "growth hormone-secreting pituitary adenoma"[tiab] OR "growth hormone secreting pituitary adenoma"[tiab] OR "pituitary acth hypersecretion"[MeSH] OR "pituitary acth hypersecretion"[tiab] OR "ACTH-Secreting Pituitary Adenoma*"[tiab] OR "Corticotroph Adenoma*"[tiab] OR "Cushing syndrome"[MeSH] OR "Cushing syndrome"[tiab] OR "Cushing's Syndrome"[tiab] OR "Hypercortisolism"[tiab] OR "Cushing disease"[tiab] OR "Cushing's disease"[tiab] OR "non-functioning adenoma*"[tiab] OR "non-functioning pituitary adenoma*"[tiab] OR "non-functioning macroadenoma*"[tiab] OR "nonfunctioning adenoma*"[tiab] OR "nonfunctioning pituitary adenoma*"[tiab] OR "nonfunctioning pituitary macroadenoma*"[tiab] OR "nonfunctioning macroadenoma*"[tiab] OR "nonfunctioning microadenoma*"[tiab]) AND ("Health Care Surveys"[MeSH] OR "Health Care Survey*"[tiab] OR "Patient Outcome Assessment"[MeSH] OR "Patient Outcome Assessment*"[tiab] OR "Quality of Life"[MeSH] OR "Quality of Life"[tiab] OR "Life Qualit*"[tiab] OR "Health-Related Quality Of Life"[tiab] OR "Health Related Quality Of Life"[tiab] OR "HR-QOL"[tiab] OR "Patient Reported Outcome Measure*"[tiab] OR "Patient Reported Outcome*"[tiab] OR "Patient-Reported Outcome*"[tiab] OR "Patient Outcome Assessment*"[tiab] OR "Patient-Centered Outcome*"[tiab] OR "Survey*"[tiab] OR "Questionnaire*"[tiab] OR "patient-reported symptom*"[tiab] OR "Patient Satisfaction"[MeSH] OR "Patient satisfaction"[tiab] OR "patient-reported experience measure"[tiab] OR "Patient experience"[tiab] OR "Health Care Survey*"[tiab] OR "Healthcare Survey*"[tiab] OR "Functional Status"[MeSH] OR "Functional Status"[tiab] OR "Health Behavior"[MeSH] OR "Health Behavior"[tiab] OR "Short-Form Health Survey*"[tiab] OR "Functional status"[tiab] OR "Health behavior*"[tiab] OR "Health-Related Behavior*"[tiab] OR "Health Related Behavior"[tiab] *OR "Self report*"[tiab] OR "Self-report*"[tiab] OR "Self-report"[tiab] OR "Self-reported"[tiab] OR "Outcome instrument*"[tiab] OR "Health scor*"[tiab] OR "Health status"[tiab] OR "Health outcome*"[tiab] OR "Observer-reported"[tiab] OR "Nurse-reported"[tiab] OR "Caregiver-reported"[tiab] OR "Caregiver-reported"[tiab] OR "Partner-reported"[tiab] OR "Subjective outcome*"[tiab]* OR *"SF36"[tiab] OR "SF-36"[tiab] OR "SF 36"[tiab] OR "EQ5D"[tiab] OR "EQ-5D"[tiab] OR "EQ 5D"[tiab] OR "EORTC"[tiab] OR "NHP"[tiab] OR "Nottingham health profile"[tiab] OR "LBNQ"[tiab] OR "Subjective wellbeing"[tiab] OR "Subjective well-being"[tiab] OR "sf-20"[tiab] OR "sf-6D"[tiab] OR "ghq-12"[tiab] OR "ghq-28"[tiab] OR "ghq-30"[tiab] OR "general health questionnaire"[tiab] OR "gwbs"[tiab] OR "general well-being scale"[tiab] OR "whoqol-bref"[tiab] OR "who-qol"[tiab] OR "World Health Organization Quality of Life Scale"[tiab] OR "sip"[tiab] OR "15D"[tiab] OR "SCL-90 (-R)"[tiab] OR "Symptom Checklist 90 (revised)"[tiab] OR "SRT"[tiab] OR "symptom rating test"[tiab] OR "ACROQoL"[tiab] OR "SSS"[tiab] OR "Quality of Life Questionnaire"[tiab] OR "SSS"[tiab] OR "PASQ"[tiab] OR "Patient-assessed-Acromegaly Symptom Questionnaire"[tiab] OR "QLS-H"[tiab] OR "QoL-AGHDA"[tiab] OR "HADS"[tiab] OR "Hospital Anxiety Depression Scale"[tiab] OR "MFI-20"[tiab] OR "Multidimensional Fatigue Inventory"[tiab] OR "MDI"[tiab] OR "Major Depression Inventory"[tiab] OR "NRS-pain"[tiab] OR "Numerical Rating Scale-pain"[tiab] OR "CFQ"[tiab] OR "Cognitive Failure Questionnaire"[tiab] OR "FACT"[tiab] OR "Functional Assessment of Cancer Therapy"[tiab] OR "Social Adjustment Scale"[tiab] OR "FSFI"[tiab] OR "Female Sexual Function Index"[tiab] OR "SSQ"[tiab] OR "Social Support Questionnaire"[tiab] OR "SQ"[tiab] OR "Symptom Questionnaire"[tiab] OR "BDI"[tiab] OR "Beck Depression Inventory"[tiab] OR "MBSRQ"[tiab] OR "Multidimensional Body-Self Relations Questionnaire"[tiab] OR "PSLES"[tiab] OR "Presumptive Stressful Life Events Scale"[tiab] OR "HIT-6"[tiab] OR "Headache Impact Test scale"[tiab] OR "CSCL"[tiab] OR "Coping Strategies Checklist"[tiab] OR "AIMS2"[tiab] OR "Arthritis Impact Measurement Scale 2"[tiab] OR "CPRS"[tiab] OR "Comprehensive Psychopathological Rating Scale"[tiab] OR "MSSQ"[tiab] OR "KSQ"[tiab] OR "Kellner's Symptom Questionnaire"[tiab] OR "DCPR"[tiab] OR "Diagnostic Criteria for Psychosomatic Research"[tiab] OR "PSI"[tiab] OR "Psychosocial Index"[tiab] OR "DAQ"[tiab] OR "Dysfunction Analysis Questionnaire"[tiab] OR "iMTA"[tiab] OR "IMCQ"[tiab] OR "iPCQ"[tiab] OR "medical consumption questionnaire"[tiab])* AND ("English"[LA] NOT ("Animals"[MeSH] NOT "Humans"[MeSH]) NOT ("Case Reports"[ptyp] OR "case report"[ti] OR "Review"[ptyp] OR "review"[ti]))

b. Embase

(exp hypophysis tumor/OR "Pituitary Neoplasm*".ti,ab. OR exp hyperprolactinemia/OR "Hyperprolactinemia".ti,ab. OR "Hyperprolactinaemia".ti,ab. OR "pituitary adenoma*".ti,ab. OR exp prolactinoma/OR "Prolactinoma*".ti,ab. OR "Microprolactinoma*".ti,ab. OR "Macroprolactinoma*".ti,ab. OR "Giant prolactinoma*".ti,ab. OR "Pituitary Tumor*".ti,ab. OR exp hyperpituitarism/OR exp acromegaly/OR "Acromegal*".ti,ab. OR exp gigantism/OR "Gigantism".ti,ab. OR exp growth hormone secreting adenoma/OR "growth hormone-secreting pituitary adenoma".ti,ab. OR "growth hormone secreting pituitary adenoma".ti,ab. OR exp Cushing disease/OR "Cushing disease".ti,ab. OR "pituitary acth hypersecretion".ti,ab. OR "ACTH-Secreting Pituitary Adenoma*".ti,ab. OR "Corticotroph Adenoma*".ti,ab. OR exp Cushing syndrome/OR "Cushing syndrome".ti,ab. OR "Cushing's Syndrome".ti,ab. OR "Hypercortisolism".ti,ab. OR "Cushing's disease".ti,ab. OR "non-functioning adenoma*".ti,ab. OR "non-functioning pituitary adenoma*".ti,ab. OR "non-functioning macroadenoma*".ti,ab. OR "nonfunctioning adenoma*".ti,ab. OR "nonfunctioning pituitary adenoma*".ti,ab. OR "nonfunctioning pituitary macroadenoma*".ti,ab. OR "nonfunctioning macroadenoma*".ti,ab. OR "nonfunctioning microadenoma*".ti,ab.) AND (exp Health Care Survey/OR exp outcome assessment/OR "patient outcome assessment*" .ti,ab. OR exp Quality of Life/OR "Patient Reported Outcome Measure*".ti,ab. OR "Patient Reported Outcome*".ti,ab. OR "Patient-Reported Outcome*".ti,ab. OR "Patient Outcome Assessment*".ti,ab. OR "Patient-Centered Outcome*".ti,ab. OR "Survey*".ti,ab. OR "Questionnaire*".ti,ab. OR "patient-reported symptom*".ti,ab. OR "Life Qualit*".ti,ab. OR "Health-Related Quality Of Life".ti,ab. OR "Health Related Quality Of Life".ti,ab. OR "HR-QOL".ti,ab. OR exp patient satisfaction/OR "Patient satisfaction".ti,ab. OR "patient-reported experience measure".ti,ab. OR "Patient experience".ti,ab. OR "Health Care Survey*".ti,ab. OR "Healthcare Survey*".ti,ab. OR exp functional status/OR "Functional status".ti,ab. OR exp health Behavior/OR "Health behavior*".ti,ab. OR "Health-Related Behavior*".ti,ab. OR "Health Related Behavior".ti,ab. OR "Short-Form Health Survey*".ti,ab. *OR "Self report*".ti,ab. OR "Self-report*".ti,ab. OR "Self-reported".ti,ab. OR "Outcome instrument*".ti,ab. OR "Health scor*".ti,ab. OR "Health status".ti,ab. OR "Health outcome*".ti,ab. OR "Observer-reported".ti,ab. OR "Nurse-reported".ti,ab. OR "Caregiver-reported".ti,ab. OR "Partner-reported".ti,ab. OR "Subjective outcome*".ti,ab.* OR *"SF36".ti,ab. OR "SF-36".ti,ab. OR "SF 36".ti,ab. OR "EQ5D".ti,ab. OR "EQ-5D".ti,ab. OR "EQ 5D".ti,ab. OR "EORTC".ti,ab. OR "NHP".ti,ab. OR "Nottingham health profile".ti,ab. OR "LBNQ".ti,ab. OR "Subjective wellbeing".ti,ab. OR "Subjective well-being".ti,ab. OR "sf-20".ti,ab. OR "sf-6D".ti,ab. OR "ghq-12".ti,ab. OR "ghq-28".ti,ab. OR "ghq-30".ti,ab. OR "general health questionnaire".ti,ab. OR "gwbs".ti,ab. OR "general well-being scale".ti,ab. OR "whoqol bref".ti,ab. OR "who-qol".ti,ab. OR "World Health Organization Quality of Life Scale".ti,ab. OR "sip".ti,ab. OR "15D".ti,ab. OR "SCL-90 (-R)".ti,ab. OR "Symptom Checklist 90 (revised)".ti,ab. OR "SRT".ti,ab. OR "symptom rating test".ti,ab. OR "ACROQoL".ti,ab. OR "SSS".ti,ab. OR "Quality of Life Questionnaire".ti,ab. OR "PASQ".ti,ab. OR "Patient-assessed-Acromegaly Symptom Questionnaire".ti,ab. OR "QLS-H".ti,ab. OR "QoL-AGHDA".ti,ab. OR "HADS".ti,ab. OR "Hospital Anxiety Depression Scale".ti,ab. OR "MFI-20".ti,ab. OR "Multidimensional Fatigue Inventory".ti,ab. OR "MDI".ti,ab. OR "Major Depression Inventory".ti,ab. OR "NRS-pain".ti,ab. OR "Numerical Rating Scale-pain".ti,ab. OR "CFQ".ti,ab. OR "Cognitive Failure Questionnaire".ti,ab. OR "FACT".ti,ab. OR "Functional Assessment of Cancer Therapy".ti,ab. OR "Social Adjustment Scale".ti,ab. OR "FSFI".ti,ab. OR "Female Sexual Function Index".ti,ab. OR "SSQ".ti,ab. OR "Social Support Questionnaire".ti,ab. OR "SQ".ti,ab. OR "Symptom Questionnaire".ti,ab. OR "BDI".ti,ab. OR "Beck Depression Inventory".ti,ab. OR "MBSRQ".ti,ab. OR "Multidimensional Body-Self Relations Questionnaire".ti,ab. OR "PSLES".ti,ab. OR "Presumptive Stressful Life Events Scale".ti,ab. OR "HIT-6".ti,ab. OR "Headache Impact Test scale".ti,ab. OR "CSCL".ti,ab. OR "Coping Strategies Checklist".ti,ab. OR "AIMS2".ti,ab. OR "Arthritis Impact Measurement Scale 2".ti,ab. OR "CPRS".ti,ab. OR "Comprehensive Psychopathological Rating Scale".ti,ab. OR "MSSQ".ti,ab. OR "KSQ".ti,ab. OR "Kellner's Symptom Questionnaire".ti,ab. OR "DCPR".ti,ab. OR "Diagnostic Criteria for Psychosomatic Research".ti,ab. OR "PSI".ti,ab. OR "Psychosocial Index".ti,ab. OR "DAQ".ti,ab. OR "Dysfunction Analysis Questionnaire".ti,ab. OR "iMTA".ti,ab. OR "IMCQ".ti,ab. OR "iPCQ".ti,ab. OR "medical consumption questionnaire".ti,ab.)* AND (English.la.) NOT ("Case Report"/OR "case report".ti,ab) NOT (exp "Review"/OR "review".ti,ab.) NOT ("rct".ti,ab.) NOT (exp "Animals"/NOT exp "Humans"/)

c. Web of Science

TS=("Pituitary Neoplasm*" OR "Hyperprolactinemia " OR "Hyperprolactinaemia" OR "pituitary adenoma*" OR "Prolactinoma*" OR "Microprolactinoma*" OR "Macroprolactinoma*" OR "Giant prolactinoma*" OR "Pituitary Tumor*" OR "hyperpituitarism" OR "acromegal*" OR "gigantism" OR "growth hormone-secreting pituitary adenoma" OR "growth hormone secreting pituitary adenoma" OR "pituitary acth hypersecretion" "ACTH-Secreting Pituitary Adenoma*" OR "Corticotroph Adenoma*" OR "Cushing syndrome" OR "Cushing's Syndrome" OR "Hypercortisolism" OR "Cushing disease" OR "Cushing's disease" OR "non-functioning adenoma*" OR "non-functioning pituitary adenoma*" OR "non-functioning macroadenoma*" OR "nonfunctioning adenoma*" OR "nonfunctioning pituitary adenoma*" OR "nonfunctioning pituitary macroadenoma*" OR "nonfunctioning macroadenoma*" OR "nonfunctioning microadenoma*") AND TS=("Health Care Survey*" OR "Patient Outcome Assessment*" OR "Quality of Life" OR "Life Qualit*" OR "Health-Related Quality Of Life" OR "Health Related Quality Of Life" OR "HR-QOL" OR "Patient Reported Outcome Measure*" OR "Patient Reported Outcome*" OR "Patient-Reported Outcome*" OR "Patient Outcome Assessment*" OR "Patient-Centered Outcome*" OR "Survey*" OR "Questionnaire*" OR "patient-reported symptom*" OR "Patient satisfaction" OR "patient-reported experience measure" OR "Patient experience" OR "Health Care Survey*" OR "Healthcare Survey*" OR "Functional Status" OR "Functional Status" OR "Health Behavior" OR "Health Behavior" OR "Short-Form Health Survey*" OR "Functional status" OR "Health behavior*" OR "Health-Related Behavior*" OR "Health Related Behavior" *OR "Self report*" OR "Self-report*" OR "Self-reported" OR "Outcome instrument*" OR "Health scor*" OR "Health status" OR "Health outcome*" OR "Observer-reported" OR "Nurse-reported" OR "Caregiver-reported" OR "Caregiver-reported" OR "Partner-reported" OR "Subjective outcome*"* OR *"SF36" OR "SF-36" OR "SF 36" OR "EQ5D" OR "EQ-5D" OR "EQ 5D" OR "EORTC" OR "NHP" OR "Nottingham health profile" OR "LBNQ" OR "Subjective wellbeing" OR "Subjective well-being" OR "sf-20" OR "sf-6D" OR "ghq-12" OR "ghq-28" OR "ghq-30" OR "general health questionnaire" OR "gwbs" OR "general well-being scale" OR "whoqol-bref" OR "who-qol" OR "World Health Organization Quality of Life Scale" OR "sip" OR "15D" OR "SCL-90 (-R)" OR "Symptom Checklist 90 (revised)" OR "SRT" OR "symptom rating test" OR "ACROQoL" OR "SSS" OR "Quality of Life Questionnaire" OR "SSS" OR "PASQ" OR "Patient-assessed-Acromegaly Symptom Questionnaire" OR "QLS-H" OR "QoL-AGHDA" OR "HADS" OR "Hospital Anxiety Depression Scale" OR "MFI-20" OR "Multidimensional Fatigue Inventory" OR "MDI" OR "Major Depression Inventory" OR "NRS-pain" OR "Numerical Rating Scale-pain" OR "CFQ" OR "Cognitive Failure Questionnaire" OR "FACT" OR "Functional Assessment of Cancer Therapy" OR "Social Adjustment Scale" OR "FSFI" OR "Female Sexual Function Index" OR "SSQ" OR "Social Support Questionnaire" OR "SQ" OR "Symptom Questionnaire" OR "BDI" OR "Beck Depression Inventory" OR "MBSRQ" OR "Multidimensional Body-Self Relations Questionnaire" OR "PSLES" OR "Presumptive Stressful Life Events Scale" OR "HIT-6" OR "Headache Impact Test scale" OR "CSCL" OR "Coping Strategies Checklist" OR "AIMS2" OR "Arthritis Impact Measurement Scale 2" OR "CPRS" OR "Comprehensive Psychopathological Rating Scale" OR "MSSQ" OR "KSQ" OR "Kellner's Symptom Questionnaire" OR "DCPR" OR "Diagnostic Criteria for Psychosomatic Research" OR "PSI" OR "Psychosocial Index" OR "DAQ" OR "Dysfunction Analysis Questionnaire" OR "iMTA" OR "IMCQ" OR "iPCQ" OR "medical consumption questionnaire")* LA=(English) NOT TS=("veterinary" OR "rabbit*" OR "animal" OR "mouse" OR "mice" OR "rodent*" OR "rat*" OR "pig*" OR "porcine" OR "horse" OR "equine" OR "cow*" OR "bovine" OR "goat*" OR "sheep" OR "ovine" OR "canine" OR "dog*" OR "feline" OR "cat*") NOT TS=("Case Report") NOT TS=("review")

Search strategies used for (a) Pubmed, (b) Embase (c) Web of Science on September 16th, 2022.

Supplementary Table 2 In- and exclusion criteria

Inclusion criteria	Exclusion criteria
Population: patients with refractory hormone producing pituitary adenomas	Primarily including children Less than 5 refractory patients
Use of patient reported outcome measures	Not (yet) publicized
English language	Reviews, letters to editors, expert opinions, case reports No full text available

In- and exclusion criteria for study enrollment.

Supplementary Table 3 Data extraction

Data extracted	Data presented as
Study design	Cohort/cross-sectional
Number of participants	N
Number of refractory participants	N (%)
Population	acromegaly/CD/gonadotropinoma/NFPA/prolactinoma/ TSH-oma/control
Female gender	N (%)
Size of adenoma: macroadenoma	N (%)
Hypopituitarism	N (%)
Treatment modality	Surgery/reoperation/TSA/craniotomy/RT/LINAC RT/med/ Lanreotide/SMS/DA/CBG/Bilat. Adrenalectomy/GKS
PROM(s)	ACCQ/AcroQoL/CushingQoL/Tuebingen CD-25/PIT QOL/ BDI/EPQ-RK/EQ-5D/EQ-5D-5L/ HADS/MBSRQ/ SCL-90-R/ SF-12/SF-36/RAND-26/TPQ/15D
Results of PROMs	Mean ± SD or median [IQR] unless specified otherwise
Duration of disease	Month/year
Duration of follow-up	Week/month/year

Data extracted from included articles. *AcroQoL* Acromegaly Quality of Life Questionnaire; *ACCQ* Acromegaly Comorbidities & Complaints Questionnaire; *bilat.* bilateral; *BDI* Beck Depression Inventory; *CBG* cabergoline; *CushingQoL* Cushing Quality of Life Questionnaire; *CD* Cushing's Disease; *DA* dopamine agonist; *EQ-5D* EuroQoL-5; *EQ-5D-5L* 5-level EuroQoL-5; *GKS* gamma knife surgery; *HADS* Hospital Anxiety and Depression Scale; *IQR* interquartile range; *LINAC* linear accelerator; *MBSRQ* multidimensional body-self relations questionnaire; *med* medication; *NFPA* non-functioning pituitary adenoma; *PIT QOL* Pituitary Quality of Life; *PROM* patient reported outcome measure; *SCL-90-R* Symptom Checklist-90-Revised; *SD* standard deviation; *SF-36* Short Form 36; *RAND-26* Research and Development-36; *RT* radiotherapy; *TSA* transsphenoidal adenectomy; *TSH-oma* thyroid stimulating hormone producing pituitary adenoma; *Tuebingen CD-25* Tuebingen Cushing's disease Quality of Life Inventory; *15D* 15-dimentional.

Supplementary Table 4 Description of used PROMs

Category	PROM	Outcomes	Results (range)	Validaty in pituitary disease	Interpretation *Higher scores indicate*
Disease specific	ACCQ [1]	Type and severity of comorbidity and complaints related to acromegaly	**Total (0-24)**	-	More discomfort
	AcroQoL [2]	HR-QoL in acromegaly	Physical (0-100) Psychological (0-100) Appearance[a] (0-100) Personal relations[a] (0-100) **Total (0-100)**	AC	Better HR-QoL
	CushingQ-oL [3]	HR-QoL in Cushing's Disease	Psychosocial (0-100) Physical (0-100) **Total: (0-100)**	CD	Better HR-QoL
	Tuebingen CD-25 [4, 5]	HR-QoL in Cushing's Disease	Depression (0-100) Sexual activity (0-100) Environment (0-100) Eating behavior (0-100) Bodily restrictions (0-100) Cognition (0-100) **Total (0-100)[b]**	CD	Worse HR-QoL
Pituitary specific	PIT QOL [6]	HR-QoL in patients with pituitary disease	General and emotional (0-126) Social (0-56) Health problems related to pituitary disease (0-140) Treatment related (0-21) Relationship with physician (0-28) **Total (0-371)**	-	Better HR-QoL
Generic HR-QoL	EQ-5D-5L [8, 9]	General HR-QoL	Mobility (0-5) Self-care (0-5) Usual activities (0-5) Pain/discomfort (0-5) Anxiety/depression (0-5) **EQ-5D index scores (0-1)** **VAS (0-100)**	-	Worse HR-QoL
	SF12/ SF-36 / RAND-36 [11-13]	General HR-QoL	Physical functioning (0-100) Role physical (0-100) Bodily pain (0-100) General Health (0-100) Social functioning (0-100) Role emotional (0-100) Mental health (0-100) Vitality (0-100) **Mental component score (0-100)** **Physical component score (0-100)**	-	Better HR-QoL
	15D [14]	General HR-QoL	Moving (0-1) Seeing (0-1) Hearing (0-1) Breathing (0-1) Sleeping (0-1) Eating (0-1) Speech (0-1) Eliminating (0-1) Usual activities (0-1)	-	Better HR-QoL

Supplementary Table 4 Description of used PROMs *(continued)*

Category	PROM	Outcomes	Results (range)	Validaty in pituitary disease	Interpretation *Higher scores indicate*
			Mental functioning (0-1) Discomfort (0-1) Depression (0-1) Distress (0-1) Vitality (0-1) Sexual function (0-1) **Total (0-1)**		
Symptom specific	TPQ [15, 16]	Habitual behavior	Novelty seeking (0-34) Harm avoidance (0-34) Reward dependence (0-30)	-	Stronger emphasis on habitual behavior
	BDI [18]	Signs and intensity of depression	**Total (0-21)**[c]	-	Worse depression
	HADS [21]	Depression and anxiety in hospital or outpatient clinic settings	**Total (0-21)**	-	More anxiety and depression
	SCL-90-R [22]	Psychopathology	Somatization (0-100) Obsessiveness-compulsiveness (0-100) Interpersonal sensitivity (0-100) Depression (0-100) Anxiety (0-100) Hostility (0-100) Phobic anxiety (0-100) Paranoid ideation (0-100) Psychoticism (0-100) **Global severity Index (0-100)** **Positive Symptom Distress Index (0-100)** **Positive Symptom Total (0-100)**	-	Higher distress or disturbance
	MBSRQ [25, 26]	Body satisfaction	Appearance evaluation (1-5) Appearance orientation (1-5) Fitness evaluation (1-5) Fitness orientation (1-5) Health evaluation (1-5) Health orientation (1-5) Body areas satisfaction (1-5) **Mean item score** (1-5)	-	More body image satisfaction

AcroQoL Acromegaly Quality of Life Questionnaire; *ACCQ* Acromegaly Comorbidities & Complaints Questionnaire; *BDI* Beck Depression Inventory; *CushingQoL* Cushing Quality of Life Questionnaire; *EQ-5D-5L* 5-level EuroQoL-5; *GHD* growth hormone deficiency; *HADS* Hospital Anxiety and Depression Scale; *MBSRQ* multidimensional body-self relations questionnaire; *NA* not applicable; *NHP* Nottingham Health Profile; *PIT QOL* Pituitary Quality of Life; *PROM* patient reported outcome measure; *SCL-90-R* Symptom Checklist-90-Revised; *SF-36* Short Form 36; *RAND-26* Research and Development-36; *TPQ* Cloninger's Tridimensional Personality Questionnaire; *Tuebingen CD-25* Tuebingen Cushing's disease Quality of Life Inventory; *15D* 15-dimentional.

[a] Psychological subscale.

[b] Nader et al. [28] presented categorized results (mild/severe). Mild: scores > percentile rank 84 of age- and gender-specific cut-off values. Severe: scores > percentile rank 95 of age- and gender-specific cut-off values.

[c] Alcalar et al. [29] and Nader et al. [28] presented categorized results using different cutoff values. Alcalar et al.: <17 points: absence of depression. ≥17 points: presence of depression. Nader et al.: ≤10 points: no depression, 11-17 points: mild to moderate depression, ≥18 points: severe depression.

[d] The 34-item version was used.

[e] More negative scores also indicate bigger discrepancy between perceived and ideal body type.

[f] IPAQ-6 is the short version of IPAQ.

Supplementary Table 5 ISOQOL scoring details

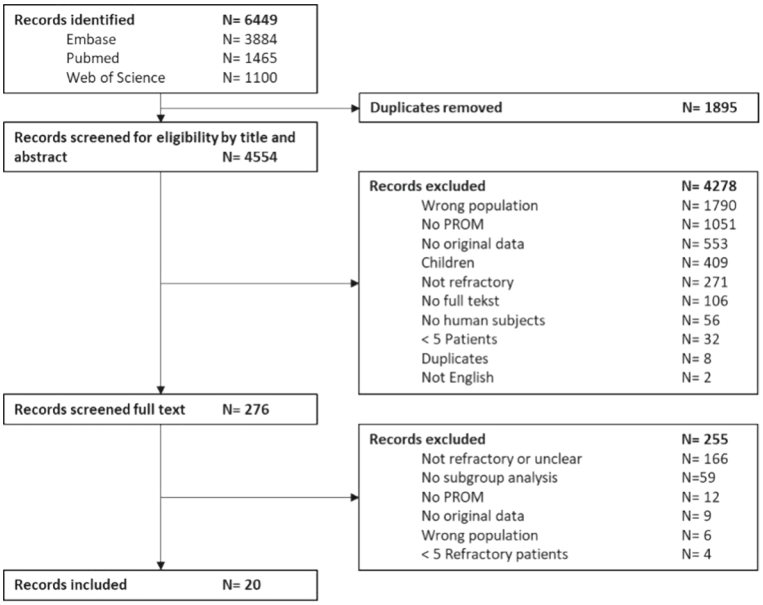
Section	Criterium	Scoring details
Title and abstract	The PRO should be identified as an outcome in the abstract	
	For 1° outcome: The title of the paper should be explicit as to the cohort study including a PRO	This item was scored 1 if at least quality of life, wellbeing, symptoms or related terms were mentioned in the title
Introduction, background and objectives	The PRO hypothesis should be stated and should specify the relevant PRO domain(s) if applicable	
	For 1° outcome: The introduction should contain a summary of PRO research that is relevant to the cohort study	
	For 1° outcome: Additional details regarding the hypothesis should be provided, including the rationale for the selected domain(s), the expected direction(s) of change, and the time points for assessment	
Outcomes registration	The mode of administration of the PRO tool and the methods of collecting data (e.g. telephone, other) should be described	
	The rationale for choice of the PRO instrument used should be provided	This item was also scored 1 if the used PROM was disease-specific
	Evidence of PRO instrument validity and reliability should be provided or cited	
	The intended HRQL data collection schedule should be provided	This item was scored NA in cross-sectional studies
	PROs should be identified in the trial protocol; post hoc analyses should be identified	This item was scored NA if there was no need for post hoc testing because only two groups were compared
	The status of PRO as either a primary or secondary outcome should be stated	This item was also scored 1 if the PROM was the only outcomes and therefore clearly the primary outcome
	For 1° outcome: A citation for the original development of the PRO instrument should be provided	
	For 1° outcome: Windows for valid PRO responses should be specified and justified as being appropriate for the clinical context	
Sample size	For 1° outcome: There should be a power/sample size calculation relevant to the PRO based on a clinical rationale (e.g. anticipated effect size)	
Statistical methods	There should be evidence of appropriate statistical analysis and tests of statistical significance for each PRO hypothesis tested	
	Statistical approaches for missing data should be explicitly stated, and the extent of missing data should be stated	This item was scored 1 if explicitly stated that there was no missing data
	For 1° outcome: The manner in which multiple comparisons have been addressed should be provided	
Participant flow	A flow diagram or a description of the allocation of participants (if applicable) and those lost to follow-up should be provided for PROs specifically	This item was scored NA in cross-sectional non-intervention studies
	The reasons for missing data should be explained	
Baseline data	The study patients' characteristics should be described, including baseline PRO scores	

Supplementary Table 5 ISOQOL scoring details *(continued)*

Section	Criterium	Scoring details
Outcomes and estimation	The analysis of PRO data should account for survival differences between treatment groups if relevant	This item was scored NA if survival was not an outcome
	Results should be reported for all PRO domains (if multi-dimensional) and items identified by the reference instrument (i.e. not just those that are statistically significant)	
	The proportion of patients achieving predefined responder definitions should be provided where relevant	This item was scored NA if there was no PROM-based responder definition
Limitations	The limitations of the PRO components of the study should be explicitly discussed	
Generalizability	Generalizability issues uniquely related to the PRO results should be discussed, if applicable	
Interpretation	The clinical significance of the PRO findings should be discussed	This item was only scored 1 in studies that explicitly described the meaning and importance of the PRO findings in clinical context
	The PRO results should be discussed in the context of the other clinical studies	
Protocol	A copy of the instrument should be included if it has not been published previously (1 if published previously)	
Percentage of items reported by study (%)		The percentage was calculated as total points divided by the number of applicable items, multiplied by 100%

International Society for Quality of Life Research (ISOQOL) criteria modified for non-randomized controlled trials with details about scoring of this review. *1° outcome* primary outcome; *NA* not applicable; *PRO* patient reported outcome; *PROM* patient reported outcome measure.

Supplementary Table 6 Flowchart of article screening and enrollment



Flowchart of article screening and enrollment that was used in PubMed, Embase and Web of Science (searched on September 16th, 2022). *PROM* patient reported outcome measure.

Supplementary Table 7 Study characteristics per study

First author, Study design	Population	Subgroup	N	Treatment	Age in years
Alcalar [29] Cross-sectional study	CD, Healthy controls	Total	Total: 80 CD: 40 Control: 40	Primary: Surgery: 40 (100.0%) Additional: None: 29 (72.5%) Bilat. adrenalectomy[1]: 4 (10.0%) GKS: 3 (7.5%) Bilat adrenalectomy + GKS: 4 (10.0%)	Total: NR CD: 39.6 ± 10.6 Control: 35.66 ± 9.1
	Refractory	**8 (20.0%)**	**NR**	**NR**	**NR**
Carluccio [27] Cross-sectional study	CD	Total	102	TSA: 102 (100.0%)[2]	43.1 (range 14-73)
	Refractory	**8 (7.8%)**	**NR**	**NR**	**NR**
Chin [30] Cohort study	AC	Total	58	Current: Lanreotide: 58 (100.0%) Previous: Surgery only: 40 (69.0%) GKS only: 1 (1.7%) Surgery + GKS +/- RT 12: (20.7%)[3] None: 5 (8.6%)	47 (range 21-72)
	Refractory	**36 (62.1%)**	**NR**	**NR**	**NR**
Dantas [31] Cross-sectional	AC	Total	42	Surgery: 32 (76.2%) Two surgeries: 10 (23.6%) Surgery + RT: 14 (34.4%) Primary med: 10 (23.8%)	49.6, 95% CI: 45.6-53.7
	Refractory	**14 (33.3%)[5]**	**NR**	**NR**	**NR**
Dimopoulou [32] Cross-sectional Study	CD, NFPA, Healthy controls	Total	Total: 210 CD: 50 NFPA: 60 Control: 100	Total: NR CD: Surgery: 49 (98.0%) RT: 13 (26.0%) Med: 5 (10.0%) NFPA: Surgery: 52 (86.7%) RT: 15 (25.0%) Med: 0 (0.0%) Control: NA	Total: NR CD: 46.4 ± 11.6 NFPA: 60 ± 10.6 Control: 46.4 ± 11.6
	Refractory	**CD: 13 (26.0%)**	**NR**	**NR**	**NR**
Fathalla [33] Cross-sectional study	AC, incidentalomas	Total	20	Surgery: 20 (100.0%) Med: 7 (35.0%) RT: 1 (5.0%) Reoperation: 5 (25.0%)	42 ± 13.5
	Refractory	**6 (30.0%)**	**NR**	**NR**	**NR**
Gu [34] Cohort study	AC	Total	154	TSA: 154 (100.0%) SMS before surgery: 29 (19.2%)	43.9 ± 12.3
	Refractory	**44 (28.7%)**	**NR**	**NR**	**43.6 (12.9%)**

[1] Of which adenomectomy 27 (67.5%), hemihypophysectomy 8 (20.0%), adenomectomy + hemihypophysectomy 3 (7.5%), craniotomy 2 (5.0%).
[2] surgery + GKS: 9 (15.5%), surgery + GKS + CRT: 3 (5.2%).
[3] Age at diagnosis.
[4] Percentages of micro- and macroadenomas in men add up to 113%.
[5] Number of patients not reported in article. Data was shared by author upon request.
[6] Percentage of NFPA + CD (N=110).
[7] Median tumor volume 3.8 [IQR 1.4-6.2].
[8] Follow-up time 11 months ± 3.1 months.

Sex (female)	Macroadenoma	Hypopituitarism	Duration disease	Duration follow-up
Total: 55 (68.8%) CD: 31 (77.5%) Control: 24 (60.0%)	10 (25.0%)	Any: NR TSH: 7 (17.5%) LH/FSH: 3 (7.5%) DI: 1 (2.5%) ACTH: 4 (10.0%)	NR	NA
NR	**NR**	**NR**	**NR**	**NA**
78 (76.5%)	22 (21.6%)	34 (33.3%)	NR	NA
NR	**NR**	**NR**	**NR**	**NA**
29 (50.0%)	NR	0 (0.0%)	NR	24 w
NR	**NR**	**0 (0.0%)**	**NR**	**NR**
22 (52.4%)	Not reported correctly[4]	NR	12.74 y, CI 95%: 11.64-15.83	NA
NR	**NR**	**NR**	**NR**	**NA**
Total: 144 (68.6%) CD: 41 (82.0%) NFPA: 21 (35.0%) Control: 82 (82.0%)	Total[6]: 60 (54.5%) CD: 10 (20.0%) NFPA: 50 (83.3%)	Total any[f]: 84 (70.0%) CD any: 32 (64.0%) NFPA any: 45 (75.0%)	NR	NA
NR	**NR**	**NR**	**NR**	**NA**
11 (55.0%)	NR[7]	4 (20.0%)	NR[8]	NA
NR	**NR**	**NR**	**NR**	**NA**
76 (50.3%)	NR	NR	NR	6 mos
20 (45.5%)	**NR**	**NR**	**NR**	**NR**

Supplementary Table 7 Study characteristics per study *(continued)*

First author, Study design	Population	Subgroup	N	Treatment	Age in years
Guo [35] Cross-sectional	AC	Total	327	Surgery 265 (81.0%)[9] Med: 160 (48.9%)[10] RT: 110 (33.6%)	39.2 ± 9.5
		Refractory	**154 (47.1%)**	**NR**	**NR**
Hua [36] Cross-sectional	AC	Total	52	Total: NR Controlled: Surgery: 28 (93.3%) Reoperation: 10 (33.3%) Lanreotide: 13 (43.3%) RT: NR[12] (64.0%)	51.9 ± 10.1
		Refractory	**Total: 22 (42.3%) SMS (+): 11 (21.2%) SMS (-): 11 (21.2%)**	**Total: Surgery: 16 (72.7%) Reoperation: 0 (0.0%) Lanreotide: 11 (50.0%) RT: 3 (13.6%) SMS(+): Surgery: 9 (81.8%) Reoperation: 0 (0.0%) RT: 2 (18.2%) SMS (-): Surgery: 7 (63.6%) Reoperation: 0 (0.0%) RT: 1 (9.1%)**	**Total: 52.0 ± 12.1 SMS (+): 48.9 ± 12.7 SMS (-): 55.0 ± 11.1**
Milian [38] Cohort study	AC, CD, PRL, NFPA, other[18]	Total	Total: 106 AC: 29 CD: 14 PRL: 12 NFPA: 39 Other: 12[15]	TSA: 106 (100.0%) RT: 4 (3.8%)	48.0 ± 16.0
		Refractory	**Total:14(13.2%) AC: 10 (34.5%) CD[17]: 3 (21.4%) PRL[q,18]: 1(14.3%)**	**NR**	**NR**
Nader [28] Cross-sectional study	CD	Total	54	Primary: TSA: 54 (100.0%) RT: 3 (5.6%) Bilat. adrenalectomy: 4 (74.0%) Reoperation Nelson's Tumor: 1 (1.9%)	48.0 ± 15.5
		Refractory	**8 (14.8%)**	**NR**	**NR**

[9] Endoscopic TSA 131 (40.1%), microscopic TSA 122 (37.3%), craniotomy 12 (3.7%).
[10] SMS 139 (42.5%), DA 70 (21.4%), SMS+DA 49 (15.0%).
[11] Mean time from initial treatment to surveys was 10 ± 6.2 years.
[12] Number of patients who received RT not reported. Percentage cannot be converted to an absolute value due to unreported missing data or a typing error.
[13] Patients on replacement therapy reported only. Unclear if all patients with hypopituitarism were on replacement therapy.
[14] Total number of refractory patients with macroadenoma not reported. Percentage reported does not correspond with the sum of SMS(+) and SMS (-) and cannot be converted to a number of patients.
[15] Rathke's cleft cyst, sellar colloid cysts.
[16] Number of patients with any hypopituitarism not reported. Percentages cannot be converted to numbers due to unreported missing data or a typing error.
[17] Refractory CD and PRL patients were not included in further analysis, as N<5.
[18] Data available of 7 patients, missing data N=5.
[19] Average time between surgery and completion of questionnaires is 3 years (range 1 - 6 years).

	Sex (female)	Macroadenoma	Hypopituitarism	Duration disease	Duration follow-up
	201 (61.5%)	NR	NR	NR[11]	NA
	NR	**NR**	**NR**	**NR**	**NA**
	25 (50.0%)	35 (67.3%)	Any: 16 (30.8%) TSH: 11 (2.1%) ACTH: 15 (2.9%) FSH/LH: 6 (11.5%)[13]	12.6 ±7.1 y	NA
	Total: **8 (36.4%)** **SMS (+):** **5 (45.5%)** **SMS (-):** **3 (27.3%)**	**Total:** **NR[14] (75.0%)** **SMS (+):** **10 (90.9%)** **SMS (-):** **6 (54.5%)**	**Total:** **4 (18.2%)** **SMS (+):** **3 (27.3%)** **SMS (-):** **1 (9.1%)**	**Total:** **10.0 ±7.3** **SMS(+):** **11.1 ± 8.2** **SMS (-):** **8.8 ± 6.4**	**NA**
	69 (65.1%)	NR	Preoperative: Any: 35 (33.0%) 3 mos postoperative: Any: NR (24.1%)[16]	NR	12 mos
	NR	**NR**	**NR**	**NR**	**NR**
	41 (75.9%)	5 (9.3%)	NR	NR[19]	NA
	NR	**NR**	**NR**	**NR**	**NA**

Supplementary Table 7 Study characteristics per study *(continued)*

First author, Study design	Population	Subgroup	N	Treatment	Age in years
Psaras [1][20] Cross-sectional study	AC	Total	55	Primary: Surgery 55 (100.0%) Additional: Reoperation: 8 (14.5%) RT: 5 (9.1%) Med: 15 (27.3%)	54.1 ± 15.1
		Refractory	**18 (32.7%)**	**NR**	**NR**
Psaras [39][t] Cross-sectional study	AC, Healthy controls	Total	Total: 89 AC: 37 CD: 24 Control: 28	Total any surgery: 61 (100.0%)[21] AC TSA: 36 (97.3%) CD TSA: 24 (100.0%)	Total: NR AC: 52.1 ± 14.7 CD: 52.6 ± 15.7 Control: 48.9 ± 2 1.3
		Refractory	**Total: 19 (21.3%) AC: 14 (37.8%) CD: 5 (20.8%)**	**NR**	**NR**
Raappana [40] Cohort study	AC, CD, PRL, NFPA	Total	Total: 98 AC: 22 CD: 6 PRL: 17 NFPA: 53	Total: TSA: 92 (93.9%) Craniotomy: 12 (12.2%) DA treatment: 7 (7.1%) RT: 14 (14.3%) AC: Reoperation: 7 (31.8%) Craniotomy: 4 (18.2%) Med: 9 (40.9%) RT: 6 (27.2%) CD: Reoperation: 2 (33.3%) Craniotomy: 0 (0.0%) Med:0 (0.0%) RT: 0 (0.0%) PRL: Reoperation: 1 (5.9%) Craniotomy: 4 (23.5%) med: 7 (41.2%) RT: 2 (11.8%) NFPA: Reoperation: 12 (22.6%) Craniotomy: 4 (1.9%) Med: 0 (0.0%) RT: 6 (11.3%)	Total: mean 52.8 (95% CI: 49.6-56) AC: Mean 45.0 (95% CI: 39.0-51.0) CD: Mean 34.8 (95% CI: 20.0-50.0) PRL: Mean 46.4 (95% CI: 40.4-52.4) NFPA: Mean 60.0 (95% CI: 56.2-64.2)
		Refractory	**Total: 13 (13.3%) AC[23]: 3 (13.6%) CD[w]: 1 (16.7%) PRL: 5 (29.4%)**	**NR**	**NR**

[20] Psaras et al. [1] and Psaras et al. [39] report on overlapping populations.
[21] Percentage of AC + CD patients.
[22] All 23 CD patients received replacement therapy because of hypocortisolism.
[23] Refractory AC and CD patients were not included in further analysis as N<5.

	Sex (female)	Macroadenoma	Hypopituitarism	Duration disease	Duration follow-up
	28 (50.9%)	48 (87.3%)	NR	NR	NA
	NR	**NR**	**NR**	**NR**	**NA**
	Total: 54 (55.1%) AC: 18 (48.6%) CD: 17 (70.8%) Control: 19 (67.9%)	Total: 36 (59.0%)[u] AC: 32 (86.5%) CD: 4 (16.7%)	Total any: 16 (26.2%)[u] CD any: 13 (54.2%)[22] AC any: 3 (8.1%)	NR	NA
	NR	**NR**	**NR**	**NR**	**NA**
	Total: 53 (54.1%) AC: 10 (45.5%) CD: 5 (83.3%) PRL: 12 (70.5%) NFPA: 26 (48.1%)	Total: 82 (83.7%) AC: 16 (72.7%) CD: 2 (33.3%) PRL: 11 (64.7%) NFPA: 53 (100%)	Total any: 50 (51.0%) AC any: 9 (40.9%) CD any: 1 (16.7%) PRL: 8 (47.1%) NFPA: 32 (60.4%)	NR	Total: mean 6.3 y (95% CI: 5.4-7.1) CD: mean 6.0 y (95% CI: 1.1-10.8) AC: mean 7.8 y (95% CI: 6.1-9.5) PRL: mean 9.4 y (95% CI: 7.5-11.) NFPA: mean 4.7 y (95% CI: 3.6-5.7)
	NR	**NR**	**NR**	**NR**	**NR**

Supplementary Table 7 Study characteristics per study *(continued)*

First author, Study design	Population	Subgroup	N	Treatment	Age in years
Ritvonen [41] Cross-sectional	AC, CD, PRL, TSH, GON	Total	Total: 100 AC: 47 CD: 21 PRL: 26 TSH[24]: 2 GON: 4 Control: 4924	Total: TSA 100 (100.0%) Reoperation: 6 (6.0%) Med: 37 (37.0%) RT: 8 (8.0%) AC: TSA: 47 (100.0%) Reoperation: 3 (6.4%) RT: 5 (10.6%) Med: 16 (34.0%) CD: TSA: 21 (100.0%) Reoperation: 2 (9.5%) RT: 1 (4.8%) Med: 5 (23.8%) GON: TSA: 4 (100.0%) Reoperation: 1 (25.0%) RT: 2 (50.0%) Med: 0 0.0%) PRL: TSA: 26 (100.0%) Reoperation: 0 (0.0%) RT: 0 (0.0%) Med: 16 (61.5%)	Total: 53.1 ± 1.4 AC: 56.3 ± 12.5 CD: 52.3 ± 12.8 GON: 48.3 ± 17.0 PRL: 47.3 ± 16.7
		Refractory	**Total[25]: 10 (10.0%)** **AC: 5 (10.6%)** **CD[26]: 1 (4.8%)** **GON: 0 (0.0%)** **PRL[2]: 4 (15.4%)**	**NR**	**NR**
Trepp [42] Cross-sectional study	AC, NFPA	Total	Total: 55 AC: 33 NFPA: 22	Total: TSA only: 26 (47.3%) TSA + RT: 6 (10.9%) Surgery + med: 2 (3.6%) TSA + RT + med: 17 (30.9%) Craniotomy + RT: 1 (1.8%) Craniotomy + TSA + RT: 2 (3.6%) RT only: 1 (1.8%) AC: TSA only: 10 (30.3%) TSA + RT: 3 (9.1%) surgery + med: 2 (6.1%) TSA + RT + med: 17 (51.5%) RT only: 1 (6.1%) NFPA: TSA only: 16 (72.7%) TSA + RT: 3 (13.6%) Craniotomy + RT: 1 (4.5%) Craniotomy + TSA + RT: 2 (9.1%)	Total: NR AC: 50.8 ± 10.7 NFPA: 61.5 ± 14.1
		Refractory	**6 (18.2%)**	**NR**	**NR**

[24] TSH-producing adenoma not included in further analysis by author.
[25] Table 1 reports 10 patients not in hormonal remission, however in the text 9 patients are reported to have hormonally active disease.
[26] Refractory CD and PRL patients were not included in further analysis as N<5.

	Sex (female)	Macroadenoma	Hypopituitarism	Duration disease	Duration follow-up
	Total: 58 (58.0%) AC: 21 (44.7%) CD: 18 (85.7%) GON: 2 (50.0%) PRL 16 (61.5%)	Total: 72 (72.0%) AC: 39 (83.0%) CD: 7 (33.3%) GON: 3 (75.0%) PRL: 21 (80.8%)	Total: 43 (43.9%) AC: 21 (44.7%) CD: 10 (47.6%) GON: 2 (50.0%) PRL: 7 (26.8%)	NR	NA
	NR	**NR**	**NR**	**NR**	**NA**
	Total: 24 (43.6%) AC: 14 (42.4%) NFPA: 10 (45.5%)	Total: 40 (72.7%) AC: 19 (57.%) NFPA: 21 (95.5%)	NR	AC: 15.5 ± 11.2 y NFPA: 6.5 ± 7.9 y	NA
	NR	**NR**	**NR**	**NR**	**NA**

Supplementary Table 7 Study characteristics per study *(continued)*

First author, Study design	Population	Subgroup	N	Treatment	Age in years
Vandeva [43] 1. Cross-sectional 2. Cohort study	AC	Total	**Cross-sectional:** Total: 212 Active: 100 Controlled: 112 **Cohort**[27]**:** Total: 70 Controlled: 45	**Cross-sectional**: Total: TSA: 121 (57.1%) 2 or more TSA: 57 (26.9%) RT: 47 (22.2) Med: 105 (49.5%) Active: TSA: 44 (44.0), 2 or more TSA: 25 (25.0%) RT: 17 (17.0%) Med: 41 (41.0%) Controlled: TSA: 77 (68.8%) 2 or more TSA: 32 (28.6%) RT: 30 (26.8%) Med: 64 (57.1%) **Cohort**: Total: TSA: 43 (61.4) 2 or more TSA: 25 (35.7%) RT 19 (27.1%) Med: 58 (82.9%)	**Cross-sectional**: Total: NR Active: 49.5 ± 12.9 Controlled: 52.3 ± 11.6 **Cohort**: NR
		Refractory	**Cross-sectional:** **0 (0.0%)** **Cohort** **25 (35.7%)**	**Cross-sectional:** **-** **Cohort:** **TSA 12 (48.0%)** **2 or more TSA: 11 (44.0%)** **RT: 6 (24%)** **Med: 25 (88.0%)**	**NR**

[27] subset of patients with active disease at time of cross-section were enrolled in cohort study.
[28] Numbers do not correspond with percentage due to not reported missing data or a typing error.

	Sex (female)	Macroadenoma	Hypopituitarism	Duration disease	Duration follow-up
	cross-sectional: Total: 134 (63.2%) Active: 61 (61.0%) Controlled: 73 (65.2%) **Cohort**: Total: 48 (68.6%)	NR	**Cross-sectional**: Total: 77 (35.2%) Active: 44 (39.3%)[28] Controlled: 33 (33.0%)[35] **Cohort**: Total: NR Controlled: 12 (28.9%)	**Cross-sectional:** Active: 6.9 ± 7.5 y Controlled: 6.9 ± 7.8 y **Cohort**: NR	**Cross-sectional**: NA **Cohort**: Total: NR Controlled: 29.3 ± 18.8 mos
	Cross-sectional: - **Cohort:** **17 (68.0%)**	**NR**	**Cross-sectional:** - **Cohort:** **7 (28.0%)**	**NR**	**Cross-sectional:** - **Cohort:** **29 ± 19.7 mos**

Supplementary Table 7 Study characteristics per study *(continued)*

First author, Study design	Population	Subgroup	N	Treatment	Age in years
Vega-Beyhart [44] Cross-sectional study	AC, CD, PRL	Total	Total: 175 AC: 48 CD: 30 PRL: 53 NFPA: 44	Total: Surgery: 76 (43.4%) CBG: 102 (58.3%) LINAC RT: 37 (21.1%) AC total: Surgery: 30 (62.5%) CBG: 25 (52.1%) LINAC RT: 20 (41.7%) CD total: Surgery: 28 (90.0%) CBG: 25 (83.3%) LINAC RT: 10 (33.3%) PRL total: Surgery: 6 (11.3%) CBG: 49 (92.5%) LINAC RT: 2 (3.8%) NFPA total: Surgery: 12 (27.2%) CBG: 19 (43.2%) LINAC RT: 5 (11.4%)	Total: 44 ± 14 AC: Total: NR Controlled: 36 [IQR 27-51] CD: Total: NR Controlled: 29 [IQR 25-37] PRL: Total: NR Controlled: 30 [IQR 25-39] NFPA: 44 [IQR 36-54]
		Refractory	**Total: 58 (33.1%)** **AC 0 (0.0%)** **CD: 7 (23.3%)** **PRL 28 (52.8%)**	**CD:** **Surgery: 7 (100.0%)** **CBG: 3 (42.9%)** **LINAC RT: 3 (42.9%)** **PRL:** **Surgery: 4 (14.3%)** **CBG 27: (96.4%)** **LINAC RT: 1 (3.6%)**	**Total:** **NR** **CD:** **27 [IQR 19-38]** **PRL:** **27 [IQR 21-34]**
Yamamoto [45] Cross-sectional study	AC	Total	74	Surgery only 34 (45.9%) Med after surgery: 22 (29.7%) Med only: 9 (12.2%) RT 9 (12.2%) RT + med + surgery: 8 (10.8%) RT after surgery: 1 (1.2%)	62.0 [IQR 50.7-70.0]
		Refractory	**38 (51.1%)**	**NR**	**NR**

[29] Total median tumor size (cm): 1.3 [IQR 0.9-1.8].
[30] Patients on replacement therapy reported only. Unclear whether all patients with hypopituitarism were on replacement therapy.

	Sex (female)	Macroadenoma	Hypopituitarism	Duration disease	Duration follow-up
	Total: 132 (75.4%) AC: Total: 21 (43.8%) CD: Total: 29 (95.7%) PRL: Total: 47 (88.7%) NFPA: 35 (79.5%)	Total: 37 (21.1%) AC: Total: 15 (31.3%) CD: Total: 1 (3.3%) PRL: Total: 8 (15.1%) NFPA: 13 (29.5%)	Total: Pan: 25 (14.3%) ACTH: 50 (28.6%) GH: 15 (8.6%) TSH: 19 (10.9%) LH/FSH: 31 (17.8%) AC total: Pan: 7 (14.6%) ACTH: 13 (27.1%) GH: 1 (2.1%) TSH: 4 (8.3%) FSH/LH: 8 (16.7%) CD total: Pan: 4 (13.3%) ACTH: 10 (33.3%) GH: 2 (6.7%) TSH: 3 (10.0%) FSH/LH: 6 (20.0%) PRL total: Pan: 6 (11.3%) ACTH: 16 (30.2%) GH: 5 (9.4%) TSH: 6 (11.3%) FSH/LH: 10 (18.9%) NFPA: Pan: 8 (18.2%) ACTH: 11 (25.0%) GH: 7 (15.9%) TSH: 6 (13.6%) FSH/LH: 7 (15.9%)	7 [IQR 1-10] y	NA
	Total: **33 (94.3%)** **CD:** **7 (100.0%)** **PRL:** **26 (92.9%)**	**Total:** **6 (17.1%)** **CD:** **1 (14.3%)** **PRL:** **5 (17.9%)**	**CD:** **Pan: 1 (14.3%)** **ACTH: 0 (0.0%)** **GH: 1 (14.3%)** **TSH: 2 (28.6%)** **FSH/LH: 2 (28.6%)** **PRL:** **Pan: 5 (20.3%)** **ACTH: 13 (46.4%)** **GH: 4 (14.3%)** **TSH: 5 (20.3%)** **FSH/LH: 8 (28.6%)**	**NR**	**NA**
	39 (52.7%)	NR[29]	ACTH[41]: 7 (9.5%) TSH[41]: 11 (14.9%) FSH/LH[41]: 3 (4.1%) GH[30]: 1 (1.4%)	10 [3.0-16.0] y	NA
	NR	**NR**	**NR**	**NR**	**NA**

Supplementary Table 7 Study characteristics per study *(continued)*

First author, Study design	Population	Subgroup	N	Treatment	Age in years
Ye [46] Cohort study	CD, NFPA	Total	Total: 71 CD: 51 NFPA: 20	Total: NR CD: TSA: 50 (98.0%) Craniotomy: 1 (2.0%)	Mean: 42.4
	Refractory	**CD: 7 (13.7%)**	**NR**		**Mean: 38.6**

General characteristics of all included studies. Characteristics are reported for the total population, subgroups and refractory patients separately if reported as such by the author. Data not presented was not reported by the author of the article. Values expressed as mean ± SD or median [interquartile range], unless specified otherwise. *AC* acromegaly; *Bilat*. bilateral; *CBG* cabergoline; *CD* Cushing's disease; *DA* dopamine agonist; *DI* diabetes insipidus; *GHRA* growth hormone receptor antagonist; *GKS* gamma knife surgery; *LINAC* linear accelerator; *mos* months; *med* medication; *NA* not applicable; *NFPA* non-functioning pituitary adenoma; *NR* not reported; *PAN* panhypopituitarism; *PRL* prolactinoma; *RCC* Rathke's cleft cyst; *RT* radiotherapy; *SMS(+)* on somatostatin analogue treatment; *SMS(-)* not on somatostatin analogue treatment; *TSA* transsphenoidal adenectomy; *w* week; *Y* years; *95%CI* 95% confidence interval.

[31] N=49, missing data: 2.

Sex (female)	Macroadenoma	Hypopituitarism	Duration disease	Duration follow-up
NR	Total: NR CD[31]: 10 (20.4%)	NR	NR	First: mean 2.35 mos Second: mean 7.4 mos
NR	**NR**	**NR**	**NR**	**NR**

Supplementary Table 8 Risk of bias assessment per study

Category	Criterium	Alcalar [29]	Carluccio [27]	Chin [30]	Dantas [31]
Study population	Inclusions either consecutive patients or all eligible. Not a random sample	1	1	1	0
	All included patients with active disease showed clinical symptoms of the particular pituitary adenoma	0	0	0	1
	Description of the clinical symptoms and definitions of the symptoms	0	0	0	0
	Description of criteria for diagnosis of pituitary disease	1	1	1	1
	Criteria for diagnosis of pituitary disease according to the most recent international guidelines at the time of publication	1	1	1	1
	Definition of remission described	1	1	0	1
	Definition of remission according to most recent international guidelines at the time of publication	1	1	0	1
	Definition of refractory described	0	0	0	0
	Definition of intolerant described	0	0	0	0
	Treatment modalities of patients described	1	1	1	1
	Mention that treatment was according to most recent guidelines at time of publication	0	0	0	0
Data collection	Lost to follow-up <10% N (%)	NA	NA	0 7 *(13)*	NA
	Missing data for biochemical outcomes <10% N (%)	0	0 *10* *(10)* [b]	0	0
Outcomes	Missing data for PROMs <10%, N (%)	0	0 43 (30)	0	0
	Assay for measurement of GH, IGF-1, prolactin, cortisol, ACTH, FSH and LH reported and adequat[e]d	0	0	0	0
	Biochemical results at follow-up described for the entire population, not just significant results	NA	NA	1	NA
General risk of bias score (%)[e]		**43**	**43**	**31**	**43**

General risk of bias assessment of included studies using a component approach based on Analyses of Observational Studies of Etiology (COSMO-E) and Risk of Bias In Non-randomised Studies (ROBINS) criteria. *FSH* Follicle stimulating hormone; *GH* growth hormone; *IGF-1* insulin-like growth factor-1; *ISOQOL* International Society for Quality of Life Research; *LH* lutheinizing hormone; *NA* not applicable; *PROMs* patient reported outcome measures.

Dimopoulou [32]	Fathalla [33]	Gu [34]	Guo [35]	Hua [36]	Milian [38]	Nader [28]	Psaras [1]	Psaras [39]	Raappana [40]	Ritvonen [41]	Trepp [42]	Vandeva [43]	Vega-Beyhart [44]	Yamamoto [45]	Ye [46]
0	1	1	1	1	0	0	0	0	1	1	1	0	1	0	1
0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	0	1	1	0	0	0	0	0	1	0	0	1	1	1	0
1	0	1	1	0	0	0	0	0	1	0	0	1	0	1	0
1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	0
1	1	1	1	1	0	0	1	1	1	1	1	1	0	1	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0
1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	
NA	NA	0	NA	NA	0 41 *(39)*	NA	NA	NA	NA	NA	NA	0	NA	NA	0 31 (74)[a]
0	0	0	0	0	0	0	1 *0* *(0)*	1 *0* *(0)*	0	1 1 (1)	0	0	0	0	0
0	0	0	0 *115* *(26)*	0	0	0	0	0	0	0	0	0	0	0 13 (18)	0
0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
NA	NA	0	NA	NA	0	NA	NA	NA	NA	NA	NA	1	NA	NA	0
43	**29**	**50**	**50**	**13**	**6**	**7**	**29**	**29**	**43**	**36**	**29**	**38**	**29**	**36**	**6**

[a] Second follow-up.
[b] Glucocorticoid exposure.
[c] Elevated prolactin level.
[d] Scoring: a point was given if the article described the method of hormone measurement adequately enough to assume there was no clinically relevant bias in diagnosis of each of the hormone producing pituitary adenomas. *Acromegaly*: either IGF-1 or GH determination was performed and described adequately and cutoffs were presented that comply with the guidelines at time of publication i.e. *IGF-1*: inter-assay and intra-assay coefficients were <8% and adequate reference values were presented for calculation of IGF-1. If IDS-iSYS was used, without presenting reference values, this was also considered adequate, as peer reviewed reference values have been published for this system. *GH*: adequate reference values were presented. *Cushing's Disease*: adequate reference values were used. *Prolactinoma*: system, gender and age specific cutoff values were presented for serum prolactin.
[e] General risk of bias score was calculated as total points divided by the number of applicable items, multiplied by 100%.

Supplementary Table 9 ISOQOL criteria per study

Section	Criterium
Title and abstract	The PRO should be identified as an outcome in the abstract
	For 1° outcome: The title of the paper should be explicit as to the cohort study including a PRO
Introduction, background and objectives	The PRO hypothesis should be stated and should specify the relevant PRO domain(s) if applicable
	For 1° outcome: The introduction should contain a summary of PRO research that is relevant to the cohort study
	For 1° outcome: Additional details regarding the hypothesis should be provided, including the rationale for the selected domain(s), the expected direction(s) of change, and the time points for assessment
Outcomes registration	The mode of administration of the PRO tool and the methods of collecting data (e.g., telephone, other) should be described
	The rationale for choice of the PRO instrument used should be provided
	Evidence of PRO instrument validity and reliability should be provided or cited
	The intended HRQL data collection schedule should be provided
	PROs should be identified in the trial protocol; post hoc analyses should be identified
	The status of PRO as either a primary or secondary outcome should be stated
	For 1° outcome: A citation for the original development of the PRO instrument should be provided
	For 1° outcome: Windows for valid PRO responses should be specified and justified as being appropriate for the clinical context
Sample size	For 1° outcome: There should be a power/sample size calculation relevant to the PRO based on a clinical rationale (e.g., anticipated effect size)
Statistical methods	There should be evidence of appropriate statistical analysis and tests of statistical significance for each PRO hypothesis tested
	Statistical approaches for missing data should be explicitly stated, and the extent of missing data should be stated
	For 1° outcome: The manner in which multiple comparisons have been addressed should be provided
Participant flow	A flow diagram or a description of the allocation of participants (if applicable) and those lost to follow-up should be provided for PROs specifically
	The reasons for missing data should be explained
Baseline data	The study patients' characteristics should be described, including baseline PRO scores
Outcomes and estimation	The analysis of PRO data should account for survival differences between treatment groups if relevant
	Results should be reported for all PRO domains (if multi-dimensional) and items identified by the reference instrument (i.e., not just those that are statistically significant)
	The proportion of patients achieving predefined responder definitions should be provided where relevant
Limitations	The limitations of the PRO components of the study should be explicitly discussed
Generalizability	Generalizability issues uniquely related to the PRO results should be discussed, if applicable
Interpretation	The clinical significance of the PRO findings should be discussed
	The PRO results should be discussed in the context of the other clinical studies
Protocol	A copy of the instrument should be included if it has not been published previously (1 if published previously)
Percentage of items reported by study (%)	

International Society for Quality of Life Research (ISOQOL) criteria modified for non-randomized controlled trials per study. *1° outcome* primary outcome; *NA* not applicable; *PRO* patient reported outcome; *PROM* patient reported outcome measure.

Alcalar [29]	Carluccio [27]	Chin [30]	Dantas [31]	Dimopoulou [32]	Fathalla [33]	Gu [34]	Guo [35]	Hua [36]	Milian [38]	Nader [28]	Psaras [1]	Psaras [39]	Raappana [40]	Ritvonen [41]	Trepp [42]	Vandeva [43]	Vega-Beyhart [44]	Yamamoto [45]	Ye [46]
1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1
1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
0	0	1	0	0	1	0	1	1	1	0	1	0	0	1	1	1	1	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	1	0	0	0	0	0	1	1	0	1	0	0	1	1	1	0	0	0	0
0	1	1	0	0	1	1	1	1	1	1	1	1	0	1	1	1	0	1	0
0	1	1	1	1	1	0	1	1	0	0	1	0	0	1	1	1	1	1	1
NA	NA	1	NA	NA	NA	1	NA	NA	1	NA	NA	NA	NA	NA	NA	1	NA	NA	NA
0	0	1	NA	1	0	0	NA	NA	1	NA	NA	1	0	0	NA	0	0	1	0
1	1	0	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1
0	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1
0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	1	1	NA	NA	NA	0	NA	NA	0	NA	NA	NA	NA	NA	NA	0	NA	NA	1
1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
1	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	1
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
0	0	0	0	1	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0
1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1
0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
36	**44**	**62**	**35**	**46**	**54**	**35**	**61**	**57**	**46**	**48**	**52**	**29**	**38**	**54**	**52**	**46**	**46**	**38**	**48**

Supplementary Table 10 Tuebingen CD-25

First Author, year of publication	Nader [28][a]	
Disease	**CD**	
Baseline	**N (%), N=8**	
	Mild	**Severe**
Depression	4 (50%) =	1 (13%) =
Sexual activity	2 (25%) =	2 (25%) =
Environment	2 (25%) =	3 (38%) =
Eating behavior	3 (38%) =	1 (13%) =
Bodily restrictions	0 (0%) =	7 (88%) =
Cognition	1 (13%) =	3 (38%) =
Total	3 (38%) =	3 (38%) =

Tuebingen CD-25 scores for refractory patients with Cushing's Disease as reported by Nader et al. [28]. Mild: scores > percentile rank 84 of age- and gender-specific cut-off values. Severe: scores > percentile rank 95 of age- and gender-specific cut-off values. *CD* Cushing's Disease; *Tuebingen CD-25* Tuebingen Cushing's disease Quality of Life Inventory; = tested and no significant difference compared to CD patients in remission.

[a] Values estimated based on figure, absolute values were not presented.

Supplementary Table 11 EQ-5D-5L

First Author, year of publication	Guo [35]
Disease	**AC**
Baseline	**Mean/median/ percentage of patients checking "no problems" N=154**
VAS of EQ-5D	62.8 ± 21.6 =
mobility	0.018/0.000/81.8% =
Self-care	0.003/0.000/94.2% =
Usual activities	0.070/0.000/85.1% =
Pain/discomfort	0.106/0.058↑/12.3%↓
Anxiety/depression	0.089/0.049↑/11.0%↓

EQ-5D-5L scores for refractory patients with acromegaly as reported by Guo et al. [35]. *AC* acromegaly; *EQ-5D-5L* 5-level EuroQoL-5; *VAS* visual analogue scale; ↓ significantly lower compared to acromegaly patients in remission; ↑ significantly higher compared to acromegaly patients in remission; = tested and no significant difference compared to acromegaly patients in remission.

Supplementary Table 12 BDI

First Author, year of publication	Alacalar [29]	Nader [28][b]
Disease	**AC**	**CD**
Baseline	**Mean ± SD, N=8**	**N (%), N=8**
≤10 points		2 (25%) =
11-17 points		4 (50%) =
≥18 points		2 (25%) =
Total	18.9 ± 10.9 · a	

BDI scores for refractory patients with acromegaly or Cushing's Disease per study. Included studies applied different cut-offs. Alcalar et al.: <17 points: absence of depression, ≥17 points: presence of depression. Nader et al.: ≤10 points: no depression, 11-17 points: mild to moderate depression, ≥18 points: severe depression. *AC* acromegaly; *CD* Cushing's Disease; *BDI* Beck Depression Inventory; *SD* standard deviation; • no P-value reported; = tested and no significant difference compared to patients in remission.

[a] No significant difference between refractory patients, those in remission and healthy controls (no post-hoc analysis was performed).

[b] Values estimated based on figure, absolute values were not presented.

Supplementary Table 13 SCL-90-R

First Author, year of publication	Psaras [39]	
Disease	**AC**	**CD**
Baseline	**Mean ± SD, N=14**	**Mean ± SD, N=5**
Somatization	58.5 ± 32.7 •	57.2 ± 37.4 •
Obsessive-Compulsive	58.5 ± 32.3 •	70.2 ± 39.2 •
Interpersonal Sensitivity	52.0 ± 33.3 •	60.2 ± 34.6 •
Depression	57.1 ± 33.9 •	65.2 ± 42.8 •
Anxiety	51.6 ± 31.8 •	42.2 ± 36.6 •
Hostility	59.5 ± 29.3 • [a]	60.4 ± 27.5 • [a]
Phobic Anxiety	61.5 ± 26.6 •	53.8 ± 33.7 •
Paranoid Ideation	55.2 ± 27.5 •	55.0 ± 27.3 •
Psychoticism	52.0 ± 29.9 •	62.8 ± 28.5 • [a]
Global Severity Index	56.7 ± 34.3 •	76.0 ± 19.6 •
Positive symptom Total	56.9 ± 34.3 •	62.0 ± 38.3 •
Positive Symptom Distress Index	58.6 ± 28.1 •	62.6 ± 34.0 •

SCL-90-R scores for refractory patients with acromegaly and Cushing's Disease as reported by Psaras et al. [39]. *AC* acromegaly; *CD* Cushing's Disease; *SCL-90-R* Symptom Checklist-90-Revised; *SD* standard deviation. • no P-value reported.

[a] Refractory patients scored significantly higher than healthy controls.

Supplementary Table 14 MBSRQ

First Author, year of publication	Alcalar [29]
Disease	**CD**
Baseline	**Mean ± SD, N=8**
Appearance evaluation	2.99 ± 0.49 •
Appearance orientation	3.19 ± 0.54 •
Fitness evaluation	2.79 ± 0.46 • [a]
Fitness orientation	2.77 ± 0.61 •
Health evaluation	3.06 ± 1.08 • [a]
Health orientation	3.59 ± 0.83 •
Body areas satisfaction	2.56 ± 0.86 • [a]
Mean item score	3.02 ± 0.33 • [a]

MBSRQ scores for refractory patients with Cushing's Disease as reported by Alcalar et al. [29]. *CD* Cushing's Disease; *MBSRQ* multidimensional body-self relations questionnaire; *SD* standard deviation; • no P-value reported.

[a] No post-hoc analysis was performed for refractory patients and those in remission, however there was a significant difference between refractory patients, those in remission and healthy controls.

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