Lessons from rare diseases: pathophysiology of stress-related diseases and organization and evaluation of care for patients with Cushing's syndrome

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CHAPTER 9

LONG-TERM POSTOPERATIVE CUSHING'S DISEASE FOLLOW-UP USING INTEGRATED OUTCOME SQUARES: UNIFIED OUTCOME AND EVALUATION

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ABSTRACT

Purpose

Both remission and complications determine the success of transsphenoidal surgery in Cushing's disease (CD). Outcome Squared provides a unified outcome classification in time, integrating intended and adverse effects. Particular challenges in evaluating management of CD are the position of postoperative hypocortisolism and need for multiple interventions in outcome evaluation. A retrospective cohort study was used to report on long-term integrated postoperative outcome in patients with CD.

Methods

Seventy-two consecutive CD patients treated by transsphenoidal resection between 2000 to 2016 in our tertiary referral center were included. Results are presented in Outcome Squares.

Results

One year after surgery, good outcome (remission without pituitary deficiencies excluding adrenal insufficiency) was observed in 55.4%, whereas 4.6% of the patients reported poor outcome (no remission, pituitary deficiencies present). In 29.2% remission with pituitary deficiencies was observed, and 10.8% was not in remission without pituitary deficiencies. When ongoing adrenal insufficiency was included as adverse outcome at one year postoperative, only 17% had remission without pituitary deficiency (good outcome), and 68% had remission with pituitary deficiencies. With follow-up, a gradual shift to the good outcome category occurred, mainly due to recovery of the hypothalamus-pituitary-adrenal axis.

Conclusion

The majority of patients are in remission five years after transsphenoidal surgery, though in a considerable number at the expense of persistent pituitary deficiencies. The four different integrated outcome quadrants used provide an uniform, patient-centred integrated overall view of the important balance between efficacy and safety of transsphenoidal surgery in CD, and can be used in individualised patient counselling.

INTRODUCTION

Cushing's disease (CD) is a rare endocrine disease caused by an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma, resulting in endogenous glucocorticoid excess. Prominent features of glucocorticoid excess include adverse changes in body composition, adverse metabolic profiles, hypertension, and neuropsychiatric disorders.[1-3] If left untreated, the prognosis of CD is poor.[4] Selective removal of the corticotropic adenoma by transsphenoidal surgery remains the treatment modality of first choice, aiming at biochemical remission to eliminate the associated signs, symptoms, and comorbidities, and to improve quality of life.[5] Surgical outcomes traditionally focus on biochemical remission rates. However, the success of surgery is determined by the delicate balance between achievement of remission and the occurrence of long-term complications. This is particular true for CD, where failure to normalize cortisol secretion is potentially life threatening.[4] Main complications such as pituitary insufficiencies, which is described in a range of 3 to as high as 88% of surgically treated patients,[6, 7] potentially due to (over)aggressive surgical approaches, are also associated with comorbidities and reduced quality of life. [8-12]

Pituitary surgery in CD is challenging for several reasons. First, adenoma localization is demanding with previously described detection rates of ACTH-secreting pituitary microadenomas on Magnetic Resonance Imaging (MRI) techniques of approximately 60 to 88% (range 36 to 100%, the latter in a very small case series)[13-16], which means that some patients have no visible or a very small, unclear microadenoma on MRI. In addition, false positive findings on MRI do occur.[17-19] Furthermore, there might be several adenoma localizations, localizations in both sides of the gland or medially, near the stalk,[20, 21] and even extrapituitary and parasellar adenomas have been described.[22, 23] Tumors in CD are often not round or well circumscribed, binodular with small connections, not always enclosed and frequently show a diffuse growing pattern.[24] Most adenomas are deliquescent, but some may have a firm consistency, and therefore may be mistaken for normal pituitary tissue. [24] Consequently, some experienced pituitary surgeons advocate inspection of the total gland by incising the gland carefully, aiming at maximizing total resection. In CD this is generally regarded as safe for preserving pituitary function.[23, 24]

Because CD is associated with high mortality if left untreated and selective adenectomy is challenging for aforementioned reasons, more radical approaches as "hemi- or total hypophysectomy", "sella clean-out" or "bilateral adrenalectomy" resulting in life long hypopituitarism and specifically hypocortisolism are accepted for this condition only, in contrast to all other pituitary tumors where partial adenomectomy or debulking will be proposed if total resection is not feasible.[5, 24] In CD, there is a high tendency for recurrence (15-66% within five to ten years of successful surgery[24-26]), and therefore re-operations may be needed, which may be successful in experienced hands.[5, 27, 28] An unresolved question is whether the risk of recurrence is determined by the quality or approach of the surgery or rather by tumor biology.[29, 30] The management strategy of (repeated) conservative surgery with the goal of remission without pituitary failure or other complications, should be weighed against time exposed to hypercortisolism. Therefore, careful outcome measurements incorporating surgical strategies, preoperative and per-operative evaluation of chances and risks are required to reliably evaluate outcomes in the treatment of CD within and between centers. From

a patient perspective, ultimate outcome after re-intervention is of interest, while surgical series usually analyse only single interventions.

A complicating factor in thorough outcome evaluations is the multitude of endocrine evaluations and tests of CD state postoperatively prohibiting straightforward conclusions. Following surgery early on, there may be a period of profound ACTH and cortisol deficient state, because of downregulation of the activity of the hypothalamic-pituitary-adrenal (HPA)-axis during active disease. This means that in the early postoperative phase remission is reflected by preferred very low early morning cortisol concentrations which should be discriminated from (surgical) damage to the pituitary gland.[5] After recovery of HPA-axis, Cushing's remission is defined differently by normal biochemical tests results, i.e. low midnight salivary cortisol, adequate suppression after low dose dexamethasone, and normal 24 hour free urinary cortisol excretion.[5] In many cases, clinicians will need to deal with discrepant tests, and ultimately decide on the state of disease. Remission or recurrence will be based on the results of subsequent testing, integrated with the re-occurrence of clinical signs and symptoms. Although these considerations are well-adapted in clinical decision making and clinical management, in registries and outcome studies the definitions of disease state are quite heterogenous and not easy to interpret or compare.

For quality evaluations of our pituitary care path, we have recently developed an outcome evaluation method called Outcome Squared (Outcome2). Outcome2 provides a simple, patient-centered, clinically relevant representation of integrated outcomes.[31] Advantages of this method are the unified outcome classification in four categories, based on flexibly chosen definitions of intended and adverse effects, with full integration of efficacy and safety, which is needed to understand complex outcomes as is the case in pituitary surgery for CD. Outcome2 enables integrating intended and adverse effects, ranging from good to poor reflected by four integrated outcome quadrants (IOQs), merged into a cross table called outcome squares (see figure 1). When a strategy of re-interventions is adopted, the intermediate category "no remission and no adverse effects" (IOQ-3) is important, as sequential interventions may ultimately lead to remission without long-term adverse effects (good outcome, IOQ-1). However, since hypercortisolism needs to be controlled, remission with adverse effects (remission with hypopituitarism, IOQ-2) may sometimes be the only option. Furthermore, comparability of (heterogeneous) subgroups is facilitated using Outcome2, and it may therefore be a clinically helpful tool in informing patients about possible outcomes of surgery.

This study is the first to report on long-term outcome measures in patients with CD after transsphenoidal surgery, taking the delicate and clinically important balance between treatment efficacy and safety into account using the Outcome2 approach.

MATERIAL AND METHODS

Study population

All consecutive patients with CD primarily treated with transsphenoidal resection between January 1st 2000 (start of our multidisciplinary pituitary care team) and December 31st 2016 at our tertiary referral and European reference center for pituitary diseases were included in this cohort study.

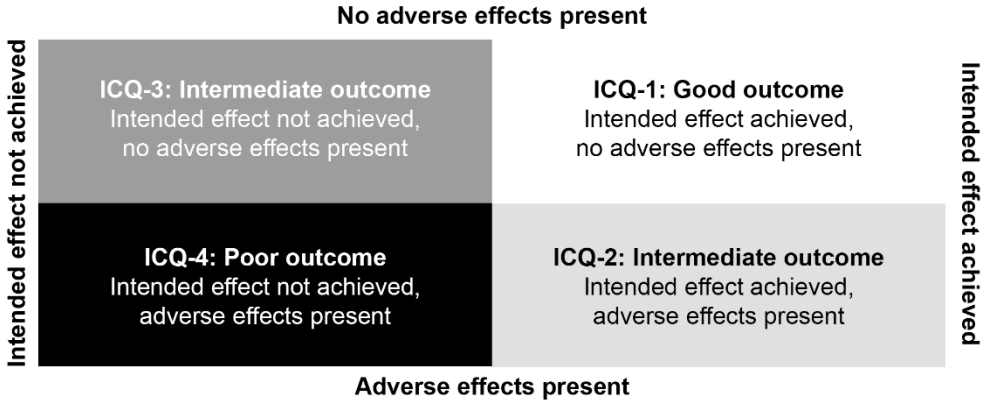

Figure 1. Outcome squares. Figure adapted from de Vries et al.[29].
Abbreviations: IOQ, Integrated Outcome Quadrant.

A retrospective chart review was performed of all patients; no exclusions were made based on tumor size or invasiveness or re-operation. There were no restrictions in adjuvant therapy in case of persistent or recurrent disease, or presurgical medical treatment with cortisol lowering agents.

Preoperative assessment

The diagnosis of CD was made based on both clinical signs and symptoms and biochemical testing, in accordance with the current clinical guidelines at time of diagnosis: increased 24 hour urinary free cortisol (UFC) excretion (> 220 nmol until 2010, > 150 nmol afterwards), insufficient suppression of morning serum cortisol after low-dose dexamethasone (1 mg) in the evening (> 50nmol/L), as well as a non-suppressed ACTH, and increased midnight salivary cortisol (> 5.7 nmol/L, available since 2004). An MRI scan (1.5-3 Tesla) with dynamic sequences was performed in all patients but one (computed tomography was used in this case due to a contraindication for MRI), and in case of inconclusive results, patients underwent bilateral inferior petrosal sinus sampling (IPSS) and usually repeated scanning. When the IPSS results were consistent with a pituitary source of ACTH overproduction, subsequent pituitary surgery with exploration of the sella was performed. Otherwise, imaging studies (CT thorax/abdomen, octreotide or gallium dotatate pet scan) were used to identify a possible ectopic ACTH-producing tumor. When no ectopic ACTH source was found, surgical treatment was only performed after a period of watchful waiting, repeated tests and after imaging or IPSS indicated a pituitary adenoma. All patients were discussed in our multidisciplinary pituitary care team, including endocrinologists, neurosurgeons, neuroradiologists, radiotherapists, ophthalmologists, and specialized pituitary nurses.

Treatment

The primary treatment was either microscopic or endoscopic transsphenoidal adenomectomy (TSA) for all included patients. The microscopic approach was used in all performed surgeries until 2002, and from 2003 onwards, the endoscopic procedure was increasingly used until it became

the standard treatment modality in our center from 2006 on.[32] Three experienced pituitary neurosurgeons performed all operations. Surgical strategy and technique are described in detail elsewhere.[33] When the adenoma was poorly or not visible on the MRI scan, multiple shallow incisions in the pituitary gland were made to localize the adenoma. In case of persistent or recurrent disease, (multiple) re-operations were performed in order to achieve remission, preferably without long-term adverse effects. However, ultimately remission with adverse effects was considered preferable over persistent CD.

Postoperative assessment and follow-up

The first postoperative biochemical evaluation was completed within two weeks after operation, usually with early morning cortisol level only. Three to six months postoperatively, remission state was assessed using both clinical criteria (hydrocortisone independency without any signs of hypercortisolism, and regression of clinical signs, or persisting dependency of hydrocortisone replacement) as well as biochemical criteria (normal suppression of morning cortisol after 1 mg dexamethasone [<50nmol/], normal 24 hour urinary free cortisol excretion, normal midnight salivary cortisol on two separate days, if not on hydrocortisone replacement therapy). Persistent disease was defined as the absence of remission upon evaluation after surgery. Disease recurrence was defined as clinical and biochemical recurrence after a period of remission of at least two to three months, according to the aforementioned criteria. Also in long-term follow-up, remission state was evaluated regularly (at least yearly) using the above mentioned criteria. For this study, follow-up data at three to six months after surgery (hereafter referred to as three months after surgery), one year, two years, and five years were used.

Efficacy parameters, adverse outcome and Outcome squares

For this study, the efficacy parameter intended effect of the intervention in our outcome integration model Outcome2 was defined as achievement of biochemical remission, either by hydrocortisone dependency or by normalization of hypercortisolism according to the current guideline (see above) and interpreted by the treating physician in case of discrepant values. [5] As described by de Vries et al.[31], Outcome2 is also suitable to evaluate alternative intended effects of surgery depending on the surgical goal, for example tumor debulking. In CD, however, the intrinsic features of the condition with its known morbidity and mortality, justifies that the aim of treatment will virtually most always be achieving complete remission of cortisol hypersecretion and not tumor debulking, as was the case in our cohort. However, the postoperative course of patients with CD requires that there are different definitions of biochemical remission in time, because early after surgery there will be adrenal deficiency and many tests to exclude recurrent hypercortisolism cannot be performed during steroid replacement therapy.

Interestingly, early postoperative adrenal insufficiency can first be seen as a preferred intended effect, while persisting in a later stage this turns into an undesired outcome. For this study, HPA-axis deficiency was considered an adverse effect when there was no tendency of recovery one year after surgery (as recovery of adrenal function usually occurs within this time period). To highlight

the consequences of this interpretation and because HPA-axis deficiency and time to recovery is relevant for outcome in patients' perspective, results are presented with and without HPA-axis deficiency included as an adverse effect from one year after surgery onwards to show outcome during follow-up.

In addition to evaluation of HPA-axis, the complication parameter, the "adverse effects" of the intervention, was (new-onset, permanent) pituitary deficiencies, because of the influence of these deficits on long-term comorbidity and quality of life. Pituitary deficiencies were defined as below normal serum values or abnormal values on currently used pituitary function tests, requiring medical management or with associated, irreversible symptoms. (Temporary) HPA-axis deficiency was taken into account separately, given the expected and intended effect of successful surgery on the activity of the HPA-axis. Diabetes insipidus (DI) was defined as polyuria (urine production >300cc/hour for 3 consecutive hours) with urine gravity < 1.005, in addition to at least one related criterium: excessive thirst, serum osmolality > 300 mosmol/kg, or serum sodium > 145 mmol/L,[34] and was also considered a pituitary function deficit if present. In case of hydrocortisone replacement in the context of postoperative steroid withdrawal syndrome with normal cortisol response during dynamic testing, the patients were not classified as HPA-axis deficient. In line with the publication of de Vries et al.[31] we focused on long-term, permanent adverse effects and did not include transient complications in these outcome squares.

For the presentation of the results based on intended effect of the surgery (remission) and adverse outcomes as described above, Outcome2 was used. This resulted in four integrated outcome quadrants (figure 1): good outcome (IOQ-1, intended effect achieved, no adverse effects), poor outcome (IOQ-4, intended effect not achieved, adverse effects present), intended effect achieved, adverse effects present (IOQ-2), and intended effect not achieved, no adverse effects (IOQ-3). Different Outcome squares were constructed for different follow-up periods in order to evaluate surgical outcome over time and also for different clinically relevant subgroups according to tumor size, surgical technique, preoperative medical pretreatment, and whether disease recurrence had occurred or not. The reported outcome includes the effect of possible re-interventions, if applicable. Recurrences and re-interventions shift the classification of patients over the four IOQs at different time points (figure 2). IOQs can be used to define outcome of a single intervention, but also of a multimodality strategy. This may result in an IOQ-1 classification when a patient with recurrent or persistent disease was reoperated and was in remission without adverse effects afterwards.

Statistical analysis

IBM SPSS statistics 25 (IBM Corp. Armonk, NY, USA) was used to perform statistical analysis and to construct Outcome2 two by two tables and piecharts. Descriptive statistics were used for describing the study population (baseline characteristics).

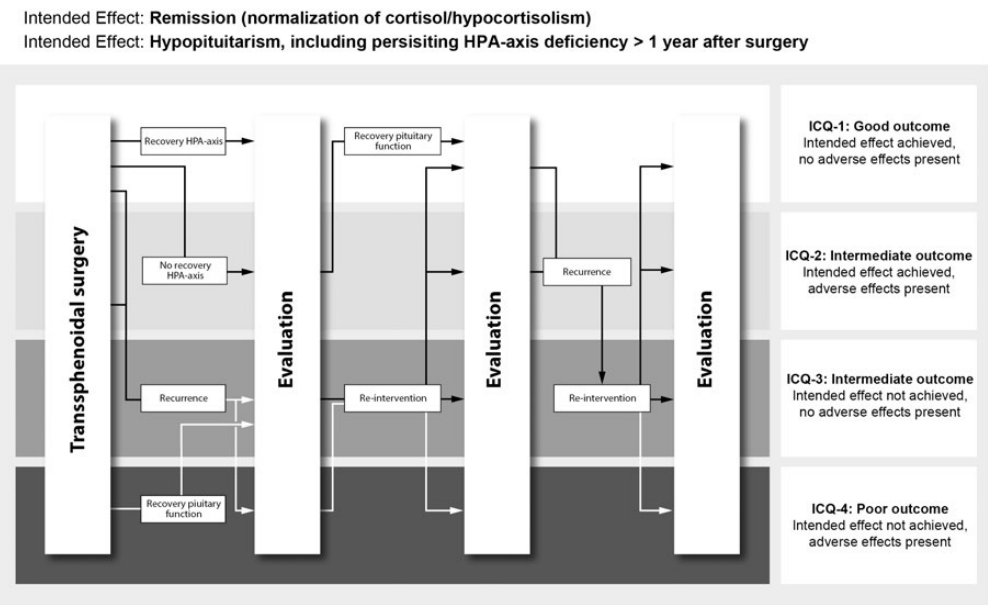

Figure 2. Conceptual framework of Cushing's disease patients shifts in Outcome[2] integrated outcome. Abbreviations: HPA-axis, Hypothalamus-Pituitary-Adrenal axis, IOQ, Integrated Outcome Quadrant.

RESULTS

Study population

In the specified time period, 74 consecutive CD patients were evaluated at our center. Two of them died/or were lost to follow-up before treatment could start. Therefore, 72 patients were surgically treated and included in this study, of whom 53 females (74%, in line with the available literature [35, 36]). The mean age at diagnosis was 45 years (range 10-80), and the mean Cushing Severity Index score[37] was 6.78 (range 0-14) during active disease. In 9 patients (12.5%) no adenoma was visible on preoperative MRI, in 8 patients (11%) a possible/uncertain adenoma was present, and in 53 patients (74%) a clear adenoma could be identified on preoperative imaging (of whom 25 showed a macroadenoma). IPSS prior to surgery was performed in 20 patients (28%). The majority of patients (n=67, 93%) was medically pretreated with cortisol lowering agents prior to surgery (metyrapone, ketoconazole, a combination of both, or pasireotide was used), as is common practice in our center. Fifteen patients (21%) underwent microscopic transsphenoidal surgery, whereas in 50 patients (69%) the endoscopic technique was used. Seven patients (10%) underwent surgery using a combined microscopic and endoscopic approach. In 57 patients (79%) a first adenoma resection was performed, 15 patients (21%) underwent a re-operation (10 because of recurrent disease, five because of persisting disease after first surgery). Sixteen patients (22%) underwent radiotherapy during follow-up, whether or not in combination with repeated transsphenoidal surgery (n= 7), multiple repeated transsphenoidal resections (n=1), or repeated transsphenoidal surgery and adrenalectomy (n=3). No sella clean outs were performed. The mean follow-up period of all patients

was 77 months (range 1-120). In ten patients (14%), recurrence occurred at any time during follow-up. (table 1)

Outcome Squares – Remission status and adverse outcome

Good outcome (IOQ-1, remission (e.g. hydrocortisone dependency or no biochemical signs of hypercortisolism) without adverse effects (e.g. ongoing hypopituitarism other than corticotroph deficiency)) was achieved in 56.5% (n=39) of patients three months after surgery, and in 55.4% (n=36) one year after surgery. Poor outcome (IOQ-4, e.g. no remission (e.g. ongoing hypercortisolism) and adverse outcome present (e.g. hypopituitarism)) was observed in 5.8% (n=4) of the patients after three months, and in 4.6% (n=3) one year after surgery. IOQ-2 (remission and adverse outcome present) listed 21.7% (n=15) of the patients three months after surgery, and 29.2% (n=19) one year after surgery, whereas 15.9% (n=11) of the patients were classified as IOQ-3 (no remission, no adverse outcome present) after three months, and 10.8% (n=7) one year post-operatively.

During prolonged follow-up, the good outcome group decreased only slightly to 53.3% (n=24) five years after surgery, mostly because patients were diagnosed with relative pituitary deficiencies other than corticotroph deficiency or disease recurrence occurred, and therefore patients shifted from IOQ-1 (good outcome) to IOQ-2 (remission and adverse outcome present) or IOQ-3 (no remission and no adverse outcome). The poor outcome group (IOQ-4) became smaller over time, with only one patient (2.2%) in this category five years after surgery, due to successful re-operations leading to remission in the other patients. The single patient in IOQ-4 was a case of mild

Table 1. Clinical characteristics of included Cushing's disease patients.

	CD patients n=72
Age, yrs (mean, range)	45 (10 - 80)
Sex, male / female (no)	19 / 53
CSI at diagnosis (mean, range)	6.78 (0 - 14)
Preoperative MRI (no, %)	
No adenoma visible	11 (15%)
Possible adenoma	8 (11%)
Clear adenoma	53 (74%)
Adenoma type, macroadenoma / microadenoma (no)	25 / 47
IPSS performed (no, %)	20 (28%)
Medical pretreatment (no, %)	67 (93%)
Surgical procedure TSA, microscopic / endoscopic* (no)	15 / 50
Follow-up time in months (mean, range)	77 (1 - 120)
Recurrence of disease (no, %)	10 (14%)
Re-intervention: TSA (one or more)	3
Re-intervention: TSA combined with RT	4
Re-intervention: RT	2

Abbreviations: CD, Cushing's disease, yrs, years, no, number, CSI, Cushing Severity Index score(37), MRI, Magnetic Resonance Imaging, TSA, transsphenoidal adenomectomy, RT, radiotherapy

*7 patients combined microscopic and endoscopic approach

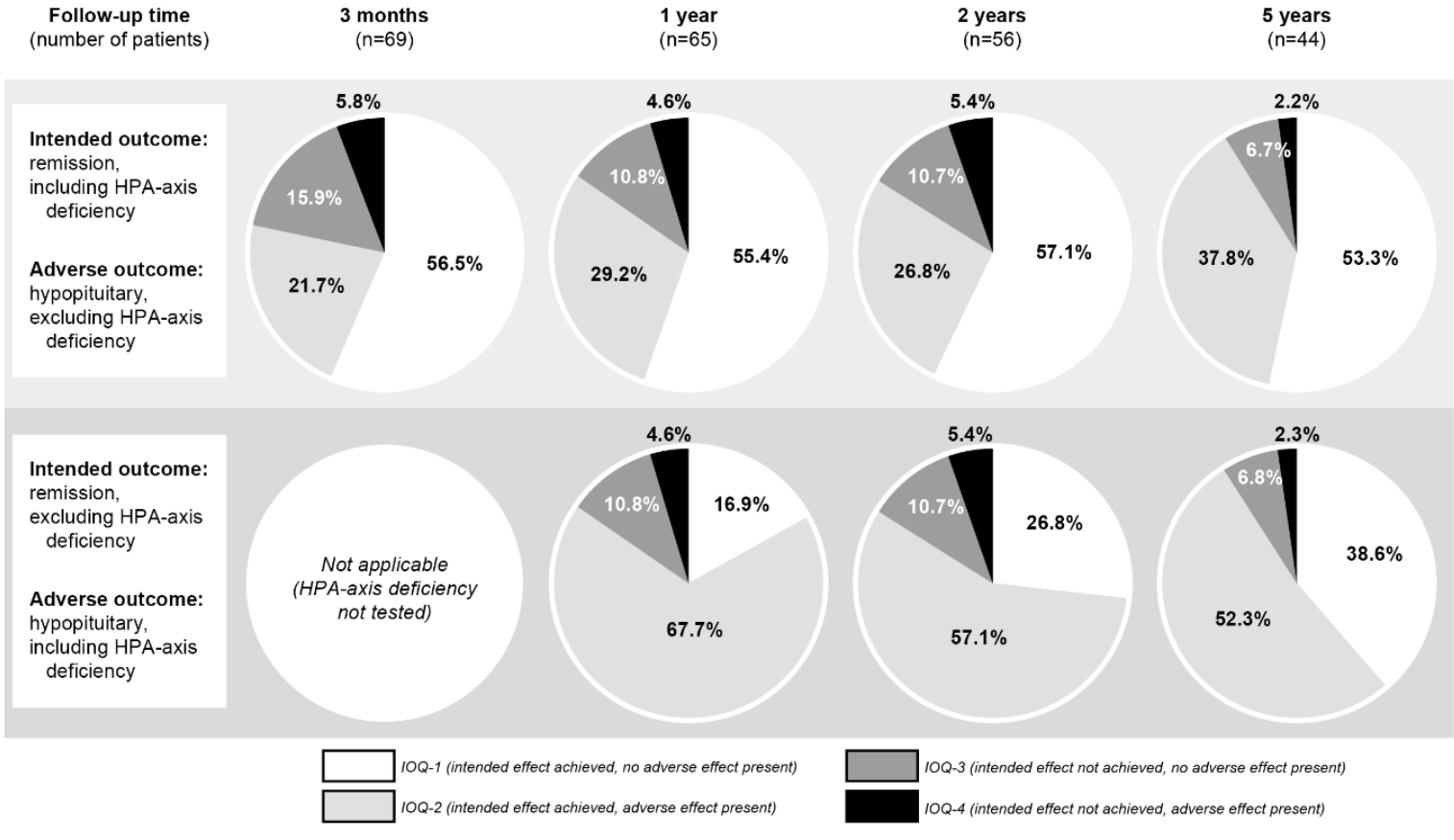

Figure 3. Outcome[2] integrated outcome quadrants after transspheniodal surgery in Cushing's disease over time.

biochemical hypercortisolism due to incomplete resection of the invasive macroadenoma, however without clinical signs and symptoms, and therefore without a wish for further treatment.

Five years after surgery, 37.8% of patients was classified as IOQ-2 (remission and adverse outcome present) and 6.7% as IOQ-3 (no remission, no adverse outcome), the latter group also decreasing over time due to successful re-operations. The patients in IOQ-3 five years after surgery were diagnosed with recurrence of disease just before this time point, and no re-intervention was performed yet at the moment of the five year evaluation. Figure 3 shows pie charts of the Outcome2 integrated outcome quadrants over the follow-up time of five years as described above.

In the third column of figure 3, the same follow-up time is displayed, only in these Outcome2 pie chart series the HPA-axis deficiencies are included in the adverse outcome category. Of the 46 patients with HPA-axis deficiencies three months after surgery, 33 patients (78.6%) had persisting adrenal insufficiency one year after surgery (four patients lost to follow-up), 21 patients (53.8%) two years after surgery (seven patients lost to follow-up), and 12 patients (42.9%) five years after surgery (18 patients lost to follow-up). One year after surgery, 16.9% of the patients (n=11) are in remission without adverse effects (IOQ-1), and 67.7% of the patients in remission (n=44) did have adverse effects mainly due to corticotroph deficiency (IOQ-2). The proportion of patients in IOQ-1 (good outcome) improved gradually over time to 38.6% (n=17) due to restoration of pituitary functioning (mainly recovery of HPA-axis functioning), and 52.3% (n=23) were classified in IOQ-2 after five years of follow-up (remission, but ongoing hypopituitarism). The number of patients in IOQ-3 and IOQ-4 also decreased over time, due to successful re-operations and restoration of the HPA-axis functioning.

Of special interest is the group of CD patients without remission after surgery (IOQ-3 and IOQ-4). One year after initial surgery, three patients were in the poor outcome category (IOQ-4). In two of these patients, poor outcome was also observed two years after surgery (one patient died between one and two years post-surgery), and one patient was still in IOQ-4 five years after surgery despite a second transsphenoidal operation (no five year follow-up data available in the other patient, no re-intervention performed during follow-up). Two of the three IOQ-4 patients had a macroadenoma (one with cavernous sinus invasion), and in one patient there was an uncertain microadenoma visible on preoperative MRI scan. Seven patients were in the intermediate outcome group without remission one year after surgery (IOQ-3). After re-intervention, all patients were in remission five years after initial surgery (four patients in IOQ-1, two patients in IOQ-2, one patient was lost to follow-up). Five of the seven IOQ-3 patients had a macroadenoma (of which four with cavernous sinus invasion), and in one patient preoperative MRI scan showed an uncertain microadenoma.

Analysis of the distribution of patients lost to follow-up at 5 years after surgery (n=27) over the IOQs at three months after surgery, showed that these patients were similarly distributed over the four categories, as was the total group of patients at the timepoint of three months follow-up.

Outcome Squares – subgroup analysis

Macroadenoma versus microadenoma

One year after transsphenoidal surgery, 92.7% (n=38) of all patients with a microadenoma (including invisible adenoma) were in remission, compared to 70.8% (n=17) of patients with a macroadenoma.

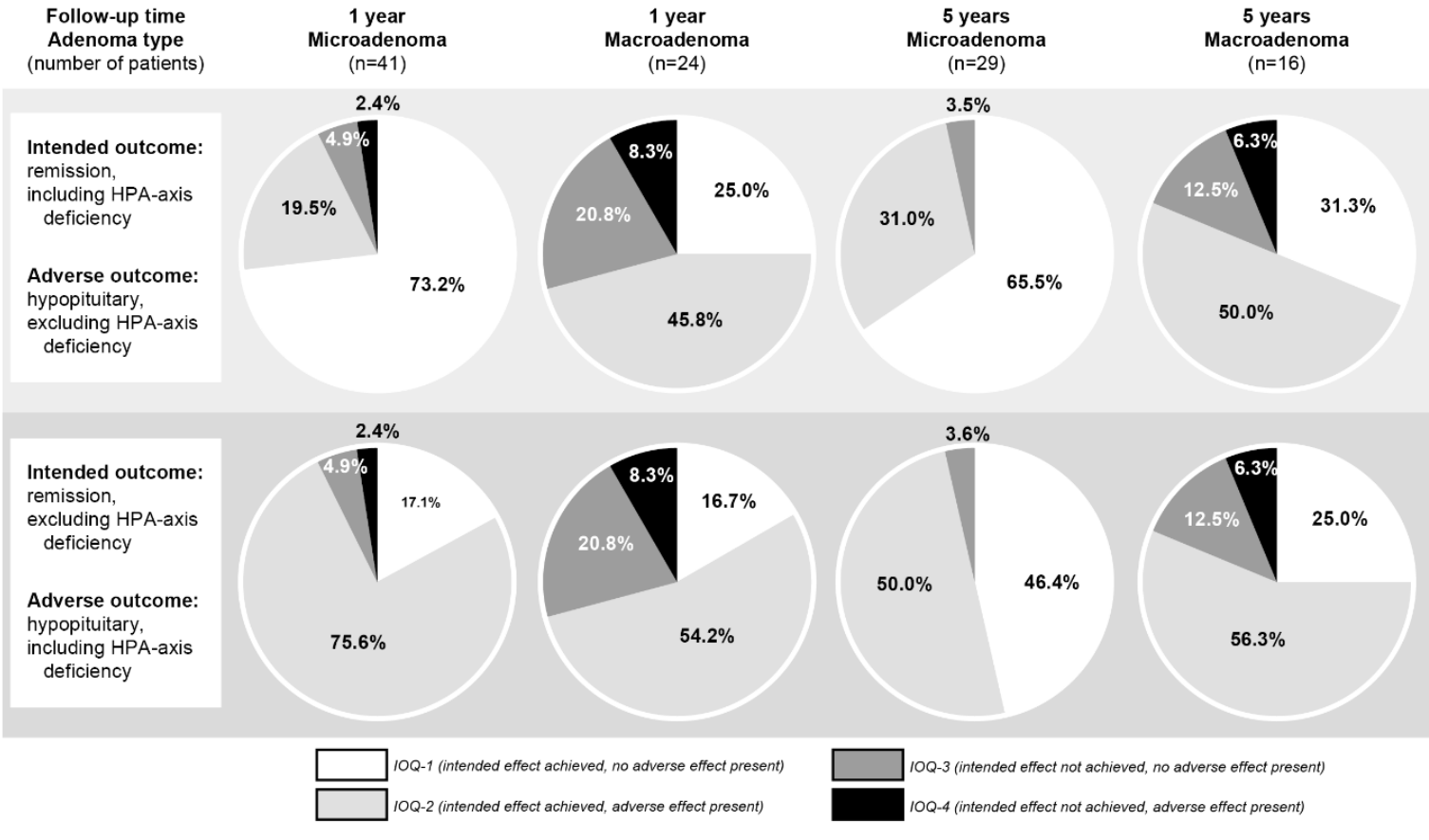

Figure 4. Outcome[2] integrated outcome quadrants in macro- versus microadenoma in Cushing's disease after transphenoidal surgery.

When we defined intended effect as biochemical remission (no hypercortisolism or adrenal insufficiency) and adverse effects as hypopituitarism excluding adrenal insufficiency at one year postoperative, for microadenoma the distribution in IOQs was as follows: IOQ-1 73.2% (n=30), IOQ-2 19.5% (n=8), IOQ-3 4.9% (n=2), and IOQ-4 2.4% (n=1). For macroadenoma patients, the distribution was as follows: IOQ-1 25.0% (n=6), IOQ-2 45.8% (n=11), IOQ-3 20.8% (n=5), and IOQ-4 8.3% (n=2). In an additional Outcome square, deficiency of the HPA-axis was included as an adverse outcome (see figure 4).

It is of note that six of the macroadenoma patients in IOQ-2 already had pre-operative pituitary deficiencies due to the macroadenoma itself, so it is debatable whether this needs to be registered as an adverse effect, with persisting deficiencies after surgery. In nine of the 47 microadenoma patients and in 16 of the 25 macroadenoma patients a re-intervention was performed during follow-up.

The long-term follow-up results (five years after surgery) using the Outcome2 method for macro- and microadenoma CD patients are also shown in figure 4. The decrease in IOQ-4 (poor outcome) patients over time was due to loss of follow-up.

A separate category concerns patients with an invisible adenoma, due to the different surgical approach as described above. In our cohort, 12.5% of the patients (n=9) did not have a visible adenoma on preoperative imaging. When looking at the outcome measurements of these patients, one year after surgery, the distribution of patients per IOQ was as follows: IOQ-1: five patients, IOQ-2 two patients, IOQ-3 one patient, IOQ-4 no patients (in one patients, outcome data was lacking). missing 1. Five years after surgery, four patients had good outcome, and three patients were in IOQ-2 (in two patients no five year follow-up data was available). The one patients in IOQ-3 one year after surgery, shifted to IOQ-2 due to repeated transsphenoidal resection in combination with radiotherapy and adrenalectomy. When including ongoing HPA-axis deficiency as an adverse effect, six patients were in IOQ-2 five years after surgery, and only one patient was in IOQ-1.

Microscopic versus endoscopic transsphenoidal resection

The results of transsphenoidal surgery by surgical technique according to the Outcome2 method are depicted in figure 5. Follow-up data were available on 15 patients who underwent microscopic surgery and 43 patients who were operated on using the endoscopic technique. Figure 5 shows the outcome one year and five years after surgery (HPA-axis deficiency excluded as adverse effect), showing that the results regarding the percentages of patients in the different IOQs did not differ significantly between the two operation technique groups. There was a tendency for more HPA-axis deficiency in the endoscopic group and more remission without deficiencies including HPA-axis deficiency after five years (IOQ-1, endoscopic 45.5% versus microscopic 33.3%). At five years follow-up, the microscopic group had more remission with deficiencies (IOQ-2, endoscopic 40.9% versus microscopic 60.0%). Since only seven patients were operated through combined endoscopic and microscopic procedure, no separate analysis was performed on this specific category.

Recurrence of disease

Since a treatment strategy consisting of multiple interventions if necessary in order to achieve remission is frequently needed in Cushing's disease and adopted by our multidisciplinary pituitary

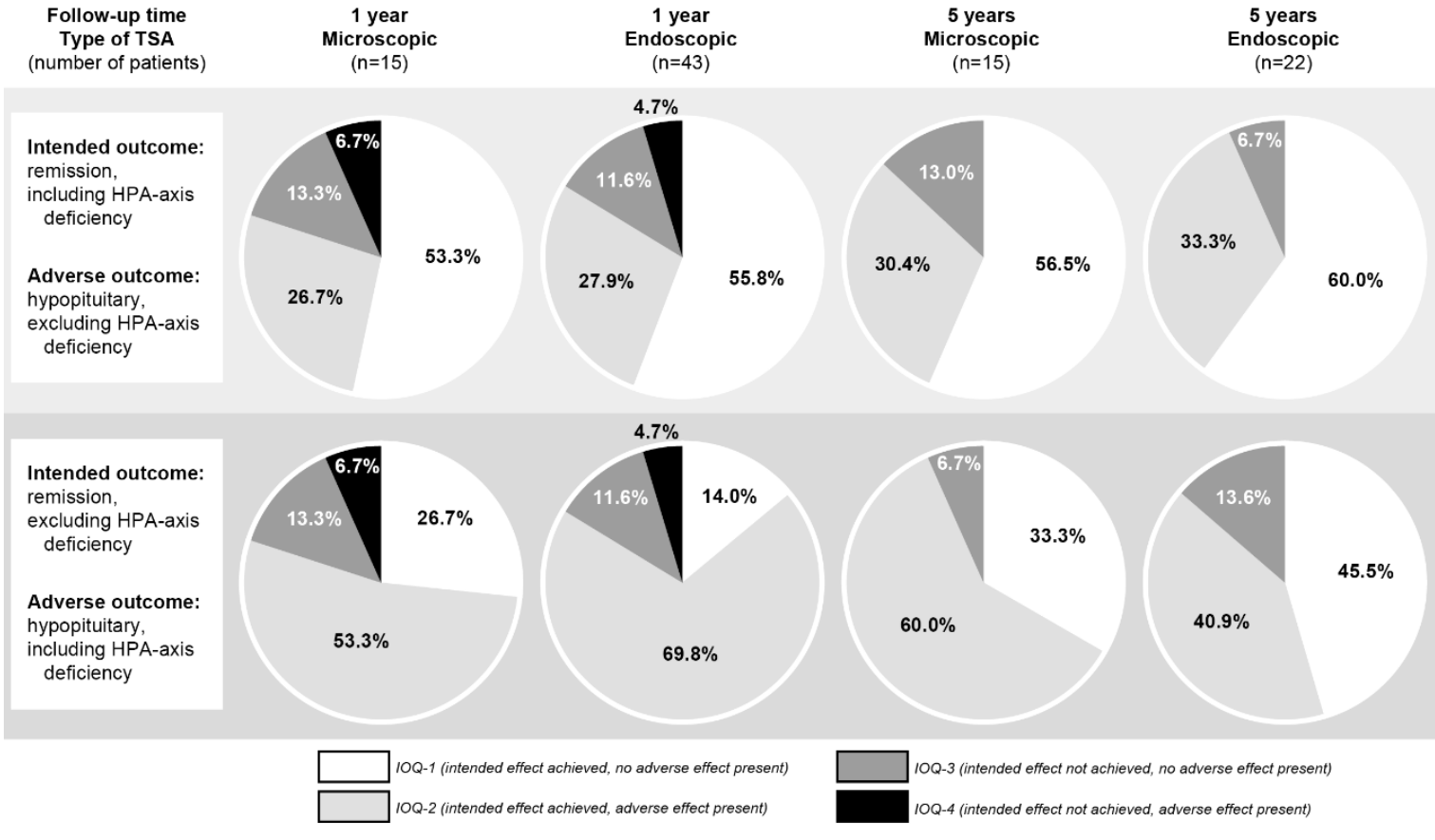

Figure 5. Outcome[2] integrated outcome quadrants in endoscopic versus microscopic transsphenoidal surgery in Cushing's disease patients.

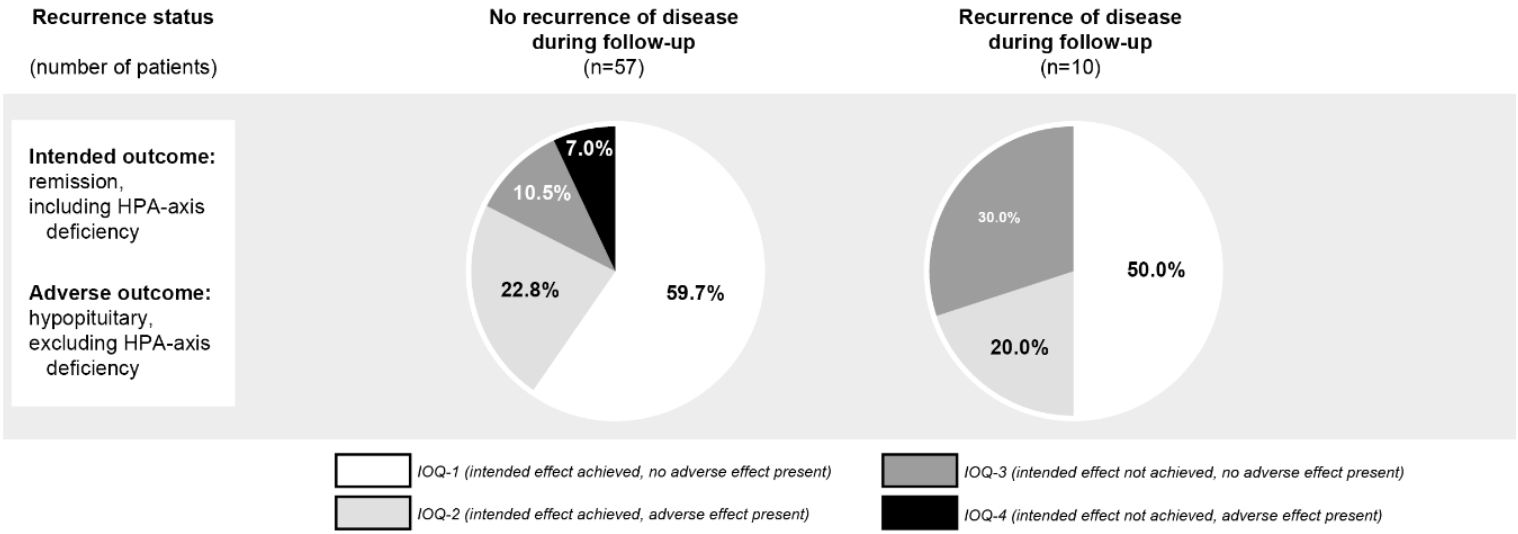

Figure 6. Outcome[2] integrated outcome quadrants in CD patients with eventual recurrence of disease versus patients without recurrence.

care team as a management approach to aim for remission without hypopituitarism, the outcome of the recurrence-of-disease group is of special interest. These patients flow through the different IOQs during the time course. During the five years of post-operative follow-up, ten patients (13.9%) manifested recurrence of disease (six macroadenoma patients, four microadenoma patients). In three of these ten patients (30.0%), recurrence of disease occurred within the first three to six months after surgery (after initial remission was biochemically confirmed), of which one was successfully re-operated within one year after first surgery.

The following re-interventions were performed: single transsphenoidal re-operation (n=2), multiple transsphenoidal re-operations (n=1), radiotherapy (n=2) or re-operation combined with radiotherapy (n=4). In one patient, no re-intervention was performed yet during follow-up time.

There were no patients with poor outcome (IOQ-4) in the recurrence-of-disease group at one year follow-up (e.g. all recurrence patients were in IOQ-3). Comparing these ten recurrence patients to the rest of de CD patients in our cohort at three months after the initial surgery, slightly less patients with an eventual recurrence were in IOQ-1 (50.0% versus 59.6% IOQ-1 in the non-recurrence group, figure 6). Of the ten patients with disease recurrence, seven were re-operated upon during follow-up time. In four of these seven patients, the re-operation was combined with radiotherapy, and one of these seven patients underwent re-operation more than once. Two patients with recurrent disease underwent radiotherapy alone in order to achieve biochemical remission. One recurrence patient did not receive any re-intervention yet during follow-up time. After re-intervention (n=9), remission was achieved in four patients (one radiotherapy alone, one multiple TSAs, two TSA combined with radiotherapy respectively), and in three patients no follow-up data was yet available as re-intervention had taken place by the end of the follow-up time. Of the four patients in remission after re-intervention, two patients were in IOQ-1 (both TSA combined with radiotherapy, with one of them having another recurrence five years after the first operation and four years after the re-intervention), two patients (one radiotherapy alone, one multiple TSAs) were in IOQ-2 at the end of follow-up. The two patients who were not in remission after re-intervention were in IOQ-3 (HPA-axis deficiency excluded as an adverse effect).

DISCUSSION

This study is the first to report on long-term outcome measures in patients with CD after transsphenoidal surgery, using Outcome2, a novel way to integrate treatment outcomes, which uniquely allows to show the delicate but clinically very important balance between treatment efficacy and safety. For CD this is of special interest as (transient) hypocortisolism can be either classified as intended, or adverse treatment effect, depending on whether the focus is on doctor's perspective or patients' perspective.

One year after surgery, good outcome was observed in 55% of the 72 included patients, whereas poor outcome was present in only 5%. When ongoing HPA-axis insufficiency was regarded as adverse outcome, only 17% of the patients showed good outcome after one year, whereas 68% was in remission with the presence of pituitary deficiencies. Over time, a gradually shift of patients to the good outcome category occurred, mainly due to recovery of the activity of the HPA-axis.

Five years after transsphenoidal surgery, the majority of patients were in remission, though a considerable proportion of patients had persistent hypopituitarism (partly explained by HPA-axis deficiency). For patients and physicians the awareness of the gradual course of recovery of HPA-axis functioning is needed when interpreting outcome, since HPA-axis deficiency is also a condition with morbidity and mortality, albeit less severe than active hypercortisolism.

Patients with microadenoma were more often in remission without new onset hypopituitarism compared to the macroadenoma patients. Also poor outcome was observed slightly more often in the macroadenoma patients, as might be expected due to the extent of the tumor and therefore the extensiveness of the surgical procedure. The results of patients with an invisible adenoma on preoperative imaging one year after surgery were not worse than the results of the rest of the cohort/microadenoma patients, despite a slightly more invasive surgical technique. These results should be taken into account in pre-operative patient counseling.

The results of the different operation techniques used in this cohort (e.g. microscopic versus endoscopic approach) did not differ significantly when comparing the IOQs. Comparing patients with eventual recurrent disease to the rest of the cohort three months after surgery, one could hypothesize more patients with eventual recurrence of disease would be in IOQ-1 direct postoperatively, due to less aggressive surgery. However, in our cohort slightly less recurrence-patients were in the good outcome group (IOQ-1) three months after surgery. The Outcome2 approach is very suitable to evaluate outcome of treatment strategies including multiple interventions instead of focusing on a single intervention. As was shown by the results of this study, even after multiple and combined interventions remission without adverse effects (IOQ-1) can be achieved and re-interventions can be considered as save. The poor outcome group (IOQ-4) is an interesting category both from patients' and doctors perspective. In our cohort, the poor outcome group is small. Macroadenoma patients and patients with an invisible/uncertain adenoma on preoperative MRI scan appeared to be at increased risk of poor outcome.

The remission rates obtained from this study are in line with previously published (small) studies on surgical outcome in CD.[38-40] An important difference between our study and other studies on surgical results in CD is that we included all surgeries, including those for giant/invasive adenomas, apoplexy and re-operations. The results of this large cohort study are theoretically generalizable to all CD patients treated by transsphenoidal adenomectomy, however, the generalizability may be reduced by the specific setting in our tertiary referral hospital, since all patients in this study were operated by experienced neurosurgeons and difficult procedures were not shunned, and the time period of inclusion.

In the current available literature, there are no other cohort studies presenting their surgical results against the important balance between the efficacy and safety of surgical treatment. This balance is of particular importance in the CD population, as the delicate balance between remission and ongoing pituitary gland injury is of major importance for the patient's wellbeing and quality of life.[8-12] Outcome2 can be used for uniform reporting of results and provide more accurate information at a glance for individualized patient counselling in the physician's office. With the presentation of results of this study, a care provider can easily recognize patient groups with good or adverse outcomes and modify treatment strategies accordingly if applicable. The use of Outcome2 can

provide comparisons of outcomes of different treatment strategies, for example medical therapy versus radiotherapy in persistent disease, and other outcomes relevant to patients and their quality of life (e.g. symptomatology, burden of disease, functional outcome) can be incorporated in the four outcome categories (IOQs) by adjusting the definitions of intended and adverse effects. The Outcome2 method for integrating outcome reveals specific elements of interest for each outcome group. For instance, the "intended effect at a cost" group (IOQ-2) shows which patients are paying a price for cure, and in the "no harm done" group (IOQ-3) an additional intervention may be useful to still achieve the treatment goal. It would be of interest to future research to include quality of life measures in the definitions of the four IOQs, to even further refine the outcome analysis. The Outcome2 approach is also very suitable to evaluate outcome of treatment strategies including multiple interventions instead of focusing on a single intervention. As was shown by the results of this study, even after multiple and combined interventions remission without adverse effects (IOQ-1) can be achieved and re-interventions can be considered as save. The form of outcome integration as depicted by the four IOQs can be used for the comparison between centres and studies, provided that identical definitions and outcome are used. In the pituitary field, we propose to use the Outcome2 approach, however, international consensus is needed. The advantages of the Outcome2 approach include a unified outcome measure regardless of the type of intervention or measurements used, taking the balance between efficacy and safety/adverse effects into account, actionable evaluation purposes providing insight in the shift of patients over different outcome categories over time, and insight in the impact of HPA-axis deficiency which is most relevant from a patients' perspective.

When interpreting the results of this study, a few limitations need to be taken into account. First of all, selective loss to follow-up could have led to selection bias. However, analysis of the distribution of patients lost to follow-up at five years after surgery over the IOQs after three months of follow-up showed these patients were similarly distributed over the four categories/IOQs as was the total group of patients at that point in time. Various reasons including both very poor health status as well as excellent health could have led to loss to follow-up, therefore the direction in which the results may have been biased could not be determined. Secondly, by dividing patients in four outcome categories, the number of patients per group were small in certain subgroup analyses. Furthermore, patients treated according to the microscopic surgical approach underwent surgery in a different time period compared to the patients treated by means of endoscopic surgery, since patients were not randomized to a certain operation technique, but were treated by the technique used at that time. This might have resulted in differences between these two subgroups. Baseline patients characteristics, such as the presence of comorbidities, size and invasiveness of the tumor, medical pretreatment and CSI score, did however not differ between the two groups. Over time, diagnostic imaging has changed with respect to the quality of MRI, resulting in better visualization of suspect lesions to target during surgery. Therefore, the effect of the imaging technique can theoretically not be separated from the effect of the surgical technique. Moreover, the volume of transsphenoidal operations per year in our center has increased over the years. It is well described that the surgeons volume of pituitary interventions is crucial to its outcomes.[41] Nonetheless, with the increase of the number of transsphenoidal operations in our center over the years, there was also an increase in

more difficult procedures, e.g. giant or invasive adenomas, which makes it challenging to determine the direction in which this might have biased our results. The determination of the goal/intended effect of treatment of each patient is discussed in our multidisciplinary pituitary care team, which plays a key role in pituitary care in the Leiden University Medical Center.

In conclusion, this study is the first to report on long-term outcome measures in a large cohort of CD patients after transsphenoidal surgery using the Outcome2 integrated outcome approach. This study shows that the majority of patients are in remission five years after transsphenoidal surgery, though in a considerable part of the patients at the expense of persistent failure of pituitary functions, including ongoing hypocortisolism. Application of the four different IOQs used provides an uniform, overall view at a glance of the important balance between efficacy and safety of the transsphenoidal adenomectomy in CD, and can be a helpful tool in individualised patient counselling.

REFERENCES

1. Lindholm J, Juul S, Jorgensen JO, Astrup J, Bjerre P, Feldt-Rasmussen U, et al. Incidence and late prognosis of cushing's syndrome: a population-based study. J Clin Endocrinol Metab. 2001;86(1):117-23.
2. Fernandez-Rodriguez E, Stewart PM, Cooper MS. The pituitary-adrenal axis and body composition. Pituitary. 2009;12(2):105-15.
3. Pereira AM, Tiemensma J, Romijn JA. Neuropsychiatric disorders in Cushing's syndrome. Neuroendocrinology. 2010;92 Suppl 1:65-70.
4. Plotz CM, Knowlton AI, Ragan C. The natural history of Cushing's syndrome. Am J Med. 1952;13(5):597-614.
5. Nieman LK, Biller BM, Findling JW, Murad MH, Newell-Price J, Savage MO, et al. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2015;100(8):2807-31.
6. Chandler WF, Schteingart DE, Lloyd RV, McKeever PE, Ibarra-Perez G. Surgical treatment of Cushing's disease. J Neurosurg. 1987;66(2):204-12.
7. Trainer PJ, Lawrie HS, Verhelst J, Howlett TA, Lowe DG, Grossman AB, et al. Transsphenoidal resection in Cushing's disease: undetectable serum cortisol as the definition of successful treatment. Clin Endocrinol (Oxf). 1993;38(1):73-8.
8. Bunevicius A, Laws ER, Vance ML, Iuliano S, Sheehan J. Surgical and radiosurgical treatment strategies for Cushing's disease. J Neurooncol. 2019;145(3):403-13.
9. Svider PF, Raikundalia MD, Pines MJ, Baredes S, Folbe AJ, Liu JK, et al. Inpatient Complications After Transsphenoidal Surgery in Cushing's Versus Non-Cushing's Disease Patients. Ann Otol Rhinol Laryngol. 2016;125(1):5-11.
10. Crespo I, Santos A, Webb SM. Quality of life in patients with hypopituitarism. Curr Opin Endocrinol Diabetes Obes. 2015;22(4):306-12.
11. Webb SM, Santos A, Aulinas A, Resmini E, Martel L, Martinez-Momblan MA, et al. Patient-Centered Outcomes with Pituitary and Parasellar Disease. Neuroendocrinology. 2020;110(9-10):882-8.
12. Crespo I, Valassi E, Santos A, Webb SM. Health-related quality of life in pituitary diseases. Endocrinol Metab Clin North Am. 2015;44(1):161-70.
13. Kasaliwal R, Sankhe SS, Lila AR, Budyal SR, Jagtap VS, Sarathi V, et al. Volume interpolated 3D-spoiled gradient echo sequence is better than dynamic contrast spin echo sequence for MRI detection of corticotropin secreting pituitary microadenomas. Clin Endocrinol (Oxf). 2013;78(6):825-30.
14. Yamada S, Fukuhara N, Nishioka H, Takeshita A, Inoshita N, Ito J, et al. Surgical management and outcomes in patients with Cushing disease with negative pituitary magnetic resonance imaging. World Neurosurg. 2012;77(3-4):525-32.
15. Portocarrero-Ortiz L, Bonifacio-Delgadillo D, Sotomayor-Gonzalez A, Garcia-Marquez A, Lopez-Serna R. A modified protocol using half-dose gadolinium in dynamic 3-Tesla magnetic resonance imaging for detection of ACTH-secreting pituitary tumors. Pituitary. 2010;13(3):230-5.
16. Lacroix A, Feelders RA, Stratakis CA, Nieman LK. Cushing's syndrome. Lancet. 2015;386(9996):913-27.
17. Wind JJ, Lonser RR, Nieman LK, DeVroom HL, Chang R, Oldfield EH. The lateralization accuracy of inferior petrosal sinus sampling in 501 patients with Cushing's disease. J Clin Endocrinol Metab. 2013;98(6):2285-93.
18. Ilias I, Torpy DJ, Pacak K, Mullen N, Wesley RA, Nieman LK. Cushing's syndrome due to ectopic corticotropin secretion: twenty years' experience at the National Institutes of Health. J Clin Endocrinol Metab. 2005;90(8):4955-62.
19. Hall WA, Luciano MG, Doppman JL, Patronas NJ, Oldfield EH. Pituitary magnetic resonance imaging in normal human volunteers: occult adenomas in the general population. Ann Intern Med. 1994;120(10):817-20.
20. Mendola M, Dolci A, Piscopello L, Tomei G, Bauer D, Corbetta S, et al. Rare case of Cushing's disease due to double ACTH-producing adenomas, one located in the pituitary gland and one into the stalk. Hormones (Athens). 2014;13(4):574-8.
21. Andrioli M, Pecori Giraldi F, Losa M, Terreni M, Invitti C, Cavagnini F. Cushing's disease due to double pituitary ACTH-secreting adenomas: the first case report. Endocr J. 2010;57(9):833-7.
22. Ohnishi T, Arita N, Yoshimine T, Mori S. Intracavernous sinus ectopic

adrenocorticotropin-secreting tumours causing therapeutic failure in transsphenoidal surgery for Cushing's disease. Acta Neurochir (Wien). 2000;142(8):855-64.

23. Koizumi M, Usui T, Yamada S, Fujisawa I, Tsuru T, Nanba K, et al. Successful treatment of Cushing's disease caused by ectopic intracavernous microadenoma. Pituitary. 2011;14(3):295-8.
24. Hofmann BM, Hlavac M, Martinez R, Buchfelder M, Muller OA, Fahlbusch R. Long-term results after microsurgery for Cushing disease: experience with 426 primary operations over 35 years. J Neurosurg. 2008;108(1):9-18.
25. Aranda G, Ensenat J, Mora M, Puig-Domingo M, Martinez de Osaba MJ, Casals G, et al. Long-term remission and recurrence rate in a cohort of Cushing's disease: the need for long-term follow-up. Pituitary. 2015;18(1):142-9.
26. Atkinson AB, Kennedy A, Wiggam MI, McCance DR, Sheridan B. Long-term remission rates after pituitary surgery for Cushing's disease: the need for long-term surveillance. Clin Endocrinol (Oxf). 2005;63(5):549-59.
27. Friedman RB, Oldfield EH, Nieman LK, Chrousos GP, Doppman JL, Cutler GB, Jr., et al. Repeat transsphenoidal surgery for Cushing's disease. J Neurosurg. 1989;71(4):520-7.
28. Ram Z, Nieman LK, Cutler GB, Jr., Chrousos GP, Doppman JL, Oldfield EH. Early repeat surgery for persistent Cushing's disease. J Neurosurg. 1994;80(1):37-45.
29. Braun LT, Rubinstein G, Zopp S, Vogel F, Schmid-Tannwald C, Escudero MP, et al. Recurrence after pituitary surgery in adult Cushing's disease: a systematic review on diagnosis and treatment. Endocrine. 2020;70(2):218-31.
30. Braun LT, Zopp S, Vogel F, Honegger J, Rubinstein G, Schilbach K, et al. Signs, symptoms and biochemistry in recurrent Cushing disease: a prospective pilot study. Endocrine. 2021;73(3):762-6.
31. de Vries F, Lobatto, D.J., Verstegen, M.J.T., Schutte, P.J., Notting, I.C., Kruit, M.C., Ahmed, S.F., Pereira, A.M., van Furth, W.R., Biermasz, N.R. Outcome Squares integrating efficacy and safety, as applied to functioning pituitary adenoma surgery. J Clin Endocrinol Metab. 2021;Mar 6(dgab138).
32. Broersen LHA, van Haalen FM, Biermasz NR, Lobatto DJ, Verstegen MJT, van Furth WR, et al. Microscopic versus endoscopic transsphenoidal surgery in the Leiden cohort treated for Cushing's disease: surgical outcome, mortality, and complications. Orphanet J Rare Dis. 2019;14(1):64.
33. van Furth WR, de Vries F, Lobatto DJ, Kleijwegt MC, Schutte PJ, Pereira AM, et al. Endoscopic Surgery for Pituitary Tumors. Endocrinol Metab Clin North Am. 2020;49(3):487-503.
34. de Vries F, Lobatto DJ, Verstegen MJT, van Furth WR, Pereira AM, Biermasz NR. Postoperative diabetes insipidus: how to define and grade this complication? Pituitary. 2021;24(2):284-91.
35. Broersen LHA, van Haalen FM, Kienitz T, Biermasz NR, Strasburger CJ, Dekkers OM, et al. Sex Differences in Presentation but Not in Outcome for ACTH-Dependent Cushing's Syndrome. Front Endocrinol (Lausanne). 2019;10:580.
36. Valassi E, Santos A, Yaneva M, Toth M, Strasburger CJ, Chanson P, et al. The European Registry on Cushing's syndrome: 2-year experience. Baseline demographic and clinical characteristics. Eur J Endocrinol. 2011;165(3):383-92.
37. Sonino N, Boscaro M, Fallo F, Fava GA. A clinical index for rating severity in Cushing's syndrome. Psychother Psychosom. 2000;69(4):216-20.
38. Alahmadi H, Cusimano MD, Woo K, Mohammed AA, Goguen J, Smyth HS, et al. Impact of technique on cushing disease outcome using strict remission criteria. Can J Neurol Sci. 2013;40(3):334-41.
39. Atkinson JL, Young WF, Jr., Meyer FB, Davis DH, Nippoldt TB, Erickson D, et al. Sublabial transseptal vs transnasal combined endoscopic microsurgery in patients with Cushing disease and MRI-depicted microadenomas. Mayo Clin Proc. 2008;83(5):550-3.
40. Cheng RX, Tian HL, Gao WW, Li ZQ. A comparison between endoscopic trans-sphenoidal surgery and traditional trans-sphenoidal microsurgery for functioning pituitary adenomas. J Int Med Res. 2011;39(5):1985-93.
41. Honegger J, Grimm F. The experience with transsphenoidal surgery and its importance to outcomes. Pituitary. 2018;21(5):545-55.