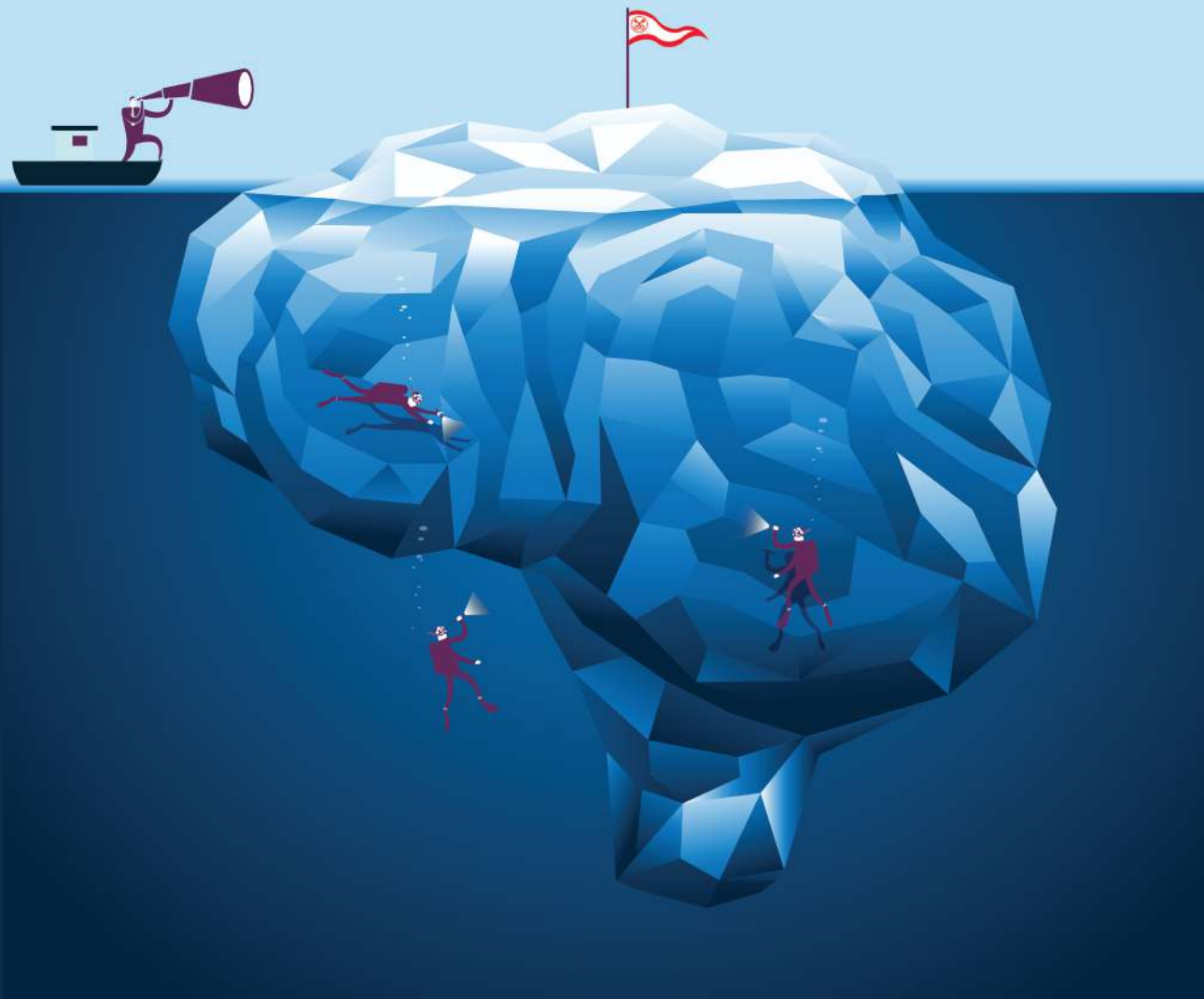
Value Based Pituitary Care

Implementing Value Based Health Care in a rare disease

Daniel Lobatto



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Voor mijn ouders,
Hanneke en Josephine

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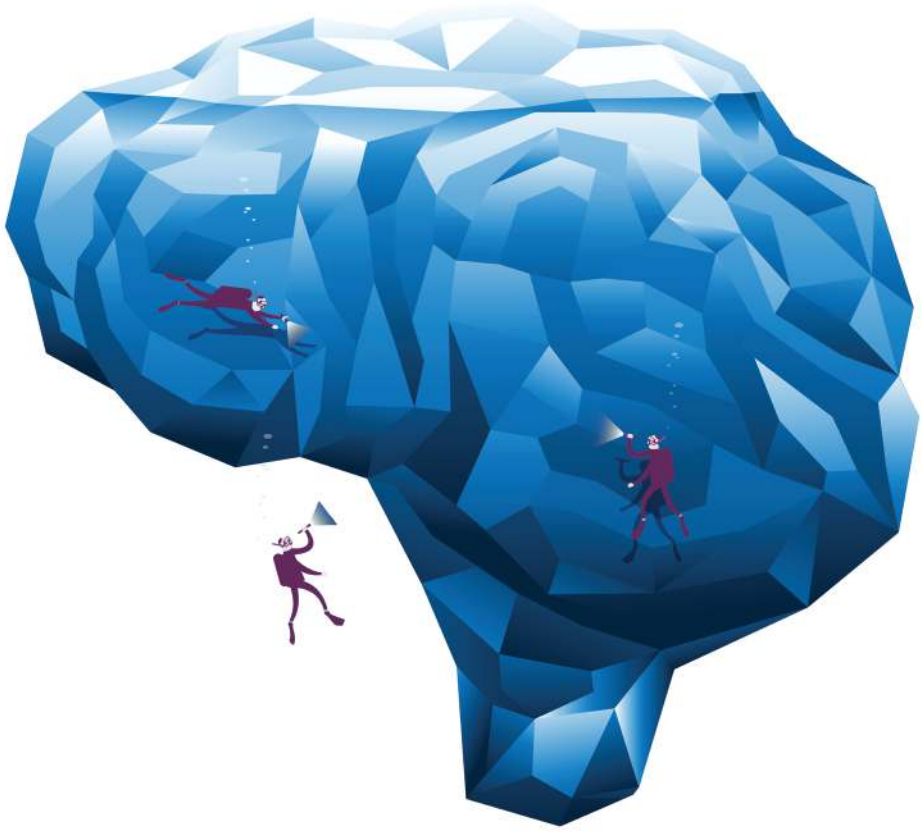

1

General introduction and thesis outline

VALUE BASED PITUITARY CARE

Implementing Value Based Health Care in a rare disease

Pituitary tumors are rare neoplasms of endocrine origin with an incidence rate of 3.9 per 100,000 persons per year [1] and a prevalence of 78 to 94 cases per 100,000 persons [2]. The presence of a pituitary tumor usually has a considerable impact on a patient's health status. As a consequence, most patients with pituitary tumors need complex and longstanding surgical and/or non-surgical care and lifelong medical follow-up. Regarding the therapeutic options, great advances have been made over the past decades, so that different treatments are now available for most types of pituitary tumors.

So far, the focus on the measurement of treatment effects has been on surgical and/or endocrinological outcomes, albeit not in a systematic way. Nowadays, however, there is a growing acknowledgement of the importance of employing a broader perspective with respect to patients' health status, including aspects such as patient experiences, health care needs, and societal participation. This broader view on health outcomes is in line with the Value Based Health Care (VBHC) model, with its overarching goal to increase value for the patient. Although the concept of VBHC is increasingly used in clinical practice, evaluations of its application in daily practice, including care for patients with a pituitary tumor, are limited.

The application of these concepts of VBHC on care for patients with a pituitary tumor is the main focus of this thesis. In this general introduction, pituitary pathology and treatment options for patients with pituitary tumors are briefly described. Furthermore, the VBHC model is introduced and the aims of the thesis are formulated.

PITUITARY

The pituitary is a gland situated at the base of the skull and can be divided into an anterior and posterior part, which orchestrate the regulation of hormones (figure 1).

The anterior pituitary

- Adrenocorticotropic hormone (ACTH) stimulates the adrenal cortex to produce cortisol, which ultimately mediates in the body's stress response.
- Growth hormone (GH) stimulates growth and repair of body tissues, such as bones and muscles.

- Thyroid-stimulating hormone (TSH) stimulates the thyroid gland to produce thyroxine to regulate basal metabolism, oxygen use, nutrient metabolism, production of ATP and calcium hemostasis.
- Follicle-stimulating hormone (FSH) stimulates the production and maturation of sex cells.
- Luteinizing hormone (LH) triggers ovulation, the production of estrogens and progesterone in women. Both play a key role in developing and maintaining the female reproductive system, as well as maintaining pregnancy. In men, LH stimulates the testes to produce testosterone, which is responsible for the maturation and maintenance of the male reproductive system, as well as the development of male secondary sex characteristics.
- Prolactin stimulates lactation (milk production) in women.

The posterior pituitary

- Antidiuretic hormone (ADH) stimulates water reabsorption by the kidneys and plays an important role in the calibration of the fluid balance.
- Oxytocin stimulates uterine contractions during childbirth.

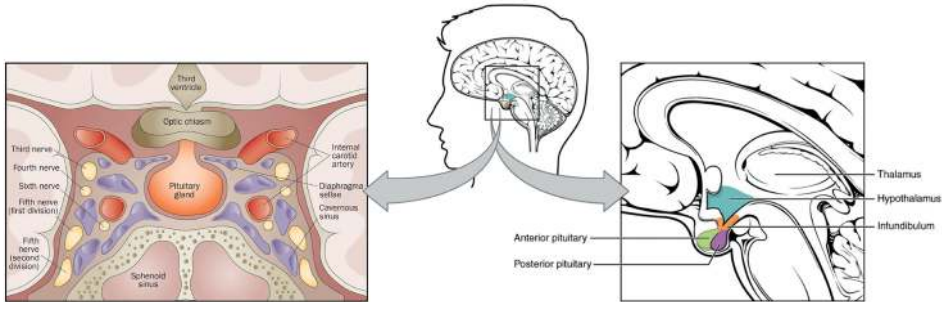

Figure 1. Anatomy of pituitary gland and its surrounding structures (left: coronal view; right: sagittal view), derived from Anatomy & Physiology: The Endocrine System and Di Leva Nature Reviews 2014

PITUITARY TUMORS

Pituitary tumors deriving from or around the pituitary are able to cause disruptions in these hormonal pathways. When pituitary tumors originate from the pituitary, they are called pituitary adenomas. These can be grossly divided into hormone secreting or non-secreting adenomas (non-functioning adenoma (NFA)). Hormone secreting tumors include: 1) GH producing tumors causing acromegaly (ACRO), 2) ACTH producing tumors causing Cushing's disease (CD), and 3) Prolactin-producing tumors called prolactinomas (PRL). Other pathologies that derive from the region of the pituitary are Rathke's cleft cysts and craniopharyngiomas, which have a different aetiology, however with an

overlapping symptomatology. Parasellar lesions, such as meningiomas, may also interact with the pituitary causing disruptions in the pituitary function. Therefore, nowadays these tumors are also included in the care pathway.

Symptomatology depends on location, size and whether a tumor secretes hormones. Location-specific symptoms are caused by compression of surrounding structures and include, among others, decreased visual acuity, bitemporal hemianopia (compression of the optic apparatus), ophthalmoplegia (compression of the third cranial nerve), pituitary hormone deficiency (compression of the pituitary), headache, and fatigue (figure 1). Hormone secreting pituitary tumors can also cause systemic signs and symptoms, such as growth of a patient's hands, feet and jaw, generalized organomegaly and corresponding comorbidity in patients with acromegaly, central obesity, stretch marks, a buffalo hump and corticosteroid-induced physical and neurocognitive multimorbidity in patients with Cushing's disease and amenorrhea/galactorrhoea in patients with a prolactinoma.

The goals and therefore also the treatment of pituitary adenomas is dependent on the individual situation (e.g. tumor type, compression of the optic chiasm, hormone hypersecretion or deficiencies, tumor volume control) (table 1).

Table 1. Treatment options for patients with a pituitary adenoma

	NFA	ACRO	CD	PRL
Primary	Surgery in case of symptomatology, wait-and-scan if not	Surgery	Surgery	Dopamine agonists
Secondary	Surgery in case of symptomatology	Surgery, if not possible somatostatin receptor ligands	Surgery, if not possible steroidogenesis inhibitors	Surgery in case of drug intolerance, drug resistance or patient preference
Chronic management	Evaluation of hormone deficiencies/excesses Supplementation of deficient hormones			

For patients with functioning tumors, for instance, the primary goal is to control/restore hypersecretion of hormones. For patients with a non-functioning adenoma, RCC or craniopharyngioma, the goal is to restore function of compressed structures. Therefore, for most pituitary tumors, primary treatment consists of surgical resection [3–5], with the exception of prolactinomas, which are primarily treated with dopamine agonists. For those patients, current practice is to perform surgery only in case of drug intolerance, drug resistance or patient preference [6]. For patients with acromegaly, secondary or alternative primary treatment consists of somatostatin receptor ligands (in most cases), or in some cases pegvisomant or dopamine agonists [3]. Secondary treatment for patients

with Cushing's disease consists of reoperation and, if not possible, of steroidogenesis inhibitors, other medical treatments, universal SRL, pasireotide, radiotherapy or bilateral adrenalectomy. For all tumors, reoperation can be considered, and when all other treatment options have been exhausted, radiotherapy can be considered. In patients with non-functioning tumors and without clear compressive symptoms, wait-and-scan may be the best option. In the absence of randomized trials between medical strategies, the evidence regarding the best treatment for which patient in which situation is scanty. In some cases, there is no obvious best treatment option and particularly for those cases, shared-decision making based on a comprehensive set of outcomes would be helpful.

Based on the aforementioned arguments, i.e. the great variety of symptoms and the variety of treatment options as well as the impact on functioning (activities and participation), patients with pituitary tumors require a highly multidisciplinary approach and lifelong follow-up. Many patients are permanently impacted by the disease and in order to optimize treatment/outcomes, knowledge of the outcomes over the full-cycle of care is necessary. Such outcomes, including information on the needs for help of patients as well as information on societal participation, are currently largely lacking in the literature.

VALUE BASED HEALTHCARE

One way to look at outcomes over the full cycle of care is through the framework of Value Based Health Care (VHBC) which was introduced in 2006 by Michael Porter and Elizabeth Teisberg and aims to organize care around a patient's medical condition. To achieve the overarching goal of VHBC, namely increasing value for the patient, outcomes can be improved or costs can be reduced [7, 8]. VHBC further aims to measure health outcomes that include all domains of health. To do so, outcomes are divided into three tiers: 1) Health status achieved or attained, 2) process of recovery, and 3) sustainability of health, which can be used as a connecting thread throughout the treatment process. This is in contrast to many current practices, which, in general, focus primarily on clinician-reported outcomes/process measures such as mortality, cure/remission, long-term morbidity and (limiting) complications, while patient-reported outcomes would be more appropriate and would better reflect what matters most for patients.

Applying VBHC could be relevant for patients with pituitary tumors, mainly due to the complexity of the disease and the highly multidisciplinary care necessary for these patients. Implementing VBHC and systematically evaluating a defined multidisciplinary care trajectory, which includes all appropriate caregivers, would help to further shape

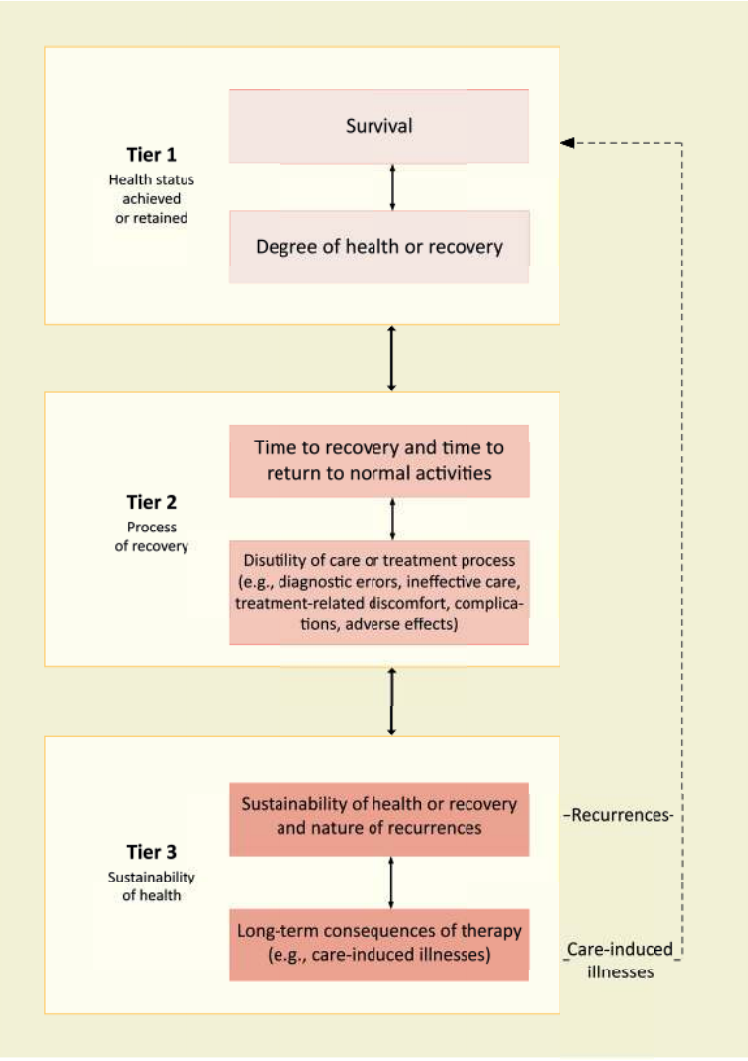

Figure 2. Three-tier model of Value Based Health Care, reproduced with permission from Porter NEJM 2010, Copyright Massachusetts Medical Society.

the care around the patient and consider outcomes that are relevant for the patient, which could lead to more effective and efficient delivery of care, tailored to the needs of individual patients.

The Leiden University Medical Center has a long history of treating patients with pituitary tumors. As the first Dutch transsphenoidal surgery was performed in Leiden in 1979, over the past several decades, the care for patients with a pituitary tumor has evolved into a high volume center which surgically treats 100-150 patients per year.

Nowadays, the Center for Endocrine Tumors Leiden (CETL) is a leading center in the European Reference Network for rare diseases. With the help of Information Technology (IT) support systems and the integration of care trajectories, we have migrated towards an Integrated Practice Unit (IPU), where the patient is at the center of care and is seen by both an endocrinologist and neurosurgeon at the outpatient clinic (an example of a care trajectory is shown in figure 3).

Previous research performed at our center has shown the impact on patients' long-term health-related quality of life (HRQoL), which ultimately improves after treatment, but remains impaired in most patients.

Although over the last couple of years there have been tremendous improvements in obtaining insight into why HRQoL remains impaired in many patients and in the care provided for pituitary tumor patients, there are still knowledge gaps that should be addressed. By applying VBHC to multidisciplinary pituitary care, we believe we will be able to obtain knowledge over the full-cycle of care, decrease the following knowledge gaps and guide patients based on outcomes:

1) There is a lack of knowledge of risk factors for postoperative complications;
2) There is limited knowledge of perioperative patient-perceived outcomes;
3) There is limited knowledge of long-term participation and the extent of healthcare usage.

AIMS AND OUTLINE OF THIS THESIS

The objective of this thesis was to study the implementation of VBHC into daily practice for patients with pituitary tumors. For this purpose, the following specific research questions were formulated:

1) What risk factors should we be aware of when treating patients with pituitary tumors?
2) What are comprehensive acute and subacute perioperative outcomes of surgically treated patients with pituitary tumors, either or not in the context of a defined short-stay care pathway?
3) To what extent can patients with pituitary tumors maintain or regain societal participation, with emphasis on paid employment?
4) What is the current healthcare utilization of patients with pituitary tumors in the chronic phase of their condition?

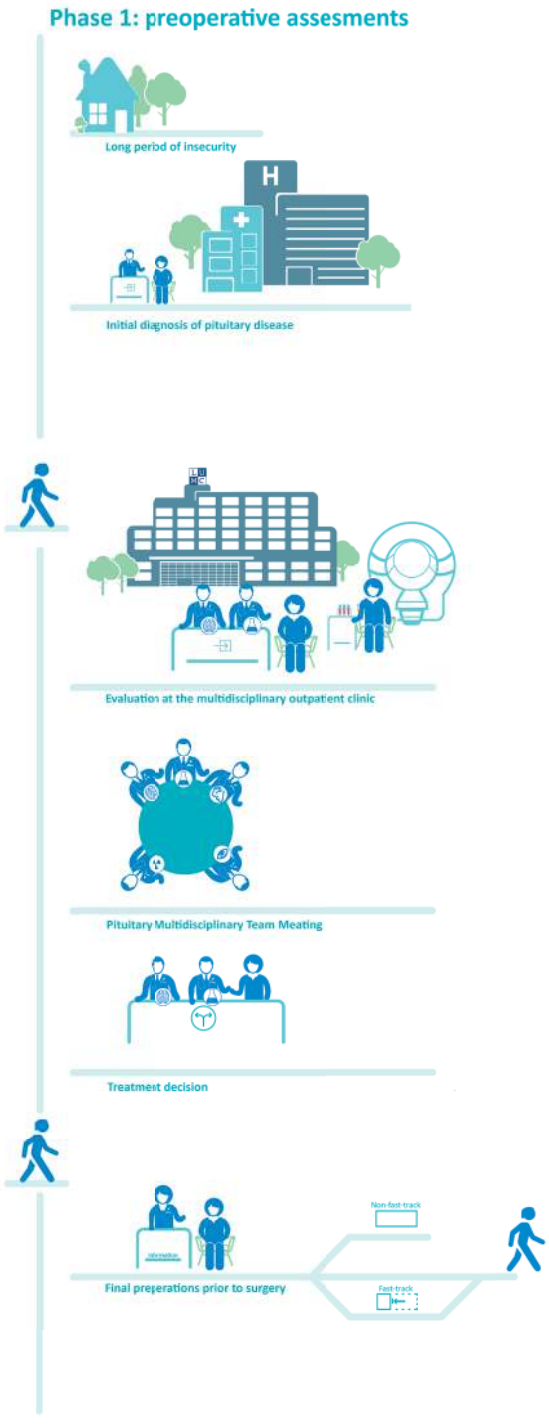

Figure 3. Example of our pituitary care trajectory (situation after implementation of a fast-track protocol).

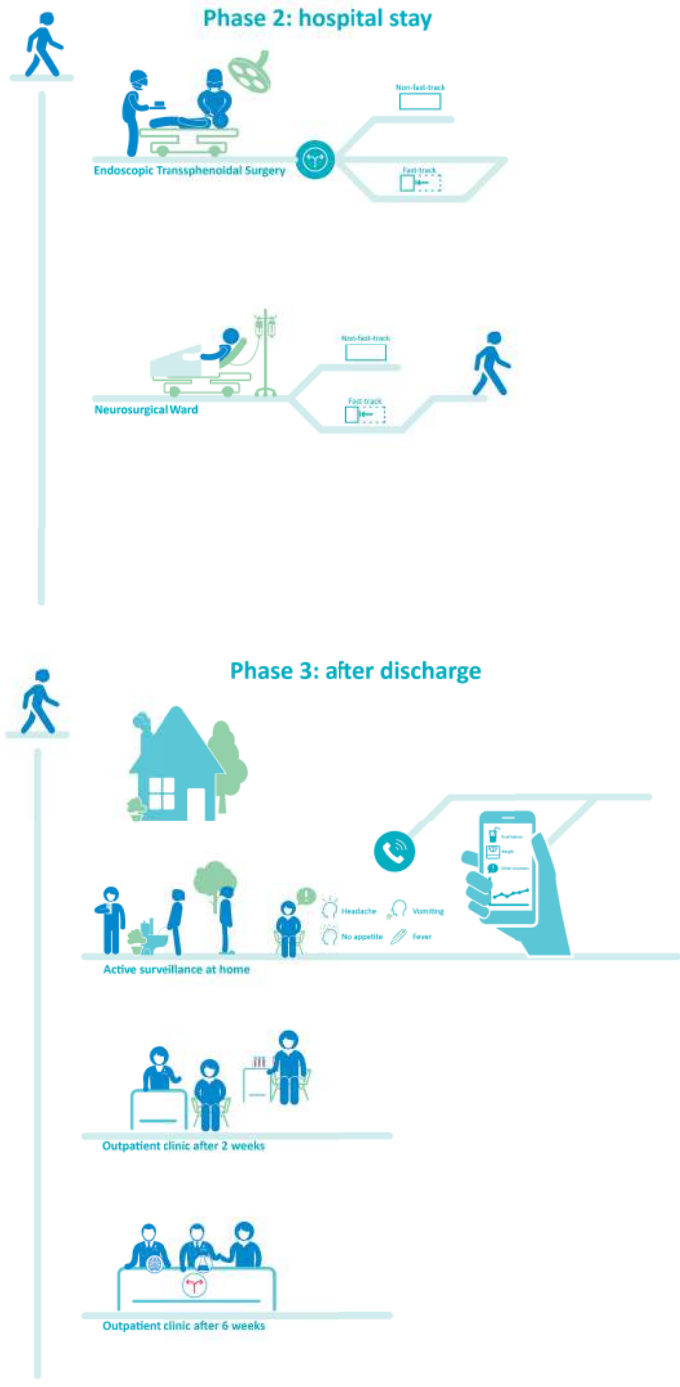

Figure 3. Example of our pituitary care trajectory (situation after implementation of a fast-track protocol). (continued)

The first three chapters of this dissertation describe overviews of existing literature that reflect considerations for the treatment of patients with pituitary tumors.

In **Chapter 2**, the study objective was to identify preoperative risk factors for postoperative complications. **Chapters 3 and 4** discuss two case studies that reflect dilemmas that physicians have to deal with during clinical practice during treatment of patients with pituitary tumors.

The following two chapters focus on the care pathway and how perioperative outcomes can be integrated into current care for patients with pituitary tumors. **Chapter 5** discusses the perioperative patient- and physician-reported outcomes according to the three-tier model of VBHC. In **Chapter 6**, we evaluated a patient-centered fast-track discharge protocol on safety, feasibility, patient-reported outcomes and costs.

The objective of **Chapter 7** was to analyze which health-issues are present in the chronic phase after treatment of a pituitary tumor, specifically patients with non-functioning adenomas. This overview provides insight into which issues are necessary to address in the chronic phase. These insights, alongside the issues regarding work reported by many patients during previous focus group interviews, led to **Chapter 8**, in which we evaluated the extent of work-related disabilities among patients with pituitary tumors.

For **Chapter 9,** the goal was twofold: (1) to assess costs, and with that (partially) complete the value quotient of having a pituitary tumor and (2) to assess which healthcare professionals are active in the treatment of patients with a pituitary tumor in order to further improve the care pathways for patients with pituitary tumors.

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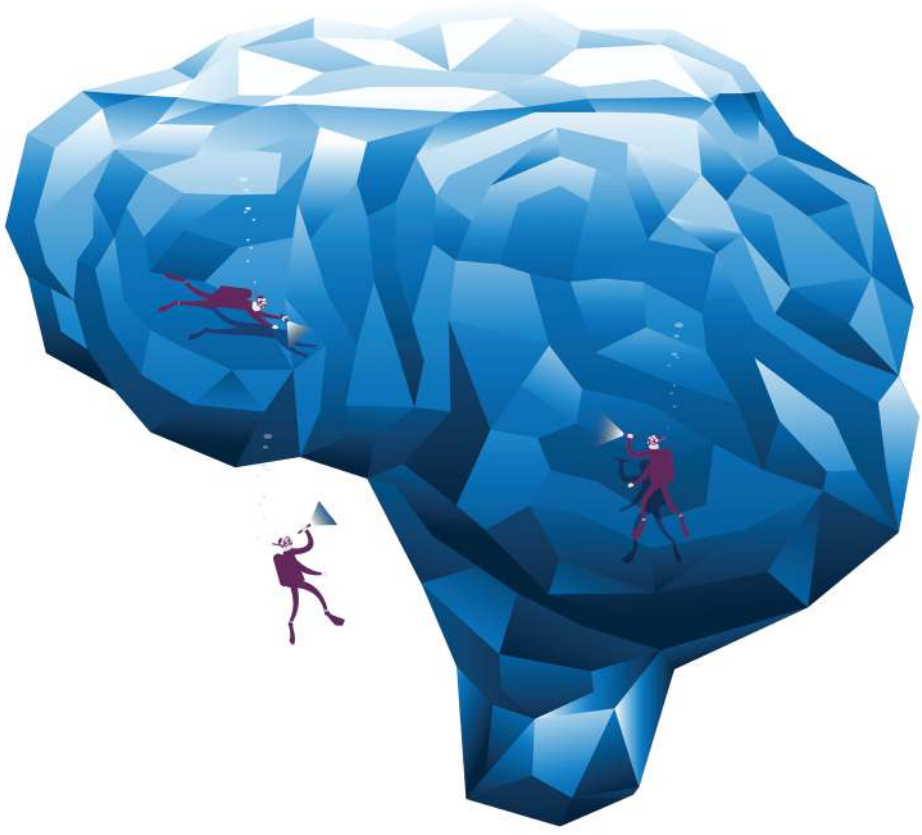
Part 1

Considerations for the treatment of a patient with a pituitary tumor



2

Preoperative risk factors for postoperative complications in endoscopic pituitary surgery: a systematic review

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Pituitary 2018

ABSTRACT

Background

The ability to preoperatively predict postoperative complication risks is valuable for individual counseling and (post)operative planning, e.g. to select low-risk patients eligible for short stay surgery or those with higher risks requiring special attention. These risks however, are not well established in pituitary surgery.

Methods

We conducted a systematic review of associations between preoperative characteristics and postoperative complications of endoscopic transsphenoidal surgery according to the PRISMA guidelines. Risk of bias was assessed through the QUIPS tool.

Results

In total 23 articles were included, containing 5491 patients (96% pituitary adenoma). There was a wide variety regarding the nature and number of risk factors, definitions, measurement and statistics employed, and overall quality of mainly retrospective studies was low. Consistent significant associations were older age for complications in general, and intraventricular extension for cerebrospinal fluid (CSF) leaks. Associations identified in some but not all studies were younger age, increased BMI, female gender, and learning curve for CSF leaks; increased tumor size for complications in general; and Rathke's cleft cysts for diabetes insipidus. Mortality (incidence rate 1%) was not addressed as a risk factor.

Conclusion

Based on current literature, of low to medium quality, it is not possible to comprehensively quantify risk factors for complications. Nevertheless, older age and intraventricular extension were associated with increased postoperative complications. Future research should aim at prospective data collection, reporting of outcomes, and uniformity of definitions. Only then a proper risk analysis can be performed for endoscopic pituitary surgery.

INTRODUCTION

Over the past two and a half decades, pituitary surgery has undergone major technical developments, the introduction of the endoscope perhaps being the most important one. Several systematic reviews show relatively better results in terms of gross total resection, with reduced complication rates for endoscopic surgery compared to microscopic surgery [1–10]. These complication rates in endoscopic transsphenoidal surgery (ETS) are relatively low; however, they can still be significant. In clinical decision-making, it is important to identify patients with an increased risk preoperatively for obvious reasons, e.g. planning and timing of the surgical intervention. Identified individual risk factors may be used to stimulate awareness in an attempt to reduce complication rates, improve patient counseling, and identify patients with an expected low-risk procedure, eligible for short stay surgery. Consultation with or even referral to a center of excellence is warranted in high risk patients to consider different surgical and alternative treatment strategies, such as medication and radiotherapy. A considerable number of clinical studies have reported on risk factors for complications after ETS; however, a systematic overview of the literature is lacking. The present study, therefore, aimed to systematically review the literature on preoperative risk factors for complications after ETS for pituitary tumors.

METHODS

A systematic review was conducted according to a predefined protocol, which was based on the PRISMA criteria for systematic reviews [11] and registered in Prospero, registration number CRD42017057835. The selection of studies, extraction of data, and assessment of the risk of bias were done by two independent reviewers (D.J.L. and F.V.). Disagreement was resolved through discussion and consensus. If discussion failed to lead to a consensus, a third researcher would be consulted; this did not occur, however.

Search strategy

A literature search was conducted on May 15 2017, with the guidance of a trained clinical librarian (J.S.). The following databases were searched: PubMed, Embase, Web of Science, Cochrane, CINAHL, Academic Search Premier and ScienceDirect. Terms included were ‘pituitary adenoma’, ‘non-functioning adenoma’, ‘acromegaly’, ‘Cushing’s disease’, ‘prolactinoma’, ‘Craniopharyngioma’, ‘Rathke’s cleft cyst’, ‘complications’, ‘risk factors’ and ‘prognosis’, and derivatives or synonyms of these words. The complete search strategy can be found in online supplement 1. Reference checking of included studies was performed to screen for additional studies.

Inclusion of articles

Inclusion criteria were: (1) articles reporting on outcomes of ETS for pituitary tumors; (2) describing an association between ≥1 preoperative characteristics and ≥1 postoperative complications; (3) published in English; (4) peer-reviewed; (5) containing original clinical data; and (6) including >10 adult patients (>18 years). Excluded studies were: (a) microscopic, endoscopic-assisted surgery, or combined microscopic and endoscopic approaches without a separate description of endoscopic results, (b) articles without a described association, and (c) articles including >10% other pathologies than pituitary adenoma.

A meta-analysis appeared to be infeasible because of heterogeneity in (the definition of) risk factors and outcomes. In addition, the number of studies assessing the same association for a complication was too small. This review focuses on complications that directly intricate the postoperative course. Perioperative CSF leaks can be managed adequately during surgery and were therefore not included. Other reviews have addressed specific complications occurring during surgery; e.g. internal carotid artery (ICA) injuries [12] or later after discharge, e.g. delayed hyponatremia [13]. Both studies, however, also included microscopic studies. The results of these studies have been used to substantiate our present conclusions.

Selection of studies

The selection consisted of two phases: (1) title and abstract screening for potentially eligible articles, and (2) full text screening of these articles. During both phases, the same inclusion and exclusion criteria were used. During phase 1, in case of doubt, the full text paper was retrieved. Since a variety of risk factors can be investigated within the same cohort, a decision was made not to omit overlapping cohorts.

Data extraction

Extracted study characteristics included: institution, study period, study design, number of patients, number of procedures, percentage females, tumor type, approach, length of stay, and duration of follow-up. Preoperative factors were categorized into groups (demographics, volumetric parameters, pathology, surgical factors, and endocrine parameters) and all potential associations were categorized into complications in general, neurosurgical and endocrine complications. Risk factors were considered consistent when they were reported as significant in ≥2 independent studies. Inconsistent when ≥2 positive or negative and ≥1 neutral (non-significant) associations were reported and conflicting when ≥1 positive and ≥1 negative associations were reported.

Risk of bias

Assessment of risk of bias was done by means of the Quality in Prognostic Studies (QUIPS) tool [14]. The QUIPS tool is the standard tool used by Cochrane to review cohort studies evaluating predictive factors for diagnosis or prognosis. The results of this evaluation were put in a "summary of findings table" (Table 1). The overall risk of bias score was assessed according to that of Lazzerini [15]. A low risk of bias was given if all six domains were scored as low, or if not more than two moderate or unknown risks of bias were identified. Moderate risk of bias was given when three or less risk of bias domains were scored moderate, or unknown, in combination with no high risk of bias. Moderate was also given when one domain was scored as a high risk of bias in combination with one or less moderate or unknown risks of bias. A high risk of bias was given when two or more domains scored a high risk of bias, or four or more moderate or unknown risk of bias.

Table 1. Summary of findings (risk of bias)

Authors	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting	Overall risk of bias
Ajlan 2016	Moderate	Moderate	Moderate	Moderate	High	High	High
Bokhari 2013	Moderate	Moderate	Moderate	Moderate	High	High	High
Boling 2016	Low	Moderate	Moderate	Moderate	Moderate	Low	High
Cavallo 2014	Moderate	Moderate	Moderate	Moderate	High	High	High
Cerina 2016	Moderate	Moderate	Low	Low	Low	Low	Low
Chabot 2015	Low	Moderate	Low	Moderate	High	Moderate	High
Chi 2013	Moderate	Moderate	Low	Moderate	Moderate	Moderate	High
Chohan 2016	Moderate	Low	Moderate	Moderate	Moderate	Moderate	High
Dallapiaza 2014	Moderate	High	Moderate	Moderate	High	Moderate	High
Dlouhy 2012	Moderate	Moderate	Low	Moderate	Low	Low	Moderate
Gondim 2011	Moderate	Low	Moderate	Low	High	Low	High
Gondim 2015	Moderate	Low	Moderate	Moderate	High	Moderate	High
Hofstetter 2012	Moderate	Low	Low	Low	High	Moderate	High
Jakimovski 2014	Moderate	Moderate	Moderate	Moderate	High	Moderate	High
Jang 2016	Moderate	Low	Moderate	Low	Moderate	Moderate	High
Karnezis 2016	Low	Moderate	Moderate	Moderate	Moderate	Low	High
Leach 2010	Moderate	Low	Moderate	Moderate	High	Moderate	High
Qureshi 2016	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	High
Senior 2008	Low	Moderate	Moderate	Low	High	Moderate	High
Sigounas 2008	Moderate	Moderate	Moderate	Low	Low	Low	Moderate
Thawani 2017	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	High
Zhan 2015	Moderate	Moderate	Moderate	Moderate	High	Moderate	High
Zhang 2014	Moderate	Moderate	Moderate	Moderate	Moderate	Low	High

RESULTS

Search

The search resulted in 2596 unique titles and abstracts. The screening of titles and abstracts resulted in the selection of 472 full-text articles retrieved for the second phase of the selection process. Finally, 23 articles were included in the present systematic review (Fig. 1).

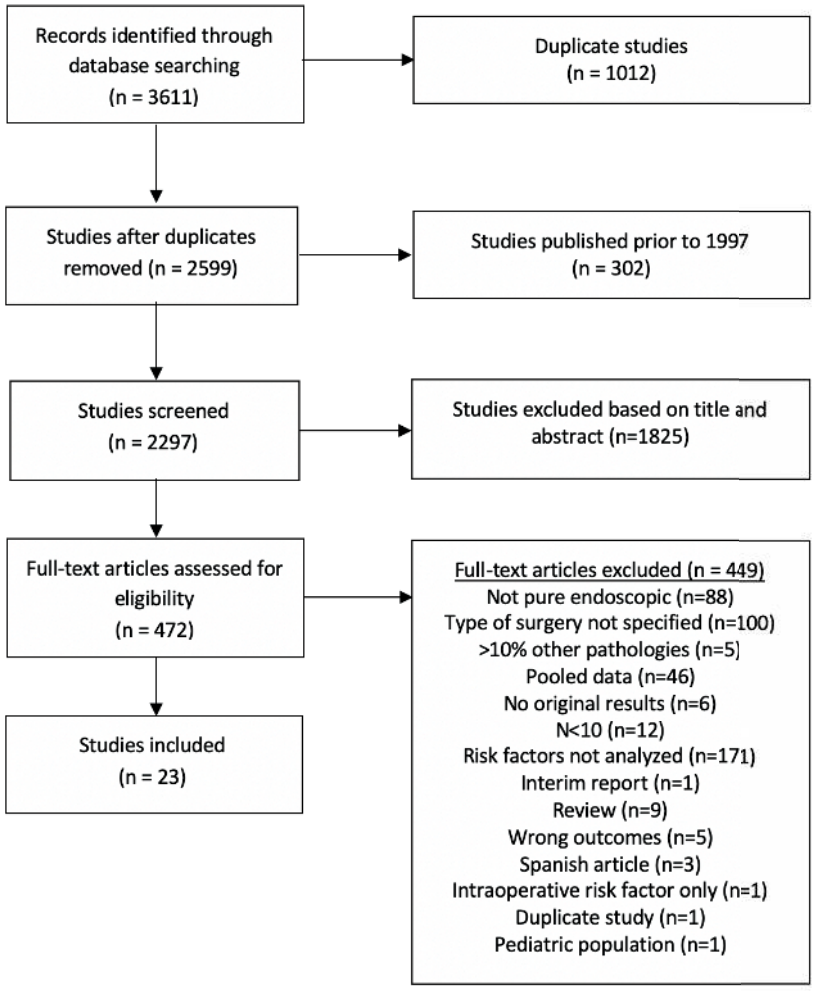

Figure 1. Flow chart of study assessment

Study characteristics

The study characteristics are summarized in Table 2. There were 3 prospective [16–18], and 20 retrospective observational cohort studies [19–27]. Publication was between 2008 and 2017 and included data from 5491 patients (median 125, IQR 78–313), of whom 2828 (52%) were female. There were 5291 pituitary adenomas (96%), 143 craniopharyngiomas (2.6%) and 39 Rathke's cleft cysts (0.7%). Seventeen studies (61%) included patients with adenomas only [16–20, 22, 23, 27–33], five studies included a mixture of tumor types [24–26, 34, 35] and one study only included patients with craniopharyngiomas [21].

Risk of bias

The results of the scoring of the methodological quality of the studies are shown in Table 1. Overall, the methodological quality was low: only one study had a low risk of bias (4.3%), two a moderate risk (8.7%) and the remaining twenty studies had a high risk of bias (87.0%). A high risk of bias was found twelve times for study confounding (median 7.5, range 0–12).

Complication rates

The incidence rates of complications described in the included studies are described in Table 3. The three most common complications were postoperative CSF leaks (median 4.5%, IQR 2.6–10.2%), serious bleedings (median 1.5%, IQR 0.6–1.7%), and permanent diabetes insipidus (median 2.7%, IQR 1.9–4.3%).

Risk factors for complications

Complications in general

Eight studies investigated the potential risk factors for complications in general [17, 19, 20, 22, 28, 30, 31, 35]. Incidence rates of complications in general were often not given. Furthermore, various definitions were used, varying from solely treating specific complications to reporting all potential complications. This included, for instance, urinary tract infections and cardiovascular complications. Some studies did not report how they defined complications in general [19, 22].

Demographics

Age was assessed in two studies. Both studies found an increased risk for older age (35,36). Age was defined as a categorical parameter: (1) age ≥70 versus <60 years (32.7 vs. 10%, $p < 0.05$) [30] and (2) age ≥50 years versus <50 OR 2.75 (95% CI 1.18–4.32, multivariate) [31]. This shows an increased risk for higher age. Female gender was investigated in one study, however no significant effect was found [31].

Table 2. Study types and demographics

Authors, institution	Study design	Study interval	Number of patients (n)	Adenomas (%)	Females (%)	Mean age (years)	Complications
Ajlan et al. 2016, California, USA	Retro	2007-2012	176	100	52	50 (median)	Postoperative CSF leak 4.5%, Bleeding 1.7%, Epistaxis 1.1%, Visual deterioration 1.1%, Permanent DI 10.2%
Bokhari et al. 2013 Kogarah, Australia	Retro	1998-2010	79	100	56	56.7	Postoperative CSF leak 2.5%, Meningitis 0, Bleeding 1.3%, Visual deterioration 1.3%, Transient DI 10%, Permanent DI 2.5%, Death 1.3%
Boling et al. 2016 6 international centers*	Retro	2002-2014	982	100	56	52	Postoperative CSF leak 5.5%, Meningitis 2.7%, Bleeding 3.7%, Death 0.5%
Cavallo et al. 2014 Naples & Bologna, Italy	Retro	1997-2012	83	0	53	50.4	Postoperative CSF leak 16.9%, Meningitis 1.2%, Bleeding 4.8%, Visual deterioration 2.4%, Overall DI 36.1%, SIADH 3.6%, Death 2.4%
Cerina et al. 2016 Zagreb, Croatia	Pro	2012-2013	70	100	60	44.4	Adrenal insufficiency 51.4%
Chabot et al. 2015 NY (3) & Illinois, USA†	Retro	2009-2014	39	100	36	56.3	Postoperative CSF leak 10.3%, meningitis 2.6%, visual deterioration 0, overall DI 7.7%
Chi et al. 2013 Renji, China	Retro	2011-2012	80	100	44	50.9	Postoperative CSF leak 5%, meningitis 1.3%, bleeding 0, visual deterioration 0, transient DI 11.3%, permanent DI 3.8%, death 0
Chohan et al. 2016 NY, USA (1)	Retro	2003-2014	62	100	34	54.2 (median)	Postoperative CSF leak 1.6%, bleeding 1.6%, visual deterioration 9.7%, permanent DI 17.7%, death 0
Dallapiazza et al. 2014 Virginia, USA	Retro	2010-2013	56	100	52	56.2	Postoperative CSF leak 7.1%, meningitis 0, epistaxis 10.7%, visual deterioration 3.6%, adrenal insufficiency 14.3%, transient DI 17.9%, permanent DI 0, SIADH 8.9%
Dlouhy et al. 2012 Iowa, USA	Retro	2005-2010	92	92	52	53.0	Postoperative CSF leak 13.5%
Gondim et al. 2011 Fortaleza, Brazil	Retro	1998-2009	301	100	55	42.4	Postoperative CSF leak 2.6%, meningitis 0.6%, bleeding 1.7%, epistaxis 2.0%, visual deterioration 0.3%, permanent DI 1.3%, death 1.0%
Gondim et al. 2015 Fortaleza, Brazil	Retro	2000-2012	374	100	59	51	Postoperative CSF leak 3.7%, bleeding 1.6%, permanent DI 2.7%, death 1.1%
Hofstetter et al. 2012 NY, USA (1)	Pro	2004-2010	71	100	46	49.9	Postoperative CSF leak 1.4%, bleeding 1.4%, visual deterioration 1.4%, permanent DI 4.2%, death 1.4%

Table 2. Study types and demographics (continued)

Authors, institution	Study design	Study interval	Number of patients (n)	Adenomas (%)	Females (%)	Mean age (years)	Complications
Jakimovski et al. 2014 NY, USA (1)	Pro	2003-2011	203	100	49	-	Postoperative CSF leak 3.0%, meningitis 1.0%, bleeding 1.5%, visual deterioration 1.0%, adrenal insufficiency 2.0%, overall DI 3.9%
Jang et al. 2016 Changwon, South Korea	Retro	1998-2014	331	100	56	47.4	Postoperative CSF leak 1.8%, meningitis 0.6%, bleeding 0.6%, epistaxis 1.2%, transient DI 4.2%, permanent DI 0.9%, SIADH 2.7%, death 0.3%
Karnezis et al. 2016 7 international centers**	Retro	2002-2014	1161	95	54	51	Postoperative CSF leak 5.9%
Leach et al. 2010 Salford, UK	Retro	2005-2007	125	87	44	51	Postoperative CSF leak 3.2%, bleeding 1.6%, epistaxis 1.6%, visual deterioration 1.6%, overall DI 4.8%, death 0
Qureshi et al. 2016 Illinois, USA	Retro	2006-2012	78	100	45	52.6	Postoperative CSF leak 1.3%, transient DI 11.5%, permanent DI 2.6%
Senior et al. 2008 N.C., USA	Retro	2000-2007	176	84	54	46	Postoperative CSF leak 11.4%, meningitis 1.1%, bleeding 0.5%, epistaxis 3.1%, visual deterioration 0, overall DI 20.2%, death 0.5%
Sigounas et al. 2008 N.C., USA	Retro	2000-2005	110	85	52	-	Postoperative CSF leak 10.0%, transient DI 13.6%, permanent DI 2.7%
Thawani et al. 2017 Pennsylvania, USA	Retro	2009-2014	203	100	49	55.7	Postoperative CSF leak 10.3%, meningitis 1.0%, bleeding 0.5%, visual deterioration 1.5%, transient DI 3.9%, permanent DI 4.4%, SIADH 5.9%, death 1.0%
Zhan et al. 2015 Shandong, China	Retro	2008-2014	313	100	40	60.1	Postoperative CSF leak 3.8%, meningitis 1.6%, bleeding 0.6%, visual deterioration 1.9%, transient DI 15.4%, permanent DI 3.8%, death 0
Zhang et al. 2014 Whenzou, China	Retro	2007-2011	326	100	46	33.3	Meningitis 9.8%

(-) not assessed
(*) South Carolina, USA; Adelaide, Australia; NY, USA (2); Toronto, Canada; Atlanta, USA; Cleveland, USA
(**) South Carolina, USA; Adelaide, Australia; NY, USA (2); Toronto, Canada; Atlanta, USA; Cleveland, USA, Alabama, USA
(†) Illinois, USA; NY, USA (3)
(1) New York Presbyterian (2) Mt. Sinai Medical Center (3) Hofstra-North Shore Long Island Jewish Hospital

Tumor characteristics

Size and volume (3 studies)

Tumor size and volume were significantly associated with increased complications in general in two out of three studies. Definitions used were (1) macroadenoma versus microadenoma OR 3.98 (2.16–5.79, multivariate) [31], (2) tumor volume >10 cm^3 versus <10 cm^3 OR 6.3 (1.6–25.0) [17], (3) tumor diameter >3 cm versus <3 cm OR 4.8 (1.2–18.6) [17], and (4) maximum tumor diameter (no significant effect) [22].

Tumor extension (4 studies)

Four out of six investigated risk factors showed increased risks for complications in general. Tumor extension was defined in five different ways: (1) intraventricular extension, (2) Knosp grade, (3) supra-/parasellar extension, (4) extension into the anterior cranial fossa (ACF), and (5) cavernous sinus invasion. Intraventricular extension OR 7.85 (2.88–21.43) [20], supra-/parasellar extension (29.9 vs. 7.5%, p = 0.002) [31], and extension into the ACF OR 1.92 (1.03–3.6) [20] were significantly associated with an increased risk in one study per risk factor.

Tumor type (1 study)

Tumor type was investigated in one study; however, no significant effect was detected [31].

Surgical factors

Previous radiation was associated with an increased risk in one study (OR 8.86, 95% CI 2.05–38.28) [20]. The surgeon's learning curve was not associated with an increased risk of complications in general in two studies [19, 35].

CSF leak

Fourteen studies investigated the potential risk factors for postoperative CSF leaks [18–21, 23–25, 27, 28, 32–34, 36, 37]. Postoperative incidence rates of CSF leaks varied between 1.4 and 16.9%. Definitions varied between clinical evidence of CSF rhinorrhea to no definition given. Described risk factors include demographics such as age, gender, BMI and comorbidity as well as pathology, several volumetric parameters, and surgical factors.

Demographics

Age (6 studies)

Younger age was inconsistently associated with a higher risk of CSF leaks. Three studies, including two with overlapping cohorts [20, 34], found a significant association for younger age in a multivariable analysis with different definitions: (1) continuous: OR

0.93 (95% CI 0.88–0.98) [24] and OR 0.98 (0.97–1.00) [34], (2) categorical <40 versus >65 years OR 5.3 (1.17–24.11) [20], and (3) 40–64 versus >65 years OR 7.9 (1.88–33.4) [20]. Covariates included were: BMI and intraoperative CSF leaks.

Gender (5 studies)

In two of five studies, female gender was associated [20, 24, 25, 33, 34] with a significant increase in postoperative CSF leaks [20, 34], OR 2.4 (1.24–4.63) [20] and p = 0.045 [34]. These two large studies (n = 982; 1162) had overlapping cohorts.

Body mass index (BMI) (4 studies)

As expected, three out of four studies found a significant increase in postoperative CSF leaks in patients with a higher BMI [20, 24, 25, 34]. Various definitions were used: (1) continuous, multivariate: OR 1.61 (1.10–2.29) [24] and OR 1.06 (1.01–1.06) [34], and (2) categorical: <30 versus ≥30 OR 2.10 (1.14–3.86) [20]. Covariates included were age [24] and intraoperative CSF leakage [24], and craniopharyngiomas [34]. However, again, two of these studies had a large overlap in included patients [20, 34].

Miscellaneous (1 study)

One study evaluated various comorbidities in relation to CSF leaks (Table 3) and found a significant association only for peptic ulcer disease (p = 0.029) [34].

Tumor characteristics

Tumor size or volume (5 studies)

Only one out of five studies looking at tumor size or volume found a significant association with CSF leaks [18, 24, 25, 33, 36]. These five studies used various cut-off values ranging from below or above 10 mm to a continuous parameter of size. The only significant association was found for tumors larger than 10 mm, compared to the smaller group, suggesting that indeed microadenoma have a lower risk for CSF leaks (34 vs. 17%, p = 0.04) [25].

Tumor extension (7 studies)

Tumor extension was analyzed in seven studies [20, 21, 28, 33, 34, 36, 37], however, again, defined in four different ways: (1) intraventricular extension [20, 21, 34], (2) supra-/parasellar extension [37], (3) Knosp grade [36], and (4) cavernous sinus invasion [28, 33]. Intraventricular extension was investigated by three studies: (1) 8.9 versus 27.8% [21], (2) OR 9.49 (2.97–30.26) [20], and (3) OR 3.58 (1.70–7.59) [34]. Presence of supra-/parasellar extension was investigated by one study OR 8.08, p = 0.02 [37]. Knosp grade and cavernous sinus invasion were investigated by three studies; however, none of the studies found a significantly increased risk for postoperative CSF leaks [28, 33, 36]. In

Table 3. Described risk factor per complication

	Complications in general	Postoperative CSF leak	Intracranial infection	Bleeding	Adrenal insufficiency	Transient DI	Permanent DI	Overall DI
Demographics								
Age	+[30,31]	=[25,33,27], -[20,20,24,34]	=[27]	=[27]	=[16]	=[27]	=[27]	=[33,27]
Gender (female*)	=[31]	=[24,25,33], +[20,34]			=[16]			=[25,33]
BMI		=[25], +[20,24,34]						
Diabetes mellitus			+[38]					
Race		=[34]						=[26]
Peptic Ulcer Disease		+[34]						
Various comorbidities		=[34]						
Volumetric parameters								
Tumor size	=[22], +[17,31]	=[18,25,33], +[25]			+[16]		=[26,29,29,29], +[29]	=[25,26,33]
Tumor volume	+[17]	=[36,24,18]					=[29]	
Intraventricular extension	+[20]	+[20,21,34]	+[20]	+[20]				
Knosp	=[22], +[31]	=[36]					=[29]	
Supra-/parasellar extension	+[31]	+[37]						
Extension into the ACF	+[20]			+[20]				
Cavernous sinus invasion	=[28]	=[28,33]						
Pathology								
Tumor type	=[31]	=[18], +[25]			=[16]			
Non-functioning adenoma								=[26]
Acromegaly								=[26]
Cushing's disease		=[24]						=[26]
Prolactinoma								=[26]
RCC		+[25]					+[26]	+[25,26]

Table 3. Described risk factor per complication (continued)

	Complications in general	Postoperative CSF leak	Intracranial infection	Bleeding	Adrenal insufficiency	Transient DI	Permanent DI	Overall DI
Craniopharyngioma		+[34]						=[26]
Surgical factors								
Previous radiation	+[20]	=[20,33], +[34]		+[20]				
Previous surgery		=[24,34,33]					=[26,26]	=[25,26,26]
Learning curve	=[19,35]	=[19,23,32], +[18]				=[32]	=[32]	=[19,23]
Endocrine parameters								
Preoperative prolactin/ TSH/testosterone/cortisol					=[16]			
Preoperative T4/ IGF-1/FSH/LH					+[16]			
Urinary-free cortisol (nmol/24h)					+[16]			

* Prognostic factor has a higher change of outcome
+ Positive effect; indicating a significant higher risk
- Negative effect; indicating a significant lower risk
= Neutral; relation studied, however no increased/decreased risk found

summary, intraventricular extension is a clear adverse factor, while supra-/parasellar extension is only confirmed in one study.

Pathology (4 studies)

Four studies looked at the relationship between various forms of pathology and CSF leaks [18, 24, 25, 34]. Three studies looked at associations of individual tumor types, namely for Cushing's disease [24], craniopharyngioma [34] and RCC [25]. RCC OR 2.6 ($p < 0.001$) [25], craniopharyngioma versus adenoma patients ($p < 0.001$) [34] and Cushing's disease, no association [24]. Inconsistent results were found for two studies looking at tumor type in general as a predictor for postoperative CSF leaks. As expected, cystic lesions, i.e. craniopharyngioma and RCC, appear to harbor the highest risks; however, they were only described once per risk factor.

Surgical factors

Previous surgery (3 studies)

Previous surgery was not reported as a risk factor for CSF leaks [24, 33, 34].

Radiation (3 studies)

Even though the frequency of surgical resection after radiotherapy is low, one study found an increased risk for patients with prior radiotherapy; 4/14 patients had a postoperative CSF leak [34]. The other two studies did not find an association [20, 33].

Learning curve (4 studies)

One out of four studies considering the surgeon's learning curve found a significant increase in postoperative CSF leaks [18, 19, 23, 32]. Different cut off values were used in all four: (1) early (27 cases), middle (26 cases) and late (26 cases): no significant effect [19], (2) case 1–40 versus 41–80: no significant effect [23], (3) case 1–50 versus 51–203: 10 versus 0.7% ($p = 0.004$) [18], and (4) case 1–9 versus 10–78: no significant effect [32]. In summary, learning curve is an inconsistent risk factor, which only showed an effect after >50 cases in one study.

Intracranial infections

Two out of three studies reporting associations found a significant association for intracranial infections [20, 27, 38]. Intracranial infections had an incidence rate of 0–9.8%. Definitions varied from no definitions to symptomatology in combination with positive CSF cultures. Assessed risk factors were: (1) age (no significant effect) [27], (2) diabetes mellitus: OR 5.47 (1.09–6.49) [38] and intraventricular extension: OR 11.91 (3.64–38.95) [20]. Included covariates for diabetes mellitus were increased duration of surgery and CSF leakage.

Bleeding

Only two studies looked at risk factors for bleedings: (1) ICA injury [20], and (2) post-operative intracranial bleeds (hemorrhages) [20, 27]. Incidence rates for bleedings ranged between 0 and 4.8%. Risk factors for ICA injury included prior radiation OR 44.00 (3.73–519.00) and intraventricular extension OR 13.2 (1.35–128.91) [20]. Extension into the ACF OR 4.41 (2.04–9.51) was a risk factor for intracranial bleeds [20]. One study looked at age but did not find a significant association for intracranial bleeds [27].

Diabetes insipidus (DI)

Eight studies looked at risk factors for DI [19, 23, 25–27, 29, 32, 33]; incidence rates of DI ranged between 0.9 and 36.1%. Various definitions were used: (1) transient DI, (2) permanent DI, and (3) overall DI.

Demographics

Age (2 studies) [27, 33], gender (2 studies) [25, 33] and race (1 study) [26] were not associated with a significant increase of DI (all three definitions).

Tumor characteristics

Tumor size or volume (4 studies)

One study reported an association with permanent or overall DI [25, 26, 29, 33]. Various definitions were used: (1) transverse length >4 cm (no percentage given, $p = 0.02$) [29], (2) cranio-caudal length (no significant effect) [29], (3) antero-posterior length (no significant effect) [29], (4) maximum cross-sectional length (no significant effect) [29], (5) tumor volume >10 cm3 (no significant effect) [29], (6) continuous (no significant effect) [25, 33], and (7) micro- versus macroadenoma (no significant effect) [26].

Tumor extension (1 study)

Knosp grade was not associated with a significant increase of DI [29]. Pathology (2 studies) in overlapping cohorts, RCC was significantly associated with an increased risk of DI compared to other tumor types: (1) 47.6 versus 20.2% ($p < 0.05$) [25], and (2) 50 versus 12%, $p < 0.05$ [26]. Other pathologies were not associated with DI.

Surgical factors

Previous surgery (3 studies)

Previous surgery was defined as (1) prior non-endoscopic surgery [26], (2) prior endoscopic surgery [26], and (3) prior surgery [25]. None of them was associated with an increased risk.

Learning curve (3 studies)

Learning curve was assessed in three studies, but not associated with an increased risk of DI [19, 23, 32].

Adrenal insufficiency

One out of three studies looking at adrenal insufficiency addressed potential associations [16]. Incidence rates ranged between 2.0 and 51.4%. Definitions varied between extensive descriptions of used tests, while others only reported an insufficiency. Significant associations were found for tumor size, preoperative T4, IGF-1, FSH, LH and urinary-free cortisol. Corrected for tumor type, patients with larger tumors had an increased risk of adrenal insufficiency (OR 1.07, 95% CI 1.01–1.13). No association was found for gender, age, tumor type, prolactin, TSH, testosterone, and cortisol.

Other complications of interest

Three complications were only analyzed once: cranial nerve injury, vision loss and sinusitis. One study found a significant relationship between patients with a history of an extrasellar tumor and cranial nerve injury (OR 5.94, 95% CI 1.26–28.06) [20]. One study looked at older age and vision loss [27], while one study looked at learning curve and postoperative sinusitis [32]; both, however, did not find a significant association [27, 32]. Within the endoscopic literature, no risk factors for SIADH or mortality were found.

DISCUSSION

This systematic review on preoperative risk factors for postoperative complications in ETS identified only two consistent risk factors: older age for complications in general and intraventricular extension for CSF leakage. Clear and uniform definitions of postoperative complications were mostly missing and almost all studies were retrospective. This resulted in a lack of standard reporting of complications, causing a large variation between studies regarding reported risk factors and incidence rates of complications.

The most frequently studied complication, CSF leaks, was consistently associated with intraventricular extension. Other risk factors were not consistent, but did not report conflicting results. At this stage, we conclude that intraventricular extension increases the risk of CSF leaks and lower age, female gender, and high BMI potentially increase the risk (Table 4). The second most studied association was complications in general, for which we conclude that patients with older age (cut off ≥50–70 years) have an increased risk of complications in general. Although tumor size, volume and extension showed inconsistent results, results indicate an increased risk for larger tumors and tumors

Table 4. Summary of preoperative risk factors for postoperative complications

	Complications in general	CSF leak	Intracranial infections	Bleedings	Adrenal insufficiency	DI
Amendable						
Learning curve	=	Decreased after >50 cases	-	-	-	=
Non-amendable						
Age	Increased ≥50-70 years	Increased <65 years	=	=	=	=
Gender	=	Increased in females	-	-	=	=
BMI	-	Higher BMI or >30 kg/m^2	-	-	-	-
Diabetes mellitus	-	-	Increased risk	-	-	-
Race	-	-	=	-	-	=
Peptic ulcer disease	-	Increased risk	-	-	-	-
Large or giant tumors	Increased in larger tumors	Increased in larger tumors	=	=	Increased in larger tumors	Increased >1 cm
Invasive tumors	Increased by increased extension	Increased by increased extension	Increased by increased extension	Increased by increased extension	=	=
Tumor type	=	Increased in RCC / craniopharyngioma	-	-	=	Increased in RCC
Previous radiation	Increased risk	Increased risk	-	Increased risk	-	-
Previous surgery	-	=	-	-	-	=
Preoperative hypopituitarism/ T4/IGF-1/FSH/LH/UFC	-	-	-	-	Increased risk	-

- not assessed
= no significant association
Risk ratios can be found in supplementary table 2

with an invasive growth pattern. The third most studied complication was DI. Although found in overlapping cohorts, a significant association was found between RCC and DI. Results reported between DI and tumor size were inconsistent but were not conflicting. Therefore, increased tumor size/volume might increase the risk of DI. This should, however, be further investigated. For several other complications, i.e. intracranial infections, serious bleedings and adrenal insufficiency, described associations have only been reported once. Further confirmation of whether these risk factors indeed increase the risk of complications is needed.

A distinction can be made between amendable and non-amendable risk factors. Even though often difficult to change, these should be taken into consideration in cases with increased risks. The learning curve is perhaps one of the easiest to amend. Experience (learning curve), for instance, appears to be an important risk factor for a lower risk of CSF leaks. This was confirmed in some but not all studies, while learning curve was not associated with any other complication. Obviously, learning curve statistics can be biased since a more experienced surgeon will operate on a more complex case mix with an innate higher risk of CSF leaks, which cannot be extracted from the currently available series. In a national survey, Ciric found that for most complications, surgical learning curve is an important factor [39]. This was assessed in 1997, however, when ETS was not commonplace. Based on the available literature, we advise taking the learning curve into account and consider referral to a center of excellence in cases that harbor an increased risk for CSF leak in itself, e.g. patients with intraventricular extension, lower age, females and in patients with obesity.

Increased BMI and younger age were risk factors for postoperative CSF leaks. This might be explained by the increased intra-abdominal pressure [40]. Perhaps when time permits, one should motivate patients to lose weight to reduce risks of CSF leaks postoperatively. While age increases in the course of time, older age is also a risk factor for complications in general. One should therefore weigh the risks.

Since generally only large tumors have suprasellar, intraventricular extension or extension into the ACF, these risk factors can be considered correlated and classified under tumor size. When taking this into account, large or giant pituitary tumors are associated with complications in general and postoperative CSF leaks. Literature on endoscopic resection of giant adenoma is scarce, however increased risk of complications can be found [41]. In particular, intratumoral bleeding rates or postoperative apoplexy in tumor residual have been reported, ranging from 2.1 to 3.7% [6, 42, 43]. One could argue that in firm tumors, a combined endoscopic transsphenoidal and open transcranial approach is safest for giant adenomas to maximize tumor resection [43–45]. Even though tumor

size is often not amendable, in select cases one might consider medication to decrease tumor size, making it manageable for surgery and subsequently potentially lower the risk of complications, although this strategy is not evidence-based. However, the downside of medication is that it could change the tumor characteristics, making resection less manageable. Whether tumor shrinkage due to medication improves complication risks has not been assessed.

Pathology, also a non-amendable risk factor, might also be an important risk factor for postoperative complications. In particular, several associations were described for RCCs and craniopharyngiomas; however, only those for DI have been reported more than once (in overlapping cohorts). These two tumors have an increased risk of DI, possibly also for postoperative CSF leaks. The relationship with pathology can likely be explained by the tumor etiology. Whereas RCCs are typically located between the anterior and posterior lobe, compression/manipulation of the posterior lobe is likely to occur prior to or during surgery. Craniopharyngiomas commonly arise in the pituitary stalk, which is vulnerable to surgical manipulation; therefore, surgery is more likely to cause DI. Another risk factor found for RCCs was postoperative CSF leaks.

Despite being addressed only in one study, previous radiation showed an association between complications in general and carotid artery injury. Even though radiotherapy prior to surgery is not common, some adenomas are very therapy resistant and need additional surgery. Boling et al. presented data from nine patients who had received radiotherapy prior to surgery, showing a complication rate of 33% [20]. This might be explained by induced fibrosis, atrophy and vascular damage [46], changing the tissue structure and characteristics, making it more fragile. While presenting results of microscopic surgery, Laws also described an increased risk of vascular injury due to radiation therapy [47].

Comparison with other systematic reviews

One of the most reviewed subjects in pituitary surgery literature is the comparison between endoscopic and microscopic surgery. We found several reviews assessing the topic. Because the influence of surgical technique was the primary interest of comparison, patient-related risk factors were not investigated in these reviews. Typically, gross-total resection and complications have been compared between microscopy and endoscopy, most showing equal or superior results in favor of endoscopy; however, patient-related risk factors have not been further determined [1–10]. In the undivided (microscopic and endoscopic combined) literature, the following preoperative risk factors were found for delayed symptomatic hyponatremia by Cote [13]: higher age, female gender, larger tumor size, and Cushing disease. In the present review of endoscopic

literature, no associations for delayed hyponatremia, or SIADH, and preoperative risk factors were found, indicating that these are either not relevant for endoscopic resections, or not yet adequately studied.

Limitations and future perspectives

The main purpose of the study was to improve preoperative patient counselling and to identify high- and low-risk patients. The low quality of the studies precludes firm conclusions based on this review. Overall, most studies were retrospective and too small to allow multivariable analyses. Also, no meta-analysis could be performed because of the heterogeneity and low number of associations. Complications were often defined differently and mostly gave limited descriptions. This complicates generalizability, and future researchers should aim at clearly defining (presented) complications in an effort to improve the clinical impact of future research on daily practice. Furthermore, reporting of outcomes, not only by centers of excellence, and prospective registration will lead to further evolvement in the field. Many examples, like the Value Based Healthcare concept [48], have shown that improvement in reporting of outcomes and better registration lead to improvements in patient-relevant outcomes.

We realize that only a subset of the total number of studies reporting on complication rates in ETS could be included in this study since the vast majority did not perform risk factor analysis. Furthermore, studies that presented only pooled data between microscopic and endoscopic surgery did not give a utilizable overview of potential risk factors for complications specific for patients treated through an endoscopic transsphenoidal approach, as in many daily practices nowadays.

Although many studies assessed individual risk factors of different types of postoperative complications, there were no prognostic models found in the current literature. Prognostic models in other fields have shown added value in individualized decision-making and patient counselling. Such a model could have different types of outcomes, based on the aim of the model: complications in general, prediction of potential candidates for short stay. Before implementation of such a model, it should be thoroughly internally and externally validated.

Although on average the reported mortality rate is around 0.6%, unfortunately no associations were found in the current literature. Even though incidence rates are low, they are not negligible. Suggested improvements for definitions and registration of complications might give us a better understanding of the etiology of these complications.

CONCLUSION

We present an overview of preoperative risk factors for postoperative complications. Only two risk factors were consistently associated with increased risks: older age for complications in general and intraventricular extension for CSF leakage. This does not mean that there are no other important risk factors, and further emphasizes the need for uniform definitions, reporting of outcomes and prospective registration. The low methodological quality of included studies, inconsistent results, and lack of uniform definitions make firm conclusions difficult. Nevertheless, we believe that awareness of presented risks may benefit patient counselling and surgical case selection.

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Supplement 1. Search strategy
((”Pituitary Neoplasms/surgery”[majr] OR “Pituitary Diseases/surgery”[majr] OR “Pituitary ACTH Hypersecretion/surgery”[majr] OR “Pituitary Gland/surgery”[majr] OR “Craniopharyngioma/surgery”[Majr] OR ((“Pituitary Neoplasms”[majr] OR “Pituitary Diseases”[majr] OR “Pituitary ACTH Hypersecretion”[majr] OR “Pituitary Gland”[majr] OR “Craniopharyngioma”[majr]) AND (“surgery”[Subheading] OR “surgery”[tw] OR surgical*[tw] OR neurosurg*[tw] OR “operation”[tw] OR “surgical procedures, operative”[mesh])) OR ((Pituitary Neoplasm*[ti] OR Pituitary Tumor*[ti] OR Pituitary Tumour*[ti] OR Pituitary Cancer*[ti] OR Pituitary Carcinoma*[ti] OR ”Cushing syndrome”[ti] OR Microadenoma*[ti] OR Micro-adenoma*[ti] OR Macroadenoma*[ti] OR Macro-adenoma*[ti] OR ”rathke cleft cyst”[ti] OR ”rathke cleft cysts”[ti] OR ”rathke cyst”[ti] OR ”rathke cysts”[ti] OR ”rathke s cleft cyst”[ti] OR ”rathke s cleft cysts”[ti] OR ”rathke s cyst”[ti] OR ”rathke s cysts”[ti] OR ”rathke’s cleft cyst”[ti] OR ”rathke’s cleft cysts”[ti] OR Prolactinoma*[ti] OR Growth-hormone secreting pituitary adenoma*[ti] OR ACTH-secreting pituitary adenoma*[ti] OR Non-functioning adenoma*[ti] OR Craniopharyngioma*[ti]) AND (“surgery”[Subheading] OR “surgery”[tw] OR surgical*[tw] OR neurosurg*[tw] OR “operation”[tw] OR “surgical procedures, operative”[mesh])))) AND (”complications”[Subheading] OR ”Postoperative Complications”[Mesh] OR ”Intraoperative Complications”[Mesh] OR ”complication”[tw] OR ”complications”[tw] OR ”Diabetes Insipidus”[Mesh] OR ”diabetes insipidus”[tw] OR ”Meningitis”[Mesh] OR ”meningitis”[tw] OR ”Hypopituitarism”[Mesh] OR ”hypopituitarism”[tw] OR ”hyponatremia”[mesh] OR ”hyponatremia”[tw] OR ”Visual acuity”[mesh] OR ”decreased visual acuity”[tw] OR ”Vision, Low”[Mesh] OR ”loss of vision”[tw] OR ”Hemianopsia”[Mesh] OR ”hemianopsia”[tw] OR ”Hemorrhage”[Mesh] OR haemorrhag*[tw] OR hemorrhag*[tw] OR hematoma*[tw] OR haematoma*[tw] OR ”Sinusitis”[Mesh] OR ”sinusitis”[tw] OR ”Hyponatremia”[Mesh] OR ”hyponatremia”[tw] OR ”hyponatraemia”[tw] OR ”Cerebrospinal Fluid Leak”[Mesh] OR ”cerebrospinal fluid leak”[tw] OR ”CSF leak”[tw] OR rhinorrhea*[tw] OR ”Carotid Artery Injuries”[Mesh] OR ”Carotid Artery Injuries”[tw] OR ”Carotid Artery Injury”[tw] OR ”carotid injury”[tw] OR ”carotid injuries”[tw] OR ”Epistaxis”[Mesh] OR ”epistaxis”[tw] OR ”Pneumocephalus”[Mesh] OR ”pneumocephalus”[tw] OR ”Thrombosis”[Mesh] OR ”thrombosis”[tw] OR ”DVT”[tw] OR ”Pulmonary Embolism”[Mesh] OR ”pulmonary embolism”[tw] OR ”Blood Transfusion”[Mesh] OR ”transfusion”[tw] OR ”Pneumonia”[Mesh] OR ”pneumonia”[tw] OR ”Respiratory Insufficiency”[Mesh] OR ”Respiratory Insufficiency”[tw] OR ”respiratory failure”[tw] OR ”Infection”[Mesh] OR infection*[tw] OR ”Heart Arrest”[Mesh] OR ”Heart Arrest”[tw] OR ”cardiac arrest”[tw] OR ”Myocardial Infarction”[Mesh] OR ” myocardial infarction”[tw] OR ”Stroke”[Mesh] OR ”stroke”[tw] OR ”Death”[Mesh] OR ”death”[tw] **OR “outcome”[tw] OR “outcomes”[tw]**) AND (“Predictive Value of Tests”[Mesh] OR “predictor”[tw] OR “predictors”[tw] OR “prediction”[tw] OR “Predictive factors”[tw] OR ”Predictive factor”[tw] OR “Prediction factors”[tw] OR ”Prediction factor”[tw] OR ”Predictive Model”[tw] OR ”Predictive Models”[tw] OR ”Prediction Model”[tw] OR ”Prediction Models”[tw] OR predict*[tw] OR “Prognosis”[Mesh] OR “Prognosis”[tw] OR “prognostic factor”[tw] OR “prognostic factors”[tw] OR prognostic*[tw] OR “Risk Assessment”[Mesh] OR “Risk”[mesh] OR “risk”[tw] OR “risks”[tw])) AND (english[la] OR dutch[la]) NOT (”Case Reports”[ptyp] NOT ”Clinical Study”[Publication Type]) NOT (”Animals”[mesh] NOT ”Humans”[mesh]) NOT (”Child”[mesh] NOT (”Adolescent”[mesh] OR ”Adult”[mesh])) NOT (microscop*[ti] NOT (endoscop*[ti] OR “Endoscopy”[majr]))

Supplementary table 1. Incidence of pathology

Authors	N	NFA	Acromegaly	Cushing	Prolactinoma	TSH	FSH-LH	Craniopharyngioma	RCC	Other	Macro | Giant (%)
Ajlan 2016	176	106	24	17	27	2	0	0	0	0	77 | -
Bokhari 2013	79	39	19	4	16	1	0	0	0	0	91 | -
Boling 2016	982	982 adenoma, type not specified						0	0	0	- | -
Cavallo 2014.	83	0	0	0	0	0	0	83	0	0	- | -
Cerina 2016	70	37	5	0	28	0	0	0	0	0	- | -
Chabot 2015	39	39 adenoma, type not specified						0	0	0	85 | 15
Chi 2013	80	34	9	3	26	3		0	0	5[a]	80 | -
Chohan 2016	62	62 adenoma, type not specified						0	0	0	- | 100
Dallapiaza 2014.	56	56	0	0	0	0	0	0	0	0	100 | -
Dlouhy 2012	92	88 adenoma of which 5 Cushing, other types not specified						0	3	5[b]	- | -
Gondim 2011	301	135	68	37	48	1	12	0	0	0	66 | 16
Gondim 2015	374	374	0	0	0	0	0	0	0	0	100 | -
Hofstetter 2012.	71	45	14	2	10	0	0	0	0	0	72 | 28
Jakimovski 2014	203	138	28	14	23	0	0	0	0	0	- | -
Jang 2016	331	157	20	29	104	2	6	0	0	13[c]	70 | -
Karnezis 2016	1161	1108 adenoma, type not specified						53	0	0	- | -
Leach 2010	125	67	22	10	9	1	0	4	3	9[d]	85 | -
Qureshi 2016	78	78 adenoma, type not specified						0	0	0	96 | -
Senior 2008	176	94	15	20	10	0	0	2	21	15[e]	77 | -
Sigounas 2008	110	61	15	9	9	0	0	1	12	3[f]	71 | -
Thawani 2017.	203	74	21	19	7	1	32	0	0	0	100 | -
Zhan 2015	313	313	0	0	0	0	0	0	0	0	82 | -
Zhang 2014	326	70	45	36	175	0	0	0	0	0	76 | 14

- not assessed

[a] 5 mixed

[b] 4 connective tissue/infection, 1 metastatic lesion

[c] 4 PRL-ACTH-secreting adenomas, 9 PRL-GH-secreting adenomas

[d] 6 apoplexy, 1 pituicytoma, 1 pituitary dermoid, 1 clival chordoma

[e] 9 mixed, 2 chordomas, 1 FAS-secreting (Fatty Acid Synthetase), 2 metastasis, 1 lymphocytic hypophysitis

[f] 2 chordoma, 1 FAS-secreting

Supplementary table 2. Summary of study characteristics of prognostic cohort studies

First author, year	Study Quality	Study population	Prognostic factor	Outcome	Association
Ajlan et al., 2016	High Risk	Patients with pituitary adenomas extending in the cavernous sinus (CS) vs. no CS invasion, N=176	CS involvement	Complications in general	=
				Postoperative CSF leak	=
Bokhari et al., 2013	High Risk	Consecutively treated adenomas, N=79	Learning curve (cut off 27/26/26)	Complications in general	=
				Postoperative CSF leak	=
				Overall DI	=
Boling et al., 2016	High Risk	Multicenter cohort study in pituitary adenomas, N=982	Previous radiation	Complications in general	OR 8.86, 95% CI 2.05-38.28, p=0.003
			Intraventricular extension		OR 7.85, 95% CI 2.88-21.43, p<0.001
			extension into the ACF		OR 1.92, 95% CI 1.03-3.6, p=0.038
			Age <40 (ref. ≥65 years)	Postoperative CSF leak	OR 5.3, 95% CI 1.17-24.11, p=0.030
			Age 40-64 (ref. ≥65 years)		OR 7.9, 95% CI 1.88-33.4, p=0.005
			Gender (ref. female*)		OR 2.4, 95% CI 1.24-4.63, p=0.010
			BMI ≥30 (ref. <30)		OR 2.10, 95% CI 1.14-3.86, p=0.017
			Previous radiation		=
			Intraventricular extension		OR 9.49, 95% CI 2.97-30.26
			Intraventricular extension	Intracranial infection	OR 11.91, CI 95% 3.64-38.95; p<0.001
			Previous radiation	Bleeding (ICA injury)	OR 44.00, 95% CI 3.73-519.00, p=0.003
			Intraventricular extension		OR 13.20, 95% CI 1.35-128.91, p=0.026
			extension into the ACF	Bleeding (intracranial bleeds)	OR 4.41 95% CI 2.04-9.51, p<0.001
			History of extrasellar tumor	Cranial nerve injury	OR 5.94, 95% CI 1.26-28.06, p=0.025

Supplementary table 2. Summary of study characteristics of prognostic cohort studies (continued)

First author, year	Study Quality	Study population	Prognostic factor	Outcome	Association
Cavallo et al., 2014	High Risk	Consecutively treated craniopharyngiomas, N=83, adenoma 0%	Third ventricle involvement	Postoperative CSF leak	=
Cerina et al., 2016	Low Risk	Consecutively treated newly diagnosed pituitary adenomas, N=70	Age (continuous)	Adrenal insufficiency	=
			Gender (ref. male)		=
			Tumor size 23 mm (ref. 17 mm)		OR 1.070, 95% CI 1.013-1.129, p=0.015[+] (adjusted for tumor type)
			Tumor type		=
			Preoperative prolactin		=
			Preoperative T4		p=0.008
			Preoperative TSH		=
			Preoperative IGF-1		p=0.039
			Preoperative Testosterone		=
			Preoperative FSH		p=0.016
			Preoperative LH		p=0.001
			Preoperative cortisol		=
			Preoperative urinary-free cortisol (nmol/24h)		p=0.041
Chabot et al., 2015	High Risk	Large (>3 cm) or giant (>4 cm) pituitary macroadenomas, N=39	Maximum tumor diameter	Complications in general	=
			Knosp scores		=

Supplementary table 2. Summary of study characteristics of prognostic cohort studies (continued)

First author, year	Study Quality	Study population	Prognostic factor	Outcome	Association
Chohan et al., 2016	High Risk	Large (>3 cm) or giant (>4 cm) pituitary adenomas, N=62	Transverse length (>4 cm)	Permanent DI	p=0.02[+]
			Cranio-caudal length		=
			Antero-posterior length		=
			Maximum cross-sectional length		=
			Tumor volume (>10 cm^3)		=
			Knosp 3-4 (ref. Knosp 1-2)		=
Chi et al., 2013	High Risk	Consecutively treated adenomas, N=80	Learning curve (cut off 40)	Postoperative CSF leak	=
				Overall DI	=
Dallapiazza et al. 2014	High Risk	Nonfunctioning macroadenomas with Knosp Grades 0–2, N=56	Tumor volume	Postoperative CSF leak	=
			Knosp grade (0 vs. 1 vs. 2)		=
Dlouhy et al., 2012	Moderate Risk	Consecutively treated primarily sellar masses, N=92, adenoma 92%	Age (continuous)	Postoperative CSF leak	OR 0.93, 95% CI 0.88-0.98, p=0.008[+]
			Gender (ref. male)		=
			BMI (per 5 kg/m^2)		OR 1.61, 95% CI 1.10-2.29, p=0.016[+]
			Tumor volume (continuous)		=
			Cushing's disease		=
			Previous surgery		=
Gondim et al., 2011	High Risk	Consecutively treated pituitary adenomas, N=301	supra-/parasellar extension	Postoperative CSF leak	OR 8.08; p=0.021
Gondim et al., 2015	High Risk	Consecutively treated elderly (age ≥ 70 years) NFA patients vs. younger patients, N=374	Age ≥70* (ref. <60 years)	Complications in general	p<0.05

Supplementary table 2. Summary of study characteristics of prognostic cohort studies (continued)

First author, year	Study Quality	Study population	Prognostic factor	Outcome	Association
Hofstetter et al., 2012	High Risk	Consecutively treated pituitary macroadenomas, N=71	Tumor volume >10 cm^3	Complications in general	OR 6.3, 95% CI 1.6-25.0; p=0.008
			Tumor diameter >3 cm		OR 4.8, 95% CI 1.2-18.6; p=0.023
Jakimovski et al., 2014	High Risk	Consecutively treated pituitary adenomas, N=203	Tumor size ≥2 cm (ref. <2 cm)	Postoperative CSF leak	=
			Tumor volume (per quartile)		=
			Tumor type, functioning adenoma (ref. NFA)		=
			Learning curve* (cut off 50)		p=0.004
Jang et al., 2016	High Risk	Consecutively treated pituitary adenomas, N=331	Age ≥50 years (ref. <50)	Complications in general	OR 2.75 95% CI 1.18-4.32, p=0.047[+]
			Gender		=
			Tumor size, macro- (ref. microadenoma)		OR 3.98, 95% CI 2.16-5.79, p=0.003[+]
			Knosp grade 3-4 (ref. 0-2)		OR 6.75, 95% CI 3.81-9.68, p<0.001[+]
			Parasellar growth*		p=0.002
			Tumor type		=

Supplementary table 2. Summary of study characteristics of prognostic cohort studies (continued)

First author, year	Study Quality	Study population	Prognostic factor	Outcome	Association
Karnezis et al., 2016	High Risk	Multicenter cohort study in pituitary adenomas and craniopharyngiomas, N=1161, 95% adenoma	Age (years)	Postoperative CSF leak	OR 0.982, 95% CI 0.967–0.997, p=0.022[+]
			Gender (ref. female*)		p=0.045
			BMI (kg/m2)		OR 1.033, 95% CI 1.007–1.059, p=0.014[+]
			ASA score		=
			Charlson Index		=
			Race		=
			Recurrence		=
			Prior skull-base operations		=
			Radiotherapy*		p=0.007
			Chemotherapy		=
			Myocardial Infarction		=
			Chronic Heart Failure		=
			Peripheral Vascular Disease		=
			Coronary Vessel Disease		=
			Dementia		=
			Chronic Pulmonary Disease		=
			Connective Tissue Disease		=
			Peptic Ulcer Disease*		p=0.029
			Mild Liver Disease		=
			Diabetes Mellitus		=
			Diabetes with Chronic Complications		=
			Hemiplegia		=
			Renal Disease		=
			Any tumor		=
			Leukemia		=
			Lymphoma		=
			Moderate or Severe Liver Disease		=
			Metastatic Solid Tumor		=
			Extension into ventricle		OR 3.585, 95% CI 1.693–7.592, p=0.001[+]
			Tumor type, craniopharyngioma* (ref: adenoma)		p<0.001

Supplementary table 2. Summary of study characteristics of prognostic cohort studies (continued)

First author, year	Study Quality	Study population	Prognostic factor	Outcome	Association
Leach et al., 2010	High Risk	Consecutively treated pituitary fossa lesions, N=125, adenoma 87%	Learning curve (cut off 53)	Complications in general	=
Qureshi et al., 2016	High Risk	Consecutively treated primary pituitary adenomas, N=78	Learning curve (cut off 9)	Postoperative CSF leak	=
				Transient DI	=
				Permanent DI	=
				Loss of pituitary function / panhypopituitarism	=
				Sinusitis	=
Senior et al., 2008	High Risk	Endoscopic transsphenoidal surgery, N=176, adenoma 84%	Age (continuous)	Postoperative CSF leak	=
			Gender		=
			BMI (continuous)		=
			Tumor size >10* vs. <10mm		p=0.04
			Tumor size >20 vs. <20mm		=
			RCC		OR 2.6; p<0.001
			Tumors other than adenomas		OR 9.0, p<0.001
			Gender	Overall DI	=
			Tumor size (not defined)		=
			RCC*		p=0.003
			Tumor types other than RCC		=
			Tumor location		=
			Revision surgery		=

Supplementary table 2. Summary of study characteristics of prognostic cohort studies (continued)

First author, year	Study Quality	Study population	Prognostic factor	Outcome	Association
Sigounas et al., 2008	Moderate Risk	Endoscopic transsphenoidal pituitary surgery, N=105, adenoma 85%	Prior nonendoscopic surgery	Permanent DI	=
			RCC*		p=0.028
			Tumor size (micro- vs. macroadenoma)		=
			Prior endoscopic surgery		=
			Gender (ref. male)	Overall DI	=
			Race		=
			Tumor size (micro- vs. macroadenoma)		=
			NFA		=
			Acromegaly		=
			Cushing's disease		=
			Prolactinoma		=
			RCC		95% CI 2.0–25.8, p=0.003
			Craniopharyngioma		=
			Prior endoscopic surgery		=

Supplementary table 2. Summary of study characteristics of prognostic cohort studies (continued)

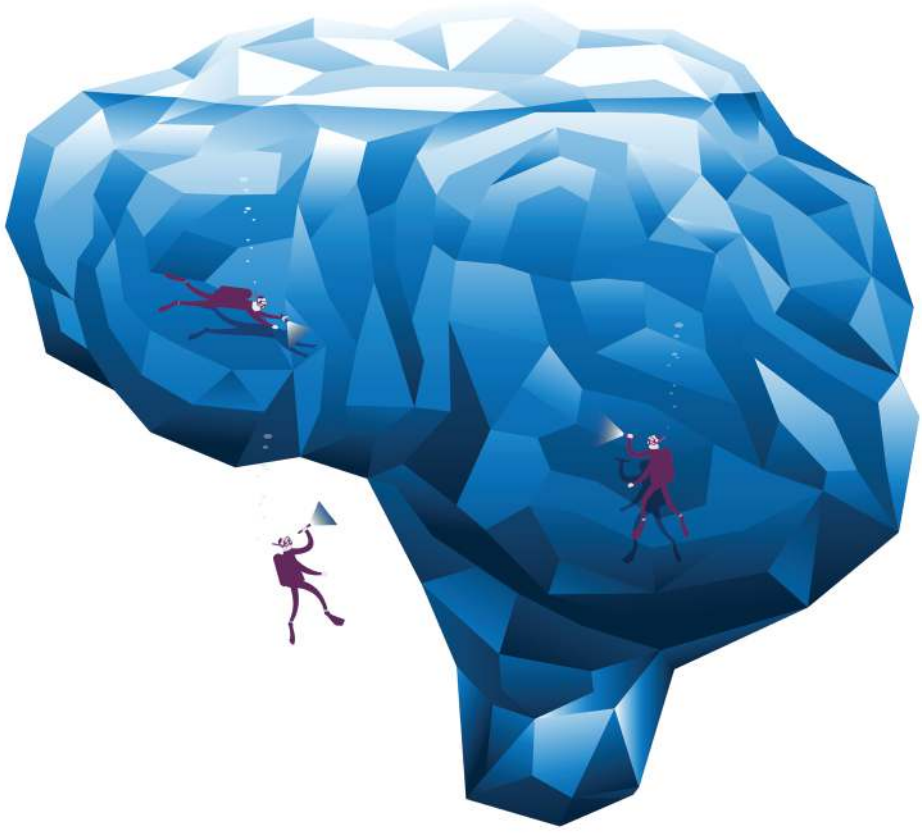
First author, year	Study Quality	Study population	Prognostic factor	Outcome	Association
Thawani et al., 2017	High Risk	Consecutively treated pituitary macroadenomas, N=203	Age (continuous)	Postoperative CSF leak	=
			Gender (ref. female)		=
			Tumor size		=
			Cavernous sinus involvement		=
			Prior surgery		=
			Prior radiation		=
			Age (continuous)	Infections (overall)	=
			Gender (ref. female)		=
			Tumor size		=
			Tumor type, functional* (ref. non-functional)		p=0.04
			Prior surgery		=
			Prior radiation		=
			Age (continuous)	Overall DI	
			Gender (female)		=
			Tumor size		=
Zhan et al., 2015	High Risk	Elderly pituitary adenoma patients (≥65 years) compared to patients aged between 40 and 55 years, N=303	Age ≥65 (ref. 40-55 years)	Postoperative CSF leak	=
				Meningitis	=
				Intracranial hematoma	=
				Transient DI	=
				Permanent DI	=
				Overall DI	=
				New hypopituitarism	=
				Visual deterioration	=

Supplementary table 2. Summary of study characteristics of prognostic cohort studies (continued)

First author, year	Study Quality	Study population	Prognostic factor	Outcome	Association
Zhang et al., 2014	High Risk	Transsphenoidal pituitary adenoma surgery, N=326	Diabetes mellitus	Intracranial infections	OR 5.47, 95% CI 1,09-6,49; p=0,009

* Prognostic factor has a higher chance of outcome

+ Based on a multivariate analysis



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Striving for the best possible quality of life in a complex Acromegaly patient: what are my options?

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Chapter 41 in the book: The Art of Neuroendocrinology; A Case-Based Approach to Medical Decision-Making (2017)

CASE DESCRIPTION

A 33-year-old male with no prior medical history presented with symptoms of acromegaly (growing hands, feet and tongue, snoring and nocturnal sweating) after being pointed out by friends and family. The patient did not notice these symptoms himself, indicating mild symptoms, however had pronounced and classic acromegalic features. Laboratory results were conclusive for growth hormone excess, with IGF-I at 5-6 times upper limit of normal (ULN) and no suppression on glucose tolerance test. There was an isodense lesion suggestive of a macroadenoma on MRI (16 x 15 millimeters). No compression of the chiasm, however possible compression of the right optic nerve. There was left sided deviation of the pituitary stalk, invasion of the right cavernous sinus was not clearly present, but could not be radiologically excluded (Figure 1A/B, 2A/B). An endoscopic transsphenoidal resection was performed aiming for curation of acromegaly. During the operation cavernous sinus invasion was not clearly visualized and typical adenoma tissue was completely resected suggesting a curative resection. During the operation there were no signs of cerebral spinal fluid (CSF) leakage and no hypopituitarism was induced. Unfortunately, postoperatively, growth hormone and IGF-I levels were still elevated and the postoperative MRI showed a residual lesion of 12 x 9 millimeters craniolaterally below the right optic nerve (Figure 1C/D, 2C/D). Octreotide LAR was started after the surgery. The patient initially responded well to medical treatment with normalization of IGF-I (ranging between 0.8 and 1.5 ULN), however the clinical effect was suboptimal with complaints of nasal obstruction, joint complaints and fatigue, aggravating towards the end of the injection interval. The patient was referred to our clinic at this point to discuss surgical options. This case aims to describe the process of discussing treatment options with a patient at the stage of initial failed surgery. We will go through alternative options and discuss our vision on which treatment is most suitable for this situation.

CONSIDERATIONS OF THE MULTIDISCIPLINARY TEAM ON INITIAL DIAGNOSIS AND MANAGEMENT

This is a typical presentation of a young male patient with acromegaly, profound tissue hypertrophy and facial changes. Despite this clinical presentation with relatively minor symptoms, the symptoms became more severe over time and probably more so in the future. There was no glucose intolerance or other severe co-morbidities. These cases frequently have a macroadenoma located basally, with a tendency to invade the cavernous sinus, compromising chances for complete surgical resection. In this case preoperative radiological imaging did not show certain cavernous sinus invasion, therefore the chance of primary surgical cure was considered feasible. With the prospect of

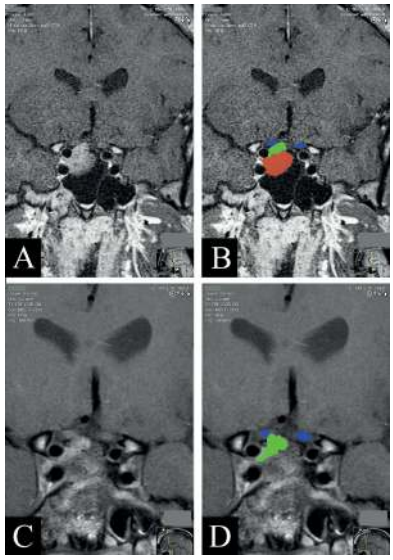

Figure 1. Coronal view A+B: preoperative T1 MRI**.** Adenoma (red + green), optic nerves (blue).
C+D: postoperative T1 MRI. Optic nerves (blue), remnant (green)

a lifelong need of medication, in young patients we prefer a primary surgical approach in an effort to try to cure a patient of his/her disease. Guidelines advocate that surgery is the first treatment in acromegaly [1], however, in recent guidelines there is a place for primary somatostatin analog treatment in patients with invasive tumors that cannot be cured through surgery. The a priori estimated cure rate for a first procedure in this particular case will probably range from 30-70% depending on the center's experience and personal opinion on treatment strategy. Younger patients tend to have a more aggressive presentation then patients with a later onset with respect to tumor mass. Therefore, tumor control is an important treatment goal in this group in addition to control of GH, IGF-I and symptoms. This can be achieved by both surgery (total resection or debulking) and somatostatin analog treatment (causing stabilization or shrinkage in most cases).

CONSIDERATIONS OF THE MULTIDISCIPLINARY TEAM ON SECONDARY MANAGEMENT

At the outpatient clinic the therapeutic options were discussed for this young male patient with clinically persisting acromegaly according to features and complaints, a visible tumor remnant (Figure 1C/D, 2C/D), while on somatostatin analogs with IGF-I levels in the high normal/slightly elevated range.

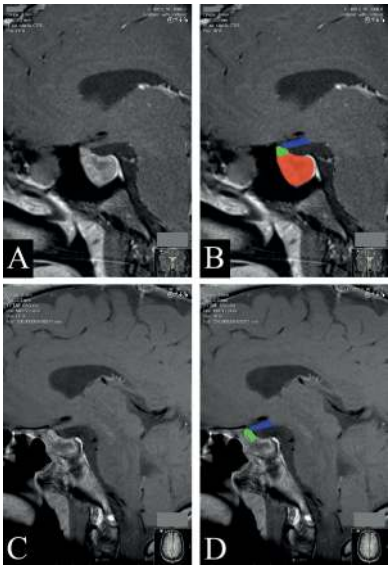

Figure 2. Sagittal view A+B: preoperative T1 MRI. Adenoma (red + green), optic nerves (blue). C+D: postoperative T1 MRI. Optic nerves (blue), remnant (green)

Presenting options to the patient

Although there have been medical improvements over the last decade, i.e. personalized medication and endoscopic surgery, there is not one single best approach. For example, a decision between lifelong treatment with medication, the possibility of surgical curation or remission through radiotherapy should be made through shared decision-making between the neurosurgeon, endocrinologist, radiotherapist and patient. It is important to include the patient's preferences whenever possible. All treatment options have benefits and potential risks, see Table 1.

Treatment goals

Acromegaly is a serious medical condition. Untreated, there is a 2-3 fold increased mortality risk, which can be reduced through effective treatment aimed at normalizing the GH excess. Most epidemiological data on mortality currently available have a majority of patients who have undergone surgery or radiotherapy [2]. However, recent studies have shown that there are no indications that these figures are different in medically treated patients [3]. Risk factors for mortality are: radiotherapy, adrenal insufficiency, diabetes, hypertension and increased GH and IGF-I values. Persistent GH and IGF-I excess predisposes for morbidity, such as hypertension, arthropathy, cardiac disease, sleep apnea and osteoporosis leading to vertebral fractures. Patients with active disease have decreased quality of life and clinical symptoms of GH excess (i.e. sweating, headache, paresthesia, swelling, joint pain, asthenia). Depending on tumor size and growth tendency, tumor volume control can be of relevance in specific cases.

In this case, there is no doubt that additional treatment is needed. The specific aims of treatment for this patient are reducing symptoms and improving quality of life. Of importance is also prevention of future development of co-morbidities and premature mortality. In addition, although the tumor remnant does not result in compression of vital organs, we need to be alert for tumor growth in the future because of the close relation with the right optic nerve. Normalization of IGF-I and GH is a 'biomarker' that can help the physician since it can indicate adequate control. IGF-I is, however not perfectly, correlated with symptoms and comorbidities, for example depending on individual GH sensitivity and yet unresolved factors. One has to take into account interpretative difficulties.

Surgical considerations for a second surgical exploration

Considering the implications of persistent growth hormone excess and the need for future tumor control, the benefits of a second surgery are clear if cure is considered feasible.

In the past the results of second surgical procedures have been less successful compared to primary surgery. When choosing for surgery one has to consider the somewhat increased risk of complications and increased difficulty of the second operation [4]. This is mainly because remnants are often more difficult to reach. In this specific case, the tumor remnant can be seen on the original MRI (Figure 1C/D, 2C/D). It is closely related to the medial opticocarotid recess (mOCR) and lack of exposure during the primary surgery is considered the reason for failure to fully expose the tumor. Since the superior part of the tumor could not be seen during the procedure this was probably the main reason for the incomplete resection. Although a supra-diaphragmatic extension of the tumor cannot be excluded.

Interpretation of a postoperative MRI can be complicated. This is where the added value of an expert neuroradiologist comes in. In this case it was difficult to distinguish the tumor remnant from regular postoperative changes, for example the quite prominent resection cavity in this case. Result of our multidisciplinary pituitary meeting was to advise a re-exploration, through an 'extended' transsphenoidal approach. For this specific case it is important to remove more bone around the mOCR to be able to reach the tumor. We consider the slightly increased risk of damage to the right optic nerve, internal carotid artery, third and sixth cranial nerves and an intra-operative CSF leak, however hypopituitarism is unlikely to develop. Timing of surgery is also an important factor to consider; one can choose between immediate re-exploration or initial continuation of medical treatment which can result in shrinkage. In our opinion immediate surgical resection is preferred here, because of possible difficulties with identification on imaging and during surgery in case of significant shrinkage of this small remnant.

Medical considerations for secondary medical treatment

Besides surgical options there are also several potential medical options to discuss with this patient. Since there are no medical treatment options that are able to cure the patient, lifelong treatment needs to be anticipated.

Somatostatin analog

The first option is to continue or optimize somatostatin analog treatment. This case has proven to be octreotide sensitive. Biochemical values have clearly decreased and are currently only slightly elevated. While in asymptomatic cases these values can be accepted, for this symptomatic case further improvement of GH excess is warranted. The dose of octreotide LAR could be increased from 30 mg to 40 mg. There is some supporting evidence that there is some additional decrease, however, in our experience this is limited. Alternative strategy is to increase the interval and apply 30 mg every 3 weeks. This is considered reasonable if symptoms aggravate towards the end of the injection interval [5]. An advantage of somatostatin analog treatment is the usual stabilization or shrinkage of the tumor remnant, so tumor control for the future.

Cabergolin treatment (or combined somatostatin/cabergolin treatment)

Addition of cabergolin in mild persisting hypersecretion is an option in some patients. Response rate of the addition is approximately 10-20%. It can be tried safely with usually little side effects, although the required dose is higher than in prolactinoma patients [1].

Pegvisomant treatment

Transition to pegvisomant monotherapy is a viable option. For biochemical control a very high response rate of 80-100% can be anticipated [6]. However, for the patient it will require transition to daily subcutaneous (s.c.) injections instead of monthly intramuscular (i.m.) injections. Improvement of acromegaly symptoms is generally very good. The main disadvantages of pegvisomant monotherapy are very high costs and the inability of tumor control since it is a drug, acting at a peripheral level, not at the tumor level. Therefore, the tumor remnant needs to be periodically monitored, especially in this case with presumed tendency of tumor growth in the long-term.

An alternative is combination therapy of somatostatin analog and pegvisomant [7, 8]. This is a quite good option, since costs are reduced, tumor control is established by somatostatin, and generally the pegvisomant interval can be extended towards a weekly dosage instead of a daily injection. The clinical and biochemical results of this combination therapy are good, also in the long-term.

Table 1. Benefits and potential risks of the treatment options

	Key reference	General success rate (cure/remission)	General complication rate	Individualized comment on success	Individualized remark on complication
Expectative approach		0%	Progression of comorbidity, increased mortality Symptoms Tumor regrowth		- Young patient with proven disease severity. - Be alert for tumor growth because of young age.
Pituitary surgery	[18-25]	0-90% depending on tumor size and surgical experience	New hypopituitarism Liquor leakage	- Estimated success rate 40% - Preference for final cure, lower costs. - Remnant was not previously explored.	Slightly increased risk of damage to the optic nerve, third and sixth cranial nerve, carotid artery and CSF leak
Medical treatment Octreotide: 4 wk injections	[1, 5, 9, 26]	Pituitary adenoma directed: Octreotide 40-50%	Octreotide: bile stones, bowel complaints, glucose disturbances.	- Known response to octreotide - High chance of tumor control with octreotide - No local risks i.e. hypopituitarism / cranial nerve damage	- Lifelong treatment needed - Complications of long-term drug treatment (bile stone)
Pasireotide: 4 wk injections	[1, 9]	Pasireotide 40-60%	Pasireotide: hyperglycemia, diabetes, bile stones		
Cabergoline: Tablets (daily – weekly)	[1, 26]	Cabergoline 10-20 % (i.e. depending on tumor receptor subtype)	Cabergoline: hypotension, nausea		
Pegvisomant: Daily s.c. injection or weekly with combination therapy	[1, 6, 26, 27]	Peripheral action: Pegvisomant 80-100%	Pegvisomant: liver enzyme abnormalities		
Radiotherapy	[12, 15, 16, 28]	69-84%, but delayed	Development of hypopituitarism 14-66%	Tumor control, possible cessation of drugs in future	Patient prefers to preserve pituitary function

Pasireotide

Pasireotide is a new treatment option in patients with SSTR 2 resistant adenoma. Comparative trials have been performed between somatostatin analog treatment (octreotide and lanreotide) and pasireotide, in which somewhat more patients are controlled with pasireotide in comparison to regular somatostatin analogs, however, at the expense of hyperglycemia needing careful follow-up and treatment if necessary and high costs [9, 10]. At present we use pasireotide incidentally in clearly SSTR 2 resistant tumors, after failed treatment with regular somatostatin analogs, usually also after pegvisomant is considered. In this case control of IGF-I on regular somatostatin analogs is nearly sufficient, therefore pasireotide is not considered at this stage.

Considerations for radiotherapy

While surgery is the primary treatment modality for acromegaly, fractioned radiotherapy and stereotactic radiosurgery should be considered for tumors with cavernous sinus involvement, when surgery is unsuccessful (subtotal resection and/or no biochemical remission) or for recurrent tumors. Remission rates for radiotherapy after unsuccessful surgery are 69 to 84% (follow-up of 6 or more years) [11, 12]. Control of tumor growth is excellent after radiotherapy, as it is achieved in more than 90% of cases on the long-term (3 to 10 years follow-up) [13, 14]. Probable side effects on the long-term are hypopituitarism (14 to 66%), injury of the cranial nerves (especially the optic nerve and system (0 to 5.5%) and development of secondary tumors (2 to 3%) [15, 16]. Compared with patients treated with surgery only, patients treated with postoperative radiotherapy tend to have an impaired quality of life, more impairments in physical function and less energy on the long-term (11.5 years) [17].

CONCLUSION

For this specific case, and many other cases similar to this one, we consider the following treatment modalities as best options: re-resection, continuation of somatostatin analogs at a somewhat higher dose and if necessary combined with pegvisomant once a week. We frequently encounter the difficulty to overcome the understandable hesitation for surgery from the patient's perspective. This complicates a rational decision between a surgical and a medical intervention.

Since both strategies have benefits and drawbacks, it is up to the treating physician to guide the patient in his/her decision-making process. Profound knowledge of both options, or combined consultation is mandatory for proper shared decision making.

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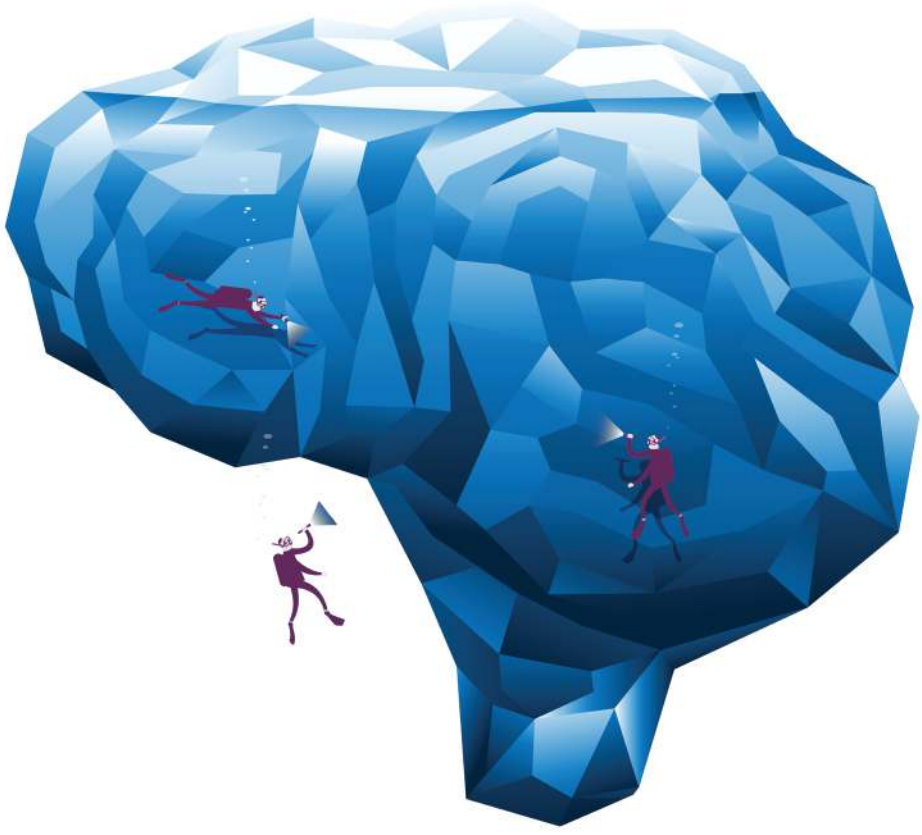

4

Striving for the best possible quality of life in a complex Cushing patient: cure or control?

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Chapter 34 in the book: The Art of Neuroendocrinology; A Case-Based Approach to Medical Decision-Making (2017)

CASE DESCRIPTION

A 48-year old-female with no prior medical history presented with progressive complaints of fatigue, insomnia, irritability, mild weight gain of 6 kilograms, sensations of tingling and moderate excess hair growth. She had no comorbidity, i.e. no diabetes or hypertension. Facial changes recognized by the general practitioner raised suspicion of hypercortisolism. After a lengthy diagnostic path, the diagnosis Morbus Cushing was confirmed. Biochemical analysis (non-suppressed serum cortisol during 1 mg dexamethasone test, and 2-3 times elevated 24-hour urinary cortisol excretion) were conclusive for hypercortisolism, which appeared to be ACTH dependent. The MRI scan showed a small (5 x 6 x 6 mm) isodense nodular lesion posterior to the pituitary stalk, suggestive of a pituitary adenoma (Figure 1). The diagnosis of Cushing's disease was made and the patient was referred for a surgical resection of the tumor following 3 months of medical pre-treatment with metyrapone. Even though during the procedure tissue suspected for adenoma was removed, the pathological investigation was negative and persistent biochemical disease activity was confirmed within 6 weeks postoperatively. At this stage a repeat MRI was made and a bilateral inferior petrosal sinus sampling was performed to confirm a pituitary origin. The patient resumed medical treatment with metyrapone, which easily normalized urinary cortisol excretion and improved the patient's symptoms to a certain extent, but she still experienced persisting complaints of fatigue, energy loss and mild weight gain. She was referred to our center to discuss further treatment options at this point.

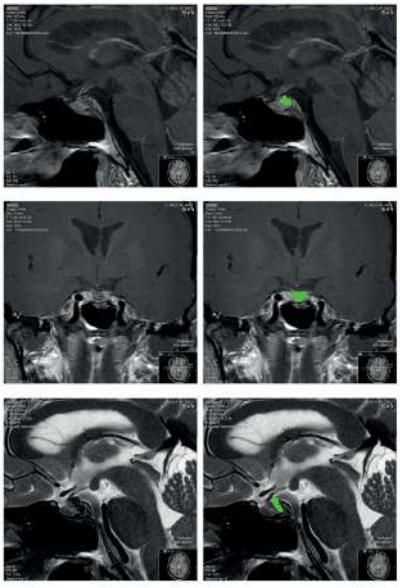

Figure 1. *Top:* Sagittal T1 view of the pituitary adenoma (green), located posteriorly of the pituitary gland**.** *Middle:* Coronal T1 view of the adenoma (green), located medially. *Bottom:* Sagittal T2 view of the pituitary adenoma (green), located posteriorly of the pituitary gland.

This case aims to describe the process of discussing treatment options with a patient at the stage of initial failed surgery. We review alternative options and discuss our vision on which treatment is most suitable for this situation.

CONSIDERATIONS OF THE MULTIDISCIPLINARY TEAM ON INITIAL DIAGNOSIS AND MANAGEMENT

Diagnosis of hypercortisolism in this patient

Diagnostic delay is very common in patients with Cushing's disease. This case was no different and the patient presented with a very clear story of something that went wrong in her life. Initial symptoms were vague; however, they became more compatible with hypercortisolism over time. Although the disease course was approximately three years, the diagnosis was made at a relatively "early" stage thanks to the awareness of the general practitioner, since the patient did not (yet) present with symptoms of hypertension, diabetes, or other signs of Cushing's disease. Although the patient was subjectively invalidated by symptoms and there was no biochemical doubt of the diagnosis, there was a lack of specific signs and comorbidity. Despite this and the apparent normal social functioning we consider Cushing to be a serious condition, with an increased risk of morbidity and mortality and in which a curative treatment is warranted of possible [1]. It is always important to remember the treatment goals of the Endocrine Society Practice Guideline and their supporting evidence and discussion:

"Treatment goals:
1.1 In patients with overt CS, we recommend normalizing cortisol levels or action at its receptors to eliminate the signs and symptoms of CS and treating comorbidities associated with hypercortisolism.
1.2 We recommend against treatment to reduce cortisol levels or action if there is not an established diagnosis of CS.
1.3 We suggest against treatments designed to normalize cortisol or its action when there is only borderline biochemical abnormality of the hypothalamic-pituitary-adrenal (HPA) axis without any specific signs of CS. The benefit of treating to normalize cortisol is not established in this setting.

Evidence for recommendations:
"Because all treatments carry risk, clinicians should establish a diagnosis of CS before administering them. ... Similarly, the consequences of mild or cyclic hypercortisolism are not clear, so that treatment guidelines cannot be generalized to those patients. However, because CS tends to progress to severe hypercortisolism, it is possible that early recog-

nition and treatment of mild or cyclic disease (values < 1.5-fold upper reference range) would reduce the risk of residual morbidity. Unfortunately, few data address this assumption. If the clinician is uncertain of the clinical diagnosis (regardless of the magnitude of biochemical perturbations), further testing over time is always the best approach."

A comparable case with even fewer symptoms and good quality of life, could have been considered as a case for a careful follow-up approach. However, the clearly decreased quality of life and weight gain and some reversal on metyrapone have led us to the conclusion that hypercortisolism was not that mild and treatment was indicated.

Diagnosis of pituitary source of ACTH dependent Cushing

The diagnosis of pituitary derived hypercortisolism (Cushing's disease) instead of an ectopic Cushing syndrome needs to be challenged in cases with no, or only a very small pituitary adenoma. In guidelines, pituitary lesions less than 6 millimeters should be considered to be a potential non-ACTH producing adenoma (incidentaloma). Therefore, a bilateral inferior petrosal sinus sampling or additional dynamic testing should be considered to support the presence of a pituitary origin. Since predictive values of all available tests have limitations and invasive sampling procedures have risks, we tend to take into account the a priori risk of having a pituitary origin or an ectopic source. In young female patients with a typical protracted course with a very high a priori risk of a pituitary derived Cushing we tend to bypass the sampling procedure. However, after the initial negative pathological findings in this case, it was decided to perform a venous sampling. It is important to realize that after surgery lateralization, i.e. preference for left or right sided lesions may be less reliable. Therefore, the purpose of this sampling was mainly to confirm the pituitary source. In general, the predictive value for confirming a pituitary origin is very good (80-100% sensitivity, 95% specificity, however lateralization is only accurate in 50% of cases) and ACTH-secreting pituitary adenomas contralateral to the sampling have been described [2–5].

Rationale for medical pre-treatment in general

Medical pre-treatment is not evidence-based medicine. However, in our clinic we prefer a brief period of medical pre-treatment mainly in an effort to improve the clinical condition of the patient. There are suggestions that surgery might be less bloody. In our experience patients prefer this pre-treatment and tend to feel better. However, comparative clinical studies on this topic are lacking, and local experience and organization of care will be leading in the choice for pre-treatment since careful follow-up is needed. The choice for metyrapone in this case is again mainly made based on availability and local experience, since other drugs (i.e. ketoconazole) can also be considered (see below).

CONSIDERATION FOR FIRST SURGICAL EXPLORATION IN THIS INDIVIDUAL PATIENT

According to all management guidelines there is no doubt that the optimal treatment is transsphenoidal surgery in an expert pituitary center [6]. The curative treatment results are very good in microadenomas, even if lesions are small or not very discriminative on the MRI-scan. Long-term data on mortality and morbidity are available. Quality of life improves, although usually does not fully normalize (Figure 2). There is a low risk of hypopituitarism, although the aim is to induce (temporary) hypocortisolism and this is frequently seen as a result of downregulation of endogenous ACTH secretion. Recently, several new medical treatments have been registered for persistent Cushing's disease. The uncertainties with respect to long-term outcome and side effects need to be weighed against the potential complications of surgery. The future will determine whether this will change the treatment of naive patients.

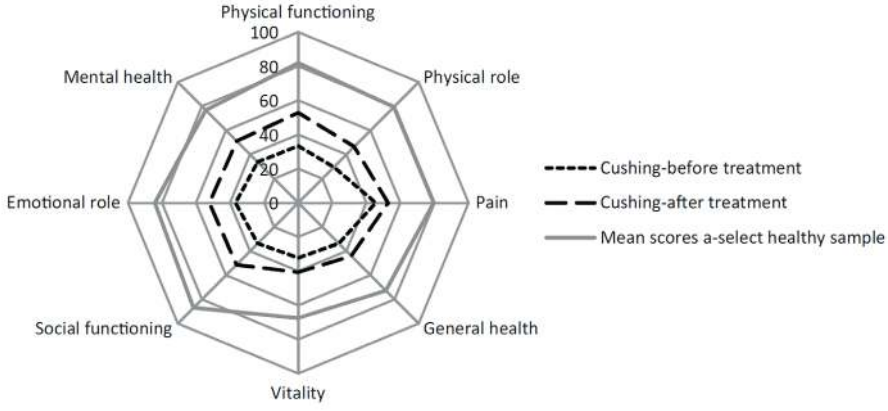

Figure 2. SF-36 scores in patients with Cushing's disease before and after treatment.
* Adapted from Andela C.D. et al. Quality of life (QoL) impairment in patients with a pituitary adenoma: a systematic review of QoL studies. Pituitary. 2015 Oct; 18(5):752-76. Copyright 2015, Springer.

CONSIDERATIONS OF THE MULTIDISCIPLINARY TEAM ON SECONDARY MANAGEMENT

Treatment options

At our clinic we favor a stepwise approach during consultation in which we present the patient with information about the therapy, including possible benefits and/or negative effects of the available treatment options. In this case, at the outpatient clinic, secondary treatment options were discussed: pituitary surgery, medication, radiation, surgery of the adrenal glands, or a combination of these options.

Transnasal surgery

A second surgery is always more complicated due to scar tissue formation. When a surgery is performed at another center, sometimes vital details of the initial surgery are lacking. This makes an assessment of surgical risks and the chance of a successful procedure somewhat less reliable. With surgery, the goal is to remove the adenoma without decreasing pituitary function: complete removal of the adenoma is the only treatment that can cure the patient. However, we should note that recurrence rates vary from 15 to 66% within 5-10 years of initially successful surgery [7–9]. During surgery there is a small risk of injuring the pituitary gland, both anterior and posterior lobes. In this case the adenoma is located posterior to the pituitary stalk. The risk of pituitary stalk injury, with complete loss of gland function, is therefore relatively high. However, this risk can only be properly assessed during surgery. When visibility is good, with a relatively bloodless surgical field, and the tumor is discernible from the gland, stalk injury is not likely to occur.

A CSF leak during surgery is anticipated in this case due to the extension of the adenoma in the supra-sellar cistern. While closure techniques have greatly improved, post-operative CSF leaks are always more likely to occur if this cistern is opened widely. Carotid injury, injury of the sixth cranial nerve, or severe blood loss from the cavernous sinus are always a concern, but modern surgical techniques limit these risks; therefore, they should not be a factor in the decision-making process. When complete selective adenoma resection appears to be unrealistic during surgery, for instance because the tumor cannot be conclusively identified, or removal of the adenoma almost certainly will cause stalk injury, the surgeon has multiple options: leave remnant tumor, complete resection despite enhanced risk of surgically induced panhypopituitarism. Experience of the surgical team and extensive pre-operative counselling are essential for adequate management during surgical decision-making.

Alternative neurosurgical options

If the pituitary function is intact, and complete surgical removal without damage to pituitary/stalk is not feasible preoperatively or this is concluded during the procedure, alternative surgical options need to be decided by the surgeon during the procedure or preferably considered and discussed at a later stage with the patient. The benefit of a partial adenoma resection in this case is useless, since it is unlikely that the patient will restore quality of life and additional treatment will remain necessary. The consideration of “debulking” might be different in cases with severe hypercortisolism or large tumors.

Hemi-, Total Hypophysectomy, Sella Clean Out

Our experience with targeted radiation for residual adenomas deeply nested in the cavernous sinus is good. However, in this case, the pituitary gland would still get a full dose of radiation when residual tumor is left, with future hypopituitarism and delayed control of hypercortisolism. Therefore, we discussed with the patient that in case a selective adenoma resection would not appear to be feasible during surgery, a sella cleanout (removing the pituitary gland with adenoma completely) would be a viable surgical option. Because of the serious consequences in terms of induced co-morbidity by this approach, we decided up front to do so only during a separate, third surgery after careful reconsideration. This would allow an evaluation of the results of the second surgery, pituitary function, Cushing status, pathology report and emotional well-being of the patient. Alternative treatment options could be discussed once again and another critically evaluated session of shared decision making could be held.

Medication

Medical treatment for Cushing's disease has also evolved. Even though we use metyrapone or ketoconazole as a pre-treatment, we generally do not favor these drugs for lifelong medical therapy. Metyrapone inhibits the adrenocorticosteroid synthesis in the adrenal gland, and as such Cushing symptoms. However, the pituitary adenoma remains unaffected.

In recent years, new medical treatments have been registered for treatment of Cushing's disease and other pharmaceutical compounds are in different stages of development. These are carefully summarized in several recent review papers and a recent endocrine society guideline [10, 11]. Combination strategies with different drugs can also be considered [12]. There are obvious potential benefits of pharmaceutical strategies, the non-invasiveness, the option to trial and error, reversible side effects, but also the drawback of delaying the ultimate aim of "cure" and high costs. Quality of life and co-morbidity outcomes have not been compared between pharmaceutical and surgical strategies and therefore cannot be considered as either advantageous or disadvantageous yet in favor of any treatment. It is important to acknowledge that most long-term outcome data are derived from surgically and/or radiotherapeutically treated patients. These data conclude that there is suboptimal outcome with respect to mortality, morbidity and quality of life and that there is a clear need for improvement. How this should be established and whether medical treatment will improve figures will not be easy to evaluate because of the need for large epidemiological studies.

Since in this case the patient had already undergone an initial surgery, the benefits of lifelong treatment approached the benefits of another surgical resection. Furthermore,

because of the mild symptomatology the necessity of immediate surgical exploration had decreased. Her pre-treatment period made clear that an optimal clinical situation had not yet been reached and the patient indicated her wish to proceed to alternatives. Pasireotide could have been tried, but this was not done because of the controlled situation with metyrapone.

Table 1. Comparison of registered medical strategies [13]

	Mechanism	Response	Side effects
Ketoconazole (oral 2-3x daily)	Inhibits steroidogenesis at several levels	Days, 44-92%	Liver toxicity, hypogonadism, drug-drug interaction, adrenal insufficiency
Metyrapone (oral 4-6x daily)	Inhibits steroidogenesis at 11 beta-hydroxylase	Days, 45-100%	Hypokalemia, hyperandrogenism
Pasireotide (S.c. 2x daily, depot)	Pituitary directed via SSTR 2 and 5	Weeks, 25%	Diabetes
Dopamin agonists (Cabergoline) (1x/week-1x daily)	Pituitary directed via D2R on corticotrophs	Weeks, 25-40%	Hypotension, dizziness

Radiation

While surgery is the primary treatment modality for Cushing's disease, fractioned radiotherapy and stereotactic radiosurgery should be considered for tumors with cavernous sinus involvement when surgery is unsuccessful (subtotal resection and/or no biochemical remission) or for recurrent tumors. Remission rates for radiotherapy after unsuccessful surgery are 63-83% and median time required for biochemical remission is 42-44 months [14, 15]. Control of tumor growth is excellent after radiotherapy, as it is achieved in more than 90% of cases in the long term (3-10 years follow-up) [16, 17]. Probable side effects in the long term are hypopituitarism (14-66%), injury of the cranial nerves (especially the optic nerve and system (0-5.5%) and development of secondary tumors (2-3%) [18, 19]. Compared with patients treated with surgery only, patients who have undergone additional radiotherapy report similar health-related quality of life in the long term (13 years) [20]. In this patient, normal pituitary function and relative young age were contributing factors in our decision to refrain from radiotherapy at this stage.

Table 2. Advantages and disadvantages of stereotactic radiosurgery and fractioned radiotherapy

Stereotactic radiosurgery	Fractioned radiotherapy
One treatment session	Multiple treatment sessions: 25-28 sessions 45-50.4 Gy at daily fractions of 1.8 Gy
More precise: small safety margins and minimum target size	Safe for nearby located radiation-sensitive tissues (e.g. optic nerve). A single high dose by SRS may cause more damage.
Only usable for small tumors: < 3 cm	Also usable for bigger tumors ≥ 3 cm

Bilateral adrenalectomy

In severe cases of Cushing's disease, bilateral adrenalectomy can be considered, with anticipated loss of adrenal function, including mineralocorticoid function [6]. There is a small chance that this stimulates pituitary adenoma growth (Nelson's syndrome), which is quite unpredictable but can be detected early with ACTH and pituitary MRI. Early stages can be managed with surgery. This therapy is not considered to be a viable option at this stage.

CLINICAL COURSE

The patient eventually opted for a second surgical exploration, which was performed after deliberately weighing risk and benefits and considering other treatment options and after 4 months of metyrapone pre-treatment. We performed an endoscopic transsphenoidal re-exploration, during which the bony opening of the sella was enlarged in all directions. A hemi-pituitary transposition was performed on the left side and adenoma tissue identified posterior to the pituitary gland. The tumor had a firm consistency, necessitating sharp dissection of the tumor planes. As expected, the tumor extended into the supra-sellar cistern and a CSF leak was encountered during surgery. There was good surgical visibility. The adenoma was identified and we decided to proceed and attempt a radical resection. Since complex surgical cases like these are performed from start to finish by two experienced pituitary surgeons, it is possible to make decisions like these together. The adenoma was cut off of the pituitary stalk, which was partially exposed. The CSF leak was closed with a small piece of abdominal fat tissue, tissue fibrin glue, and scaffold material. An external CSF drain was given for a short period post-operatively. Serum cortisol levels dropped rapidly in the post-operative days, to 0.047 µmol/L (normal range: 0.070-0.500 µmol/L), indicative of a radical resection of the adenoma. The pathology showed ACTH positive adenoma. There were no postoperative complications; specifically, there was no diabetes insipidus. The patient was discharged from the hospital in good clinical condition. Further evaluation of her symptoms and complete pituitary function are ongoing.

CONCLUSION

Choice for second surgical exploration

The decision to perform a second surgical exploration is clearly more complicated than the initial treatment decision, particularly when the first operation has been performed by another surgeon.

In the context of all new and future medical treatment options we tend to extensively discuss all possibilities to proceed, using a simplified option grid to optimally involve patients in the decision- making process (Table 3) acknowledging the challenges in managing Cushing's disease and aiming at best future quality of life. Nevertheless, the endoscopic transsphenoidal surgery remains at a very central place in the treatment algorithm.

Table 3. Example of an filled option grid to discuss treatment options with patients

	Key reference	General success rate	General complication rate	Case specific comment on treatment	Individualized remark on complication risk
Expectative approach	-	Not applicable	Severe complications of untreated Cushing's disease	Symptomatic patient in need of treatment because of complaints.	Risks grossly unknown for mild – asymptomatic cases without comorbidity
Pituitary surgery	[21–28]	~70% remission rate in microadenoma (dependent on expertise of surgeon, size, location and visibility of adenoma)	Low risk diabetes insipidus 1-5% Low risk hypopituitarism 3-14% Low risk CSF leak 2-16% Temporary nasal complaints, postoperative hyponatremia 1-8%	Small tumor size, but difficult location, 2nd operation	Considered higher risk for development of DI and a CSF leak
Medical treatment	[10, 11]	Pasireotide: 25% Ketoconazole: 44-92% Metyrapone: 45-100%	High costs, life-long treatment, uncertain long-term outcome, side effects (liver enzyme abnormalities – ketoconazole, diabetes - pasireotide)	Although biochemically properly treated, not completely satisfied during treatment with metyrapone.	No side effects and control on metyrapone observed
Radiotherapy	[14,15,18,19]	63-83%	Development of hypopituitarism 14-66% Ongoing hypercortisolism	Higher risk of damage due to location of adenoma	Patient prefers to preserve pituitary function
Bilateral adrenalectomy	[6]	100 %	100% permanent hypocortisolism and mineralocorticoid deficiency; Risk of Nelson's syndrome (5-20%)	Considered to be last resort, and not applicable in this situation without severe comorbidity	Patient prefers to preserve adrenal function

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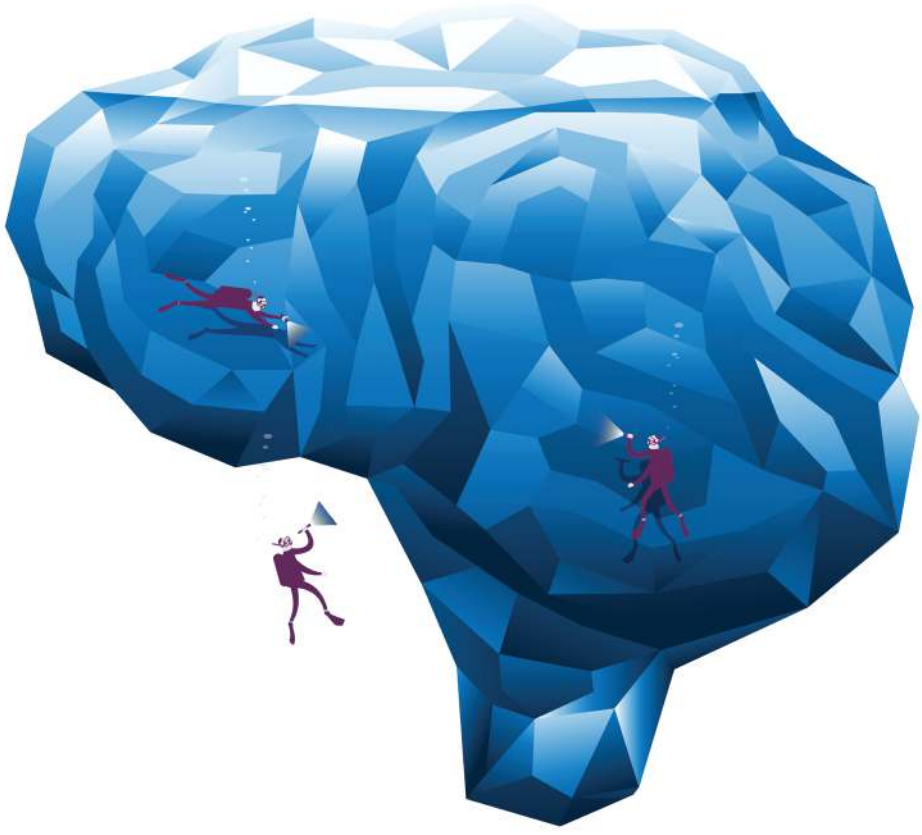
Part 2

Measurement of medical outcomes and costs in VBHC



5

Toward Value Based Health Care in pituitary surgery: application of a comprehensive outcome set in perioperative care

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ABSTRACT

Objective

Although widely advocated, applying Value Based Health Care (VBHC) in clinical practice is challenging. This study describes VBHC-based perioperative outcomes for patients with pituitary tumors up to 6 months postoperatively.

Methods

A total of 103 adult patients undergoing surgery were prospectively followed. Outcomes categorized according to the framework of VHBC included survival, degree of resection, endocrine remission, visual outcome (including self-perceived functioning), recovery of pituitary function, disease burden and health-related quality of life (HRQoL) at 6 months (Tier 1); time to recovery of disease burden, HRQoL, visual function (Tier 2); permanent hypopituitarism and accompanying hormone replacement (Tier 3). Generalized estimating equations (GEEs) analysis was performed to describe outcomes over time.

Results

Regarding Tier 1, there was no mortality, 72 patients (70%) had a complete resection, 31 of 45 patients (69%) with functioning tumors were in remission, 7 (12%, with preoperative deficits) had recovery of pituitary function and 45 of 47 (96%) had visual improvement. Disease burden and HRQoL improved in 36–45% at 6 months; however, there were significant differences between tumor types. Regarding Tier 2: disease burden, HRQoL and visual functioning improved within 6 weeks after surgery; however, recovery varied widely among tumor types (fastest in prolactinoma and non-functioning adenoma patients). Regarding Tier 3, 52 patients (50%) had persisting (tumor and treatment-induced) hypopituitarism.

Conclusions

Though challenging, outcomes of a surgical intervention for patients with pituitary tumors can be reflected through a VBHC-based comprehensive outcome set that can distinguish outcomes among different patient groups with respect to tumor type.

INTRODUCTION

Pituitary tumors are rare tumors of endocrine origin (1, 2), which can cause systemic signs and symptoms due to hormone excess or deficiency and have a direct impact on visual functioning depending on tumor type, size and location. Pituitary tumors also profoundly affect patients' long-term health-related quality of life (HRQoL) (3, 4, 5, 6), which ultimately improves after treatment, but remains impaired in most patients (5).

For most patients with a pituitary tumor, surgery is the primary treatment option. The period prior to, and shortly after, surgery is considered as a turbulent period by many patients; outcomes are typically described through clinician-reported disease parameters. These cover specific parts of the care cycle (e.g. degree of tumor resection, restoration of hormone hypersecretion (remission), recovery of visual deficits), but fail to measure to what extent the disease and treatment impact a patient's functioning and HRQoL. Therefore, it is advocated to complement these outcomes with patient-reported outcome measures (PROMS), something that has only been realized to a limited extent and to measure outcomes over the full cycle of care (primary, in- and outpatient hospital care, rehabilitation).

The current way to look at outcomes over the full cycle of care is through the framework of Value Based Health Care (VBHC). This framework, originally developed by Michael Porter and Elizabeth Teisberg, tries to increase value for the patient by improving patient-relevant outcomes and decreasing costs. According to this framework, outcomes are categorized into a three-tier hierarchy, reflecting the perceived relevance for patients: (1) health status achieved or retained, (2) process of recovery and (3) sustainability of health (7). Measuring outcomes through these three tiers will assist decision making and expectation management to add optimal value to the patient and can potentially be used to alter care trajectories depending on the somatic and psychosocial needs of patients.

In order to define value, proper outcome measurement is necessary. For patients with pituitary tumors, however, the use of outcomes across all three tiers, and in particular, the use of perioperative PROMS is limited (8, 9, 10, 11, 12, 13, 14, 15, 16, 17). This may be because the routine application of these outcome measures is considered to be complicated, time consuming and too costly. Because there is no consensus yet on a core outcome set for patients with pituitary tumors the aim of the present study was to focus on outcomes first and explore the feasibility of this approach, by measuring short- to mid-term treatment outcomes of patients with various types of pituitary tumors using a comprehensive framework, the three-tier framework of VHBC, alongside a well-defined surgical care pathway.

PATIENTS AND METHODS

Study design

This prospective longitudinal study among a cohort of consecutive patients operated for a pituitary tumor was performed between August 2016 and December 2018. The study was approved by the Ethical Committee of the Leiden University Medical Center prior to the study (p16.091).

Study setting and population

This study was conducted at a tertiary referral center, the Leiden University Medical Center (LUMC) in Leiden. The multidisciplinary treatment process was defined within a care pathway, which was specifically tailored to fit the concepts of VHBC. All consecutive patients presenting at our referral center with a pituitary tumor, older than 18 years of age, with sufficient Dutch language skills and an indication for endoscopic transsphenoidal resection of a pituitary tumor were invited to participate. Eligible patients were invited by a written letter to participate in this study by their treating endocrinologist or neurosurgeon. Consent was obtained from each patient after full explanation of the purpose and nature of all procedures used. After obtaining informed consent, patients were enrolled, and a series of questionnaires was sent at set time points.

Assessments

Outcomes were prospectively collected and are presented according to the three-tier VHBC framework. The outcome measures were selected based on their representation of the three tiers of the VBHC model and their relevance for patients (Fig. 1 and below). Questionnaires were sent or given to patients prior to surgery and at 2 days, 5 days, 6 weeks and 6 months after surgery (unless the time period the questionnaire reflects over, overlapped with the previous measurement). Time points were chosen to reflect relevant time points of the care trajectory (i.e. date of discharge or in combination with outpatient clinic appointments) and to reflect the outcomes of the tiers. This also depended on the construct a questionnaire referred to. In case of symptoms over a certain time period, they were not repeated when these periods overlapped. More specifically, the measurement on POD2 and POD5 were focused on early postoperative symptoms. Questionnaires could be filled independent of the location of the patient at the various time points and could be done either digitally or on paper, both shown to provide equivalent results (18). Detailed information on each individual questionnaire is presented in Supplementary Table 1 (see section on supplementary data given at the end of this article) and below.

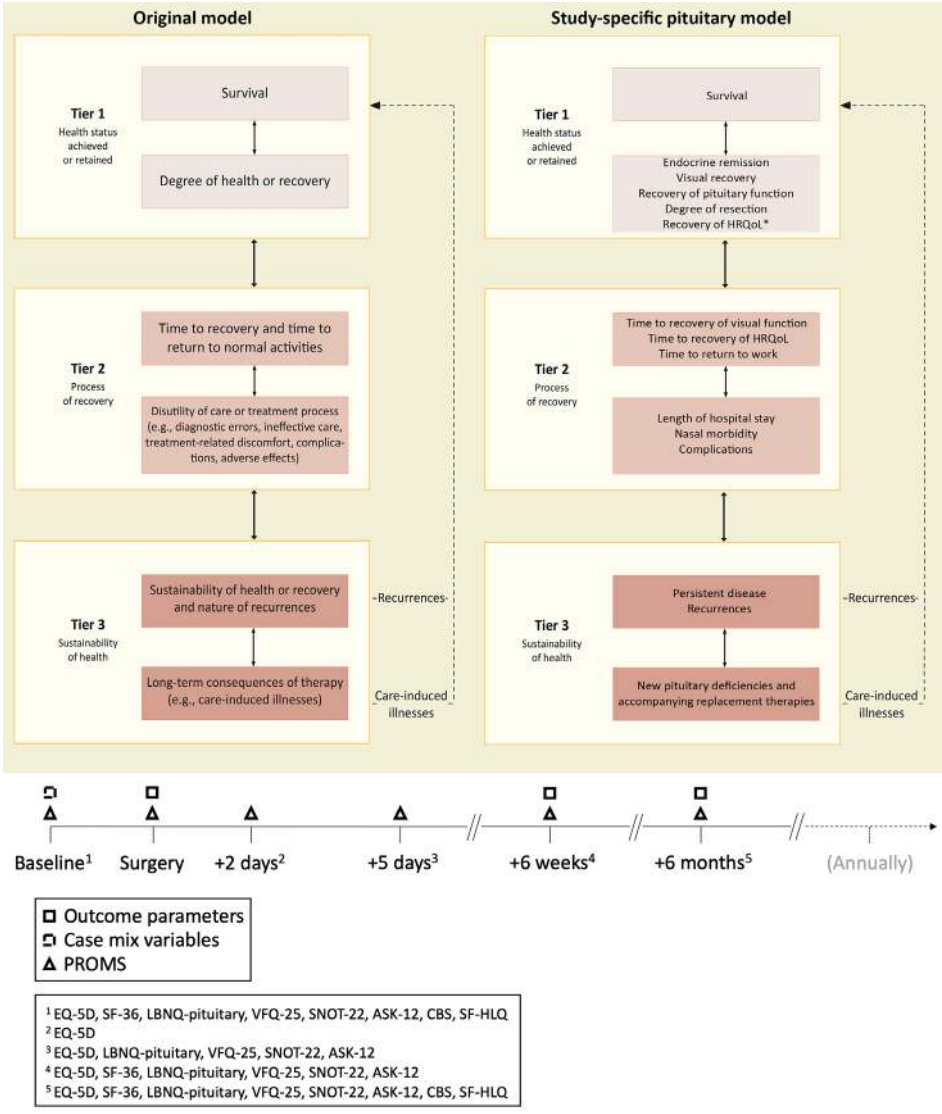

Figure 1. Disease-specific three tier model of the VBHC model for patients with a pituitary tumor.
* HRQoL, disease burden, utility
Modified from Porter et al. NEJM 2006

Feasibility

Participation was defined as the proportion of invited patients providing informed consent and completing at least one questionnaire. Retention was defined as the proportion of participants who completed the questionnaire and/or were seen at the outpatient clinic at 6 months. Response rate was calculated as the proportion of patients who re-

turned at least one questionnaire. The number of missing items per questionnaire and per time-point were also calculated.

Baseline patient characteristics

This included age, sex, marital status, level of education, comorbidities, tumor type, date of diagnosis, pituitary function, visual functioning and cerebral nerve deficits. Marital status was categorized into married/living together or not (alone, divorced, widow). Level of education was categorized into low, intermediate or high, based on the guidelines of Statistics Netherlands (CBS) (19), which correspond with the International Standard Classification of Education Fields of Training and Education 2013 of the UNESCO (20). Comorbidities were assessed with the Dutch comorbidity questionnaire, Statistics Netherlands, which assesses the most common chronic diseases and disorders in the Netherlands (21) and were categorized into diabetes mellitus, neurovascular, cardiovascular and malignancies. Tumor type was divided into (1) non-functioning pituitary adenoma (NFA), (2) acromegaly (ACRO), (3) Cushing's disease (CD), (4) prolactinoma (PRL), (5) Rathke's cleft cyst (RCC), (6) craniopharyngioma (cranio). Pituitary function was defined as (1) no deficits, (2) single hormone deficiency, (3) multiple hormone deficiencies, (4) multiple hormone deficiencies plus diabetes insipidus (DI) and (5) DI alone. Visual functioning was defined as (1) no deficits, (2) quadrant anopia or less (mild) and (3) hemianopia (severe). Prior treatment was classified into four categories: (1) no treatment, (2) prior medical (tumor) treatment, (3) prior surgery and (4) prior radiotherapy. A detailed description of the treatment algorithm, which was in line with existing guidelines, has previously been published (22, 23, 24). In addition, all patients, including patients with CD, received perioperative hydrocortisone, according to a standard protocol, regardless of tumor type. Hydrocortisone was discontinued only after confirmation of recovery of the endogenous pituitary–adrenal axis or persistent disease.

Tier 1: health status achieved or retained

Tier 1 represents the core outcomes at the endpoint of treatment, which for this study was assessed at 6 months after surgery. It included survival (yes/no), endocrine remission among patients with functioning tumors (complete/partial/no), visual recovery in those with visual impairments (visual field/acuity) (complete/ partial/no recovery/worsening), recovery of pituitary function in those with hypopituitarism (complete/ partial/ no recovery/worsening) and degree of resection (complete/partial/unsure). Endocrine remission was defined as normalized overproduction without medication. Recovery of patient-reported outcomes was defined as the minimal important change, a clinically relevant change between baseline and 6 months and calculated per patient per questionnaire as half a standard deviation (SD) difference between the two time points (25). Depending on the magnitude of the change, this was categorized into improved

(>0.5 SD), deteriorated (>0.5 SD) or no important change (<0.5 SD). Recovery of disease burden was measured through a modified version of the (Leiden Bother and Needs Questionnaire-pituitary (LBNQ-Pituitary)) (26), which was modified in order to make it suitable for repeated measurements. It ranges from 0 to 100, and higher scores indicate a greater disease burden or need for help and was not assessed on POD2. Recovery of HRQoL was measured with the short form-36 (SF-36), which ranges from 0 to 100 and was not assessed on POD2 and POD5. Higher scores for physical or mental functioning indicate better HRQoL (27). Recovery of utility (EQ-index, scale anchored at 0 (as bad as death) and 1 (perfect health)) and self-reported health status (EQ-VAS, range 0 to 100) were measured through the EuroQoL (EQ-5D-5L, Dutch Tariff) (28, 29). Higher scores indicate a better perceived health status. Visual functioning was assessed through the VFQ-25 (range 0 to 100), and higher scores indicate better visual functioning. The VFQ-25 was not assessed on POD2 (30).

Tier 2: process of recovery

This concerns the course of outcomes over time and consists of time to recovery of disease burden, HRQoL, utility and visual function (as measured through the VFQ-25). Recovery was defined as a significant improvement over time compared to baseline (mean change). Furthermore, time to return to work (short form-health and labor questionnaire (SF-HLQ)) was determined as change between baseline and 6 months (31).

Disutility of care or treatment process included length of stay, nasal morbidity over time (anterior skull base nasal inventory-12 (ASK nasal-12) (32)/sino-nasal outcome test-22 (SNOT-22)) (33) and complications (readmission <30 days, endocrine complications: transient DI/permanent DI/delayed hyponatremia/new pituitary deficiencies, neurosurgical complications: postoperative CSF leak/severe epistaxis requiring surgery/mild epistaxis/bleedings or other). For both the ASK-12 (range 0–5) and the SNOT-22 (range 0–110), higher scores indicate worse nasal functioning. The ASK-12 and SNOT-22 were not assessed on POD2.

Tier 3: sustainability of health

This concerns outcomes up to 6 months after surgical treatment, mid- to long-term effects of treatment, included new onset of permanent pituitary deficiencies, accompanying replacement therapies, additional treatments, permanent complications (of intervention and disease) and recurrences necessitating additional treatment.

Statistical analysis

Data entry and control were performed through an online survey platform (NETQ, NETQ Healthcare B.V., Utrecht, The Netherlands). All statistical analyses were performed with

SPSS 25.0 software (SPSS Inc.). Nominal variables are presented as frequencies with percentages, numerical variables as means and SD or medians with interquartile ranges (IQR), and comparisons between tumor types were performed through the Kruskal–Wallis test, where applicable. Categorical variables were calculated as frequencies with percentages and comparisons were performed through chi-square analyses and Fisher's exact test, where applicable.

Due to differences in surgical indications and surgical goals between tumor types , only descriptive statistics were presented for clinician-reported outcome measures. Because PROMS measure different constructs, PROMS were compared between tumor groups. Differences between tumor types are presented for groups larger than ten patients. Longitudinal analysis was performed via general estimating equations (GEEs) analysis and results are presented as means with corresponding 95% confidence intervals (CIs). For all analyses, the level of significance was set at $P < 0.05$ (two-sided). Missing data on the questionnaires were handled by parcel summary imputation (34).

RESULTS

A total of 142 patients with a pituitary tumor and an indication for surgery were seen at the outpatient clinic between September 2016 and July 2018, of which 103 patients (73%) decided to participate in this study. Of those not participating, 11 declined participation (8%). Other reasons for non-participation were emergency surgery (n = 10, 7%), age <18 years (n = 4, 3%), cognitive impairments (n = 7, 5%), language barrier (n = 4, 3%) and preoperative suspicion of other pathology (n = 3, 2%). All patients underwent endoscopic transsphenoidal surgery within the study period and at the end of follow-up all patients were retained. Of those, 103 completed questionnaires at baseline (100%), 101 at day 2 (98%), 100 at day 5 (97%), 99 at 6 weeks (96%) and 99 at 6 months (96%). The number of missing items per questionnaire and per time-point is described in Supplementary Table 2 and ranges between 0.1 and 8.0%.

Baseline characteristics

The median age of included patients was 53 (IQR 37–65) years, and 64 patients (62%) were female. The largest proportion of patients had been diagnosed with an NFA (n = 47, 46%), followed by 45 patients with functioning tumors (44%, range 14–16% per tumor type) and 11 patients (11%) with other pituitary region tumors (six RCC and five cranio). Preoperative hormone deficiencies were present in 50 patients (49%), and 47 patients (46%) had visual deficits. For most patients the surgical treatment was the primary surgical intervention (85%) (Table 1).

Tier 1: health status achieved or retained (after 6 months)

Survival

There was no mortality (Table 2).

Degree of health or recovery

Endocrine remission

Of the 45 patients with functioning tumors, 31 (69%) were in endocrine remission after 6 months, which was the highest among patients with CD: 80% (n = 12), followed by patients with a PRL: 75% (n = 12) and ACRO: 50% (n = 7) (Table 2).

Visual recovery

There were 47 patients with preoperative visual deficits, of which the majority with an NFA (n = 33, 70%). Complete visual recovery was achieved among 21 patients (46%), partial recovery in 24 (52%), whereas only 1 patient (2%) did not improve after surgery (Table 2).

Recovery of pituitary function

Of the 50 patients with preoperative pituitary deficiencies (49%), one or more pituitary axes recovered in 14 patients (28%) after surgery. New onset of hypopituitarism occurred in 12 patients (12% of total cohort) (Table 2).

Degree of resection

Overall, complete resection was achieved in 72 patients (70%), with the highest rate seen among patients with PRLs (n = 12, 75%), followed by patients with an NFA (n = 34, 72%), ACRO (n = 10, 71%) and CD (n = 9, 60%). Degree of resection did not always align with the, more relevant, endocrine results among patients with functioning tumors. For example, a possible radiological residual could not be excluded among two patients despite being in endocrine remission (e.g. normalization of hormone excess). Also, among five patients with persisting endocrine disease (e.g. overproduction), there was no radiological residual present (Table 2).

Self-perceived recovery

LBNQ pituitary

In total, at 6 months, 42 patients (41%) reported a clinically relevant improvement of their overall disease burden. Clinically relevant deterioration occurred in 12 patients (12%). There was a distinct difference between the various tumor types, which is best illustrated by the overall disease burden of patients with a PRL (Fig. 2A). These patients, usually refractory or intolerant to dopamine agonists, have comparable disease burden as patients with CD at baseline (mean difference 8.3, 95% CI −21.7 to 5.0, P = .22 (CD vs PRL)), which

is significantly worse compared to patients with an NFA (mean difference 27.1, 95% CI 16.1–38.1, P < .001 (PRL vs NFA) or ACRO (mean difference 26.5, 95% CI 14.6–38.3, P < .001 (PRL vs ACRO)). Patients with CD also had significantly worse scores compared to NFA (mean difference 18.8, 95% CI 9.8–27.7, P < .001 (CD vs NFA)) and ACRO (mean difference 18.1, 95% CI 8.3–27.9, P < .001 (CD vs ACRO)). Patients with a PRL, however, improved significantly after surgery (mean improvement 19.1, 95% CI 12.1–26.2, P < .001), while patients with CD did not (mean improvement 6.8, 95% CI −4.1 to 17.7, P = .22). Patients with ACRO are comparable to those with an NFA both at baseline (mean difference 0.6, 95% CI −3.3 to 5.9, P = .85), and 6 months after surgery (significant mean improvement 4.2, 95% CI 0.03–8.3, P = .05 (NFA), respectively 5.8, 95% CI 0.3–11.3, P = .04 (ACRO)).

SF-36

Concerning HRQoL, relatively more patients improved on the mental aspect of HRQoL (n = 42, 51%), than on the physical (n = 35, 34%), while there were no differences between tumor types.

EQ-5D

Utility, as measured by the EQ index, improved among 29 patients (28%), most among patients with a PRL (n = 9, 56%). Self-perceived health status improved among 33 patients (32%).

VFQ-25

Among those with preoperative visual deficits, self-reported visual functioning improved in 30 patients (64%).

Tier 2: process of recovery (0–6 months)

Time to recovery and return to normal activities

LBNQ pituitary

Regarding the course of recovery, the overall perceived disease burden improved significantly 5 days after surgery for all tumor types and remained improved in all tumor types, except for patients with CD, who returned back to baseline from 6 weeks onward (Fig. 2A).

SF-36

With regard to HRQoL, mental functioning improved significantly 6 weeks after surgery among patients with an NFA (mean improvement 4.7, 95% CI -7.8, P = .004), or a PRL (mean improvement 9.4, 95% CI 6.3–12.6, P = .002) and remained improved in both at 6 months (Fig. 2B). Physical functioning significantly deteriorated after 6 weeks for patients with an NFA (mean deterioration 4.1, 95% CI 1.6–6.5, P = .001) and returned to

baseline at 6 months (mean deterioration 1.1, 95% CI −1.9 to 4.2, P = .46). Patients with ACRO had significantly better physical functioning at 6 weeks (mean improvement 6.6, 95% CI 3.2–10.0, P < .001), which remained improved at 6 months (mean improvement 6.2, 95% CI 1.8–10.6, P = .005) (Fig. 2C).

EQ-5D

Utility deteriorated significantly 2 days after surgery among patients with an NFA (mean deterioration 0.05, 0.01–0.09, P = .02) and CD (mean deterioration 0.11, 95% CI 0.02–0.19, P = .01), however, returned to baseline at 5 days after surgery and remained unchanged during follow-up. Patients with a PRL improved significantly after 6 months (mean improvement 0.07, 95% CI 0.02– 0.12, P = .01) (Fig. 2D and E).

VFQ-25

Among patients with visual deficits, self-perceived visual functioning improved significantly 5 days after surgery compared to baseline (mean improvement 13.4, 95% CI 5.5–21.3, P = .001 (mild deficits) and 9.3, 95% CI 5.3–13.4, P < .001 (severe deficits)), and improved further during the course of follow-up (mean improvement at 6 months 21.1, 95% CI 11.7–30.6, P < .001 (mild deficits), 12.5, 95% CI 8.0–17.0, P < .001 (severe deficits)) (Fig. 2F).

Return to work

Of the 56 patients with a paid job prior to surgery, 51 (86%) still had a paid job after 6 months (Table 3).

Disutility of care or treatment process

Length of stay

The median length of hospital stay after surgery was 3 days (IQR 2–5), which was longest among patients with CD, shortest among patients with an NFA, PRL or ACRO and was significantly different between tumor types (P < .001) (Table 3).

Nasal morbidity

For all tumor types, postoperative nasal functioning as measured by the ASK nasal-12 deteriorated significantly 5 days after surgery compared to baseline (mean difference range 0.9–1.7) and remained significantly worse compared to baseline up to 6 weeks after surgery. Patients with ACRO or a PRL recovered quicker and patients did not have significantly different nasal morbidity compared to baseline at 6 weeks (mean difference 0.3, 95% CI −0.8 to 0.1, P = .14 (ACRO), 0.4, 95% CI −.02 to 1.0, P = .19 (PRL)). At 6 months, 24 patients (23%) had a clinically relevant deterioration as measured by the ASK nasal-12 (Table 3), and the mean difference ranged between −0.4 (ACRO) and 0.2 (CD) (Fig. 3).

Table 1. Baseline characteristics of 103 patients with a pituitary tumor divided per tumor type. Data are presented as n (%) or as median (IQR) where indicated.

	Total (*n* = 103)	**NFA** (*n* = 47)	**CD** (*n* = 15)	**PRL** (*n* = 16)	**RCC** (*n* = 6)	**Cranio** (*n* = 5)
Sociodemographic characteristics						
Female gender	64 (62.1)	28 (59.6)	12 (80.0)	12 (75.0)	4 (66.7)	3 (60.0)
Age in years, median (IQR)	52.9 (37.0–65.0)	59.9 (46.8–69.7)	43.3 (28.3–56.4)	32.4 (27.5–39.0)	63.6 (62.0–72.3)	43.6 (38.8–48.2)
Marital status, relationship/married	74 (71.8)	35 (74.5)	12 (80.0)	9 (56.3)	5 (83.3)	4 (80.0)
Education						
Low	29 (26.5)	16 (34.0)	4 (26.7)	2 (12.5)	3 (50.0)	1 (20.0)
Intermediate	29 (30.6)	11 (23.4)	6 (40.0)	6 (37.5)	2 (33.3)	0 (–)
High	45 (42.9)	20 (42.6)	5 (28.6)	8 (50.0)	1 (16.7)	4 (80.0)
Comorbidities						
Diabetes mellitus	5 (4.9)	2 (4.3)	1 (6.7)	0 (–)	0 (–)	0 (–)
Neurovascular disease	2 (19.4)	2 (4.3)	0 (–)	0 (–)	0 (–)	0 (–)
Cardiovascular disease*	41 (39.8)	19 (40.4)	12 (80.0)	1 (6.3)	2 (33.3)	0 (–)
Malignancies	14 (13.6)	7 (14.9)	1 (6.7)	1 (6.3)	3 (50.0)	0 (–)
Paid job	59 (59.0)	26 (59.1)	7 (46.7)	10 (62.5)	2 (33.3)	3 (60.0)
Disease-specific characteristics						
Tumor size						
Micro	22 (21.4)	0 (–)	10 (66.7)	9 (56.3)	0 (–)	0 (–)
Macro	58 (56.3)	33 (70.2)	1 (6.7)	6 (37.5)	6 (100.0)	3 (60.0)
Giant	8 (7.8)	5 (10.6)	1 (6.7)	1 (6.3)	0 (–)	1 (20.0)
Residual <1 cm	5 (4.9)	1 (2.1)	2 (13.3)	0 (–)	0 (–)	0 (–)
Residual >1cm	10 (9.7)	8 (17.0)	1 (6.7)	0 (–)	0 (–)	1 (20.0)
Knosp grade						
0	30 (29.1)	1 (2.1)	13 (86.7)	11 (68.8)	0 (–)	0 (–)
I	43 (41.7)	23 (48.9)	0 (–)	4 (25.0)	5 (83.3)	5 (100.0)

Table 1. Baseline characteristics of 103 patients with a pituitary tumor divided per tumor type. Data are presented as n (%) or as median (IQR) where indicated. (continued)

	Total (*n* = 103)	**NFA** (*n* = 47)	**CD** (*n* = 15)	**PRL** (*n* = 16)	**RCC** (*n* = 6)	**Cranio** (*n* = 5)
II	21 (20.4)	17 (36.2)	0 (–)	1 (6.3)	1 (16.7)	0 (–)
IIIA	3 (2.9)	2 (4.3)	0 (–)	0 (–)	0 (–)	0 (–)
IIIB	4 (3.9)	2 (4.3)	2 (13.3)	0 (–)	0 (–)	0 (–)
IV	2 (1.9)	2 (4.3)	0 (–)	0 (–)	0 (–)	0 (–)
Time since diagnosis in years, median (IQR)	0.8 (0.1–4.8)	0.2 (0.1–4.7)	0.5 (0.2–1.8)	5.6 (3.1–9.4)	1.3 (0.1–1.8)	0.1 (0.1–0.4)
Prior treatment						
No treatment	59 (57.3)	35 (74.5)	9 (60.0)	0 (–)	5 (-)	
Medication	29 (28.2)	3 (6.4)	4 (26.7)	16 (100.0)	0 (–)	–
Surgery	15 (14.6)	9 (19.1)	2 (13.3)	0 (–)	1 (16.7)	
Radiotherapy	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	–
Preoperative endocrine status						
No deficits	53 (51.5)	14 (29.8)	12 (80.0)	11 (68.8)	3 (50.0)	
Single hormone deficiency	12 (11.7)	8 (17.0)	2 (13.3)	0 (–)	0 (–)	–
Multiple hormone deficiencies	36 (35.0)	25 (53.2)	0 (–)	4 (25.0)	3 (50.0)	
Multiple hormone deficiencies + DI	1 (1.0)	0 (–)	0 (–)	1 (6.3)	0 (–)	–
DI alone	1 (1.0)	0 (–)	1 (6.7)	0 (–)	0 (–)	–
Preoperative visual status						
No deficits	56 (54.4)	14 (29.8)	15 (100.0)	13 (81.3)	3 (50.0)	–
Mild visual deficits	19 (18.4)	10 (21.3)	0 (–)	3 (18.8)	1 (16.7)	
Severe visual deficits	28 (27.2)	23 (48.9)	0 (–)	0 (–)	2 (33.3)	
Cranial nerve palsy	3 (2.9)	2 (4.3)	0 (–)	0 (–)	0 (–)	

Due to rounding, not all percentages of the categorical variables add up to 100%.

*Cardiovascular disease includes hypertension, atherosclerosis and myocardial infarctions.

ACRO, acromegaly; CD, Cushing's disease; Cranio, craniopharyngioma; IQR, interquartile range; *n*, number; NFA, non-functioning pituitary adenoma; PRL, prolactinoma; RCC, Rathke's cleft cyst; s.d., standard deviation

Table 2. Tier 1: health status achieved or retained at 6 months among 103 surgically treated patients with a pituitary tumor stratified according to tumor type.

	Total (*n* = 103)	**NFA** (*n* = 47)	**ACRO** (*n* = 14)	**CD** (*n* = 15)	**PRL** (*n* = 16)	**RCC** (*n* = 6)	**Cranio** (*n* = 5)
Survival, *n* (%)	103 (100)	47 (100)	14 (100)	15 (100)	16 (100)	6 (100)	5 (100)
Degree of resection, *n* (%)							
Complete resection	72 (69.9)	34 (72.3)	10 (71.4)	9 (60.0)	12 (75.0)	4 (66.7)	3 (60.0)
Residual	20 (19.4)	10 (21.3)	3 (21.4)	2 (13.3)	1 (6.3)	2 (33.3)	2 (40.0)
Unsure	6 (5.8)	3 (6.4)	1 (7.7)	1 (6.7)	1 (6.3)	0 (–)	0 (–)
No MRI	5 (4.9)	0 (–)	0 (–)	3 (20.0)	2 (12.5)	0 (–)	0 (–)
Endocrine remission of hormone excess, *n* (%)+							
Remission	31 (68.9)	–	7 (50.0)	12 (80.0)	12 (75.0)	–	–
Partial recovery	11 (24.4)	–	7 (50.0)	0 (–)	4 (25.0)	–	–
Persistent disease	3 (6.7)	–	0 (–)	3 (20.0)	0 (–)	–	–
Pituitary function, *n* (%)*							
Complete recovery	7 (11.9)	4 (10.5)	3 (50.0)	0 (-)	0 (-)	0 (-)	0 (-)
Partial recovery	7 (11.9)	4 (10.5)	1 (16.7)	0 (-)	0 (-)	2 (66.7)	0 (-)
Persistent deficits	33 (55.9)	24 (63.2)	2 (33.3)	4 (-)	3 (100.0)	0 (-)	0 (-)
Deteriorated	12 (20.3)	6 (15.8)	0 (–)	1 (-)	0 (-)	1 (33.3)	4 (100.0)
Visual outcome, *n* (%)₸							
Complete recovery	21 (45.7)	13 (40.6)	2 (66.7)	0 (–)	2 (66.7)	1 (33.3)	3 (60.0)
Partial recovery	24 (52.2)	18 (56.3)	1 (33.3)	0 (–)	1 (33.3)	2 (66.7)	2 (40.0)
Persistent deficits/acuity	1 (2.2)	1 (3.1)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)
Deteriorated	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)
LBNQ–pituitary total score, *n* (%)							
Improved	42 (40.8)	16 (34.0)	3 (21.4)	6 (40.0)	13 (81.3)	3 (50.0)	1 (20.0)
Not importantly changed	49 (47.6)	24 (51.1)	11 (78.6)	6 (40.0)	3 (18.8)	3 (50.0)	2 (40.0)
Deteriorated	12 (11.7)	7 (14.9)	0 (–)	3 (20.0)	0 (–)	0 (–)	2 (40.0)

Table 2. Tier 1: health status achieved or retained at 6 months among 103 surgically treated patients with a pituitary tumor stratified according to tumor type. (continued)

	Total (*n* = 103)	**NFA** (*n* = 47)	**ACRO** (*n* = 14)	**CD** (*n* = 15)	**PRL** (*n* = 16)	**RCC** (*n* = 6)	**Cranio** (*n* = 5)
SF-36 MCS, *n* (%)							
Improved	42 (40.8)	22 (46.8)	2 (14.3)	5 (33.3)	9 (56.3)	3 (50.0)	1 (20.0)
Not importantly changed	45 (43.7)	20 (42.6)	8 (57.1)	5 (33.3)	6 (37.5)	3 (50.0)	3 (60.0)
Deteriorated	16 (15.5)	5 (10.6)	4 (28.6)	5 (33.3)	1 (6.3)	0 (–)	1 (20.0)
SF-36 PCS, *n* (%)							
Improved	35 (34.0)	10 (21.3)	9 (64.3)	6 (40.0)	6 (37.5)	1 (16.7)	3 (60.0)
Not importantly changed	45 (43.7)	22 (46.8)	4 (28.6)	6 (40.0)	9 (56.3)	4 (66.7)	0 (–)
Deteriorated	23 (22.3)	15 (31.9)	1 (7.1)	3 (20.0)	1 (6.3)	1 (16.7)	2 (40.0)
EQ index, *n* (%)							
Improved	29 (28.2)	10 (21.3)	4 (28.6)	2 (13.3)	9 (56.3)	2 (33.3)	2 (40.0)
Not importantly changed	53 (51.5)	28 (59.6)	7 (50.0)	6 (40.0)	6 (37.5)	3 (50.0)	3 (60.0)
Deteriorated	20 (19.4)	9 (19.1)	3 (21.4)	6 (40.0)	1 (6.3)	1 (16.7)	0 (–)
EQ-VAS, *n* (%)							
Improved	33 (32.0)	13 (27.7)	3 (21.4)	3 (20.0)	8 (50.0)	3 (50.0)	3 (60.0)
Not importantly changed	35 (34.0)	17 (36.2)	6 (42.9)	4 (26.7)	6 (37.5)	2 (33.3)	0 (–)
Deteriorated	34 (33.0)	17 (36.2)	4 (28.6)	8 (53.3)	2 (12.5)	1 (16.7)	2 (40.0)
VFQ-25*, *n* (%)							
Improved	30 (63.8)	22 (66.7)	1 (7.1)	0 (–)	2 (66.7)	2 (66.7)	3 (60.0)
Not importantly changed	14 (29.8)	9 (27.3)	2 (14.3)	0 (–)	1 (33.3)	0 (–)	2 (40.0)
Deteriorated	3 (6.4)	2 (6.1)	0 (–)	0 (–)	0 (–)	1 (33.3)	0 (–)

For patient-reported outcome measures improvement/deterioration indicates a change >1/2SD.

+*‡Among those with preoperative deficits/hormone excess (except for deterioration).

ACRO, acromegaly; CD, Cushing's disease; Cranio, craniopharyngioma; EQ, EuroQoL; IQR, interquartile range; LBNQ-Pituitary, Leiden Bother and Needs Questionnaire – Pituitary; *n*, number; NFA, non-functioning pituitary adenoma; PRL, prolactinoma; RCC, Rathke's cleft cyst; SD, standard deviation; SF-36, Short Form-36; VAS, visual analog scale; VFQ-25, Visual functioning Questionnaire-25.

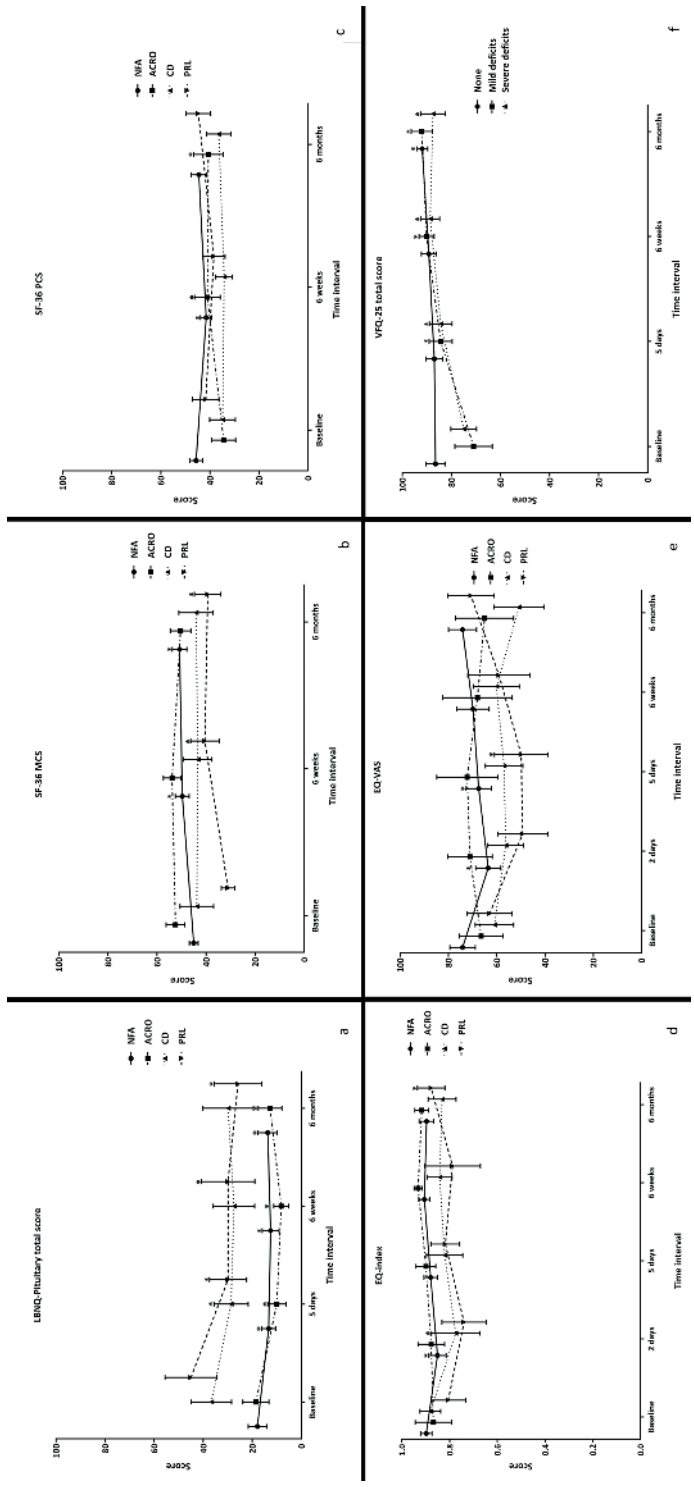

Figure 2. Perioperative patient-reported outcomes over time per tumor type.
(A) Higher scores indicate worse disease burden. (B, C, D, E and F) Higher scores indicate better health-related quality of life, utility, self-perceived health status, visual functioning. *Significant change compared to baseline (within tumor type). ACRO, acromegaly; CD, Cushing's disease; EQ, EuroQoL; LBNQ-Pituitary, Leiden Bother and Needs Questionnaire – Pituitary; NFA, non-functioning pituitary adenoma; PRL, prolactinoma; SF-36, Short Form-36; VAS, visual analog scale; VFQ-25, Visual Functioning Questionnaire-25.

Table 3. Tier 2: Process of recovery among 103 surgically treated patients with a pituitary tumor stratified according to tumor type. Data are presented as n (%) or as median (IQR) where indicated.

	Total (*n* = 103)	**NFA** (*n* = 47)	**ACRO** (*n* = 14)	**CD** (*n* = 15)	**PRL** (*n* = 16)	**RCC** (*n* = 6)	**Cranio** (*n* = 5)
Length of stay, median (IQR)	3.0 (2–5)	3.0 (2–5)	3.0 (3–4)	5.0 (4–7)	3.0 (2–5)	2.0 (2–3)	12.0 (7–12)
Return to work	51 (86.4)	23 (88.5)	9 (81.8)	6 (85.7)	10 (100.0)	2 (100.0)	1 (33.3)
ASK-12							
Improved	20 (19.4)	7 (14.9)	5 (35.7)	0 (–)	5 (31.3)	2 (33.3)	1 (20.0)
Not importantly changed	57 (55.3)	30 (63.8)	6 (42.9)	9 (60.0)	6 (37.5)	4 (66.7)	2 (40.0)
Deteriorated	24 (23.3)	10 (21.3)	2 (14.3)	6 (40.0)	4 (25.0)	0 (–)	2 (40.0)
SNOT-22							
Improved	37 (35.9)	10 (21.3)	9 (64.3)	5 (33.3)	8 (50.0)	2 (33.3)	3 (60.0)
Not importantly changed	50 (48.5)	28 (59.6)	4 (28.6)	6 (40.0)	7 (43.8)	3 (50.0)	2 (40.0)
Deteriorated	16 (15.5)	9 (19.1)	1 (7.1)	4 (26.7)	1 (6.3)	1 (16.7)	0 (–)
Complications							
Readmission	13 (12.6)	7 (14.9)	2 (14.3)	0 (–)	2 (12.5)	1 (16.7)	1 (20.0)
Any complication	50 (48.5)	20 (42.6)	5 (35.7)	8 (53.3)	10 (62.5)	2 (33.3)	5 (100.0)
Transient DI,	27 (26.2)	13 (27.7)	2 (14.3)	5 (33.3)	7 (43.8)	0 (–)	0 (–)
Permanent DI,	8 (7.8)	1 (2.1)	1 (7.1)	1 (6.7)	0 (–)	1 (16.7)	4 (80.0)
Delayed hyponatremia,	13 (12.6)	7 (14.9)	1 (7.1)	1 (6.7)	1 (6.3)	1 (16.7)	2 (40.0)
New onset pituitary deficiency	12 (11.7)	6 (12.8)	0 (–)	1 (6.7)	0 (–)	1 (16.7)	4 (80.0)
Postoperative CSF leak,	7 (6.8)	2 (4.3)	0 (–)	0 (–)	1 (6.3)	1 (16.7)	2 (40.0)
Severe epistaxis requiring surgery	2 (1.9)	0 (–)	0 (–)	0 (–)	2 (12.5)	0 (–)	0 (–)
Mild epistaxis,	5 (4.9)	2 (4.3)	2 (14.3)	1 (6.7)	0 (–)	0 (–)	0 (–)
Other*	4 (3.9)	2 (4.3)	0 (–)	0 (–)	0 (–)	1 (16.7)	1 (20.0)

IQR, interquartile range; NFA, non-functioning pituitary adenoma; ACRO, acromegaly; CD, Cushing's disease; PRL, prolactinoma; RCC, Rathke's cleft cyst; Cranio, craniopharyngioma; DI, diabetes insipidus; CSF, cerebrospinal fluid; ASK nasal-12, anterior skullbase nasal inventory; SNOT-22, Sino-nasal outcome test.
*thalamic infarction, rebleed, acute sudden deafness.

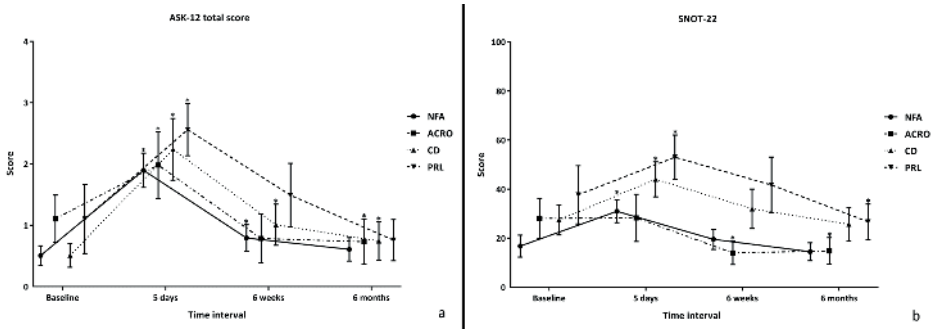

Figure 3. Perioperative patient-reported nasal functioning over time per tumor type. (A and B) Higher scores indicate worse nasal functioning burden. *Significant change compared to baseline (within tumor type). ACRO, acromegaly; ASK nasal-12, anterior skullbase nasal inventory; CD, Cushing's disease; NFA,non-functioning pituitary adenoma; PRL, prolactinoma; SNOT-22, sino-nasal outcome test.

Table 4. Tier 3: Sustainability of health. Data are presented as n (%).

	Total (*n* = 103)	**NFA** (*n* = 47)	**ACRO** (*n* = 14)	**CD** (*n* = 15)	**PRL** (*n* = 16)	**RCC** (*n* = 6)	**Cranio** (*n* = 5)
Reoperation >30 days and <6 months	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)
Chronic supplementation of pituitary deficits	52 (50.5)	34 (72.3)	3 (21.4)	5 (33.3)	3 (18.8)	3 (50.0)	4 (80.0)
Recurrence	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)
Persistent hormone excess	3 (6.7)	–	0 (–)	3 (20.0)	0 (–)	–	–

NFA, non-functioning pituitary adenoma; ACRO, acromegaly; CD, Cushing's disease; PRL, prolactinoma; RCC, Rathke's cleft cyst; Cranio, craniopharyngioma.

Complications

Neurosurgical complications were present in 19 patients (18%). Most complications did not have long-term implications; however, four patients had major complications after surgery, which typically occurred after more complex surgeries (one patient with an NFA had acute sudden deafness after a CSF leak, one patient had a postoperative hemiplegia due to multiple major intracranial hemorrhages after resection of a giant NFA and two patients had thalamic infarctions after resection of giant tumors (one NFA/one craniopharyngioma)). Endocrinological complications occurred in 41 patients (40%), which were mostly of transient nature (n = 28, 68%) (Table 3).

Tier 3: Sustainability of health

Long-term consequences of therapy

Among the 45 patients with functioning tumors, unchanged disease activity was present in 3 patients (7%), all patients with CD. During the course of the study there were no recurrences (up to 6 months after treatment) in patients in remission. New onset of pituitary hormone deficiency occurred in 12 patients (12%), most frequently of the corticotropic axis. In total, 52 patients (50%) had one or more pituitary deficiencies at the end of follow-up (Table 4).

DISCUSSION

This prospective cohort study shows that the outcomes of surgery for patients with various pituitary tumors can be well reflected using a comprehensive set of clinical and patient-reported outcomes. In general, improvement of outcomes over the full cycle of care was seen after surgery, but health status at 6 months, the process of recovery and mid- to long-term outcomes (although only partially measured) were highly variable between individuals, which is partly explained by tumor type.

While pituitary tumor surgery is usually performed with the goal to increase value for the patient, health outcomes are often primarily measured through clinician-reported outcomes, such as recovery of vision or remission of hypersecretion, rather than combining them with patient-reported outcomes (PROs). Although we are aware that long-term outcomes presented in this study can only serve as a proxy of the actual long-term outcomes, to the best of our knowledge this study is the first to describe a comprehensive set of outcomes over time for patients with a pituitary tumor through the framework of VBHC and therefore serves as a benchmark for future studies. New insights into the perioperative development of disease burden and HRQoL over time give a better understanding of the disease course and will enable shared decision making and expectation management based on perioperative outcomes in patients with different treatment options and tumor types.

Regarding disease burden, we report here for the first time the perioperative burden of disease among patients with pituitary tumors. These outcomes, in combination with the self-perceived needs for support, will enable clinicians to individualize care trajectories.

With regard to HRQoL, the limited number of studies that do report results, show an increase in HRQoL after surgical intervention compared to preoperative outcomes (as measured by the SF-36) (8, 12, 13, 14, 15, 17, 35). The interpretability of these results for clinical practice, however, is difficult since these questions focus on more general constructs instead of disease-specific issues. Although the design of the study did not allow for cause–effect relations, we hypothesize that some of the observed outcomes can be explained by the case mix of our tertial referral center, and preoperative severity of disease burden. We have a relatively high number of referrals of prolactinoma with drug intolerance, which likely negatively affects disease burden. Moreover, the timing of return to normal daily life activities frequently occurs between 6 weeks and 6 months. The perception of disease burden in that period in some patients may be negatively influenced by the confrontation of having limited energy, whereas the demands of daily life are increasing. This might in part explain why physical HRQoL deteriorated among patients with NFAs and improved among patients with ACRO.

Visual QoL was previously reported to improve after treatment (13), which was in line with results from our study. Regarding nasal morbidity, previous studies have also shown an initial increase in nasal morbidity, and most have shown restoration back to baseline after 6 months to 1 year after treatment (9, 10, 11, 14, 15), which is also in line with our findings (Table 3 and Supplementary Table 3).

Strengths, limitations and future perspectives

One of the main strengths of this study is the high participation rate and low amount of missing data. We are aware that it takes effort to motivate patients to fill out questionnaires, however, with a good Information Technology (IT) infrastructure and when feedback of results is given to patients, we believe these results can also be achieved in daily practice. Therefore, both patients and healthcare providers need to be aware of the benefits of PROMS, which can lead to targeted interventions at the individual, but also at the group level.

Although exact time to recovery cannot be reproduced due to the nature of this study, measurement points were chosen to represent routine clinical evaluations, making it more feasible that the PROMS will be implemented in the outpatient setting and will enable clinical decision making, for example, additional nasal examinations or referrals to rehabilitation centers, psychologists or sexologists. Due to the good experiences during this study we have continued assessment of PROMS at our institute, in a somewhat modified version with evaluation at baseline, 6 weeks and 6 months and yearly thereafter.

At the group level, it is important to expand the knowledge initiated by this study, since collective reporting of perioperative outcomes will enable comparison of outcomes between centers and initiate improvement trajectories. Furthermore, outcomes presented here can be considered for the development of a core outcome set (COS) for patients with a pituitary tumor. Traditionally, these COS were defined as those outcomes minimally necessary for the measurement and reporting in clinical trials of specific diseases (36). However, they can also be used for clinical practice purposes such as expectation management, evaluation of clinical care trajectories at the group and patient level, and for the comparison of outcomes between centers. This study contributes toward reducing the previous knowledge gap, which restricts proper selection of instruments to measure PROMS for a COS and further opens the path toward value driven healthcare.

One of the key limitations of our study is the relatively small number of patients, in particular for some of the tumor types, which not only hampers comparisons between groups with different diagnosis in our study, but also comparisons with other studies. For this reason, we were also unable to correct for potential confounders or effect modifiers, for example, tumor-related factors, such as tumor size. The short duration of follow-up is also a limitation, especially for the cases of hormone excess syndromes and recovery of hypopituitarism, specifically posterior pituitary deficiency. In clinical practice, for instance, it is well known that patients with CD often need longer recovery time after surgery (37), and this might (partially) explain the differences between tumor

types found in this study. Future research should extend the duration of follow-up for the analysis of perioperative outcomes, to enable interpretability of the relationship between short- and long-term outcomes and investigate the optimal time frame to properly evaluate disease burden/HRQoL. This argument also holds for remission rates. Tumor types have different outcome parameters of interest, for example endocrine remission and radiological outcome, and differences between tumor types might to some extent be explained by treatment by differences in surgical goals (treatment by indication), where optical preservation is often the goal of surgery for patients with an NFA, remission/complete resection is often the goal for functioning tumors.

Finally, to further elaborate on the value for the patient alongside the framework of VBHC, it is also necessary to also evaluate costs of treatment, as value can be increased by improving outcomes, but also by lowering costs. Assessing costs and expanding the assessment of outcomes are necessary in order to define value for the patient.

Further expansion of knowledge alongside the comprehensive set of outcomes used in this study show promising opportunities, which might lead to the identification of unexplained differences between individual patients and impairments in HRQoL.

CONCLUSION

The impact of a surgical intervention for patients with pituitary tumors can be well reflected through a comprehensive set of clinician-reported measurements in combination with PROMS. Measuring outcomes appears to be feasible. Disease-specific questionnaires in particular are able to show differences in the disease course between various tumor types. This information can help clinicians to more accurately inform patients about the expected outcome and improve the process of recovery and personalize care.

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Supplementary table 1. Overview of questionnaires used in study

Name	Covered content	Number of Items	Subscales	Scoring	Interpretation
Leiden Bother and Needs Questionnaire (LBNQ-Pituitary) (26)	Perceived disease bother and needs for support	27	Physical and cognitive complaints, mood, negative illness perceptions, social functioning, sexual functioning	0-100	Higher scores indicate greater disease bother and needs for support
Short Form-36 (SF-36) (27)	Health-Related Quality of Life	36	physical function, physical role, bodily pain, general health, vitality, social function, emotional role, mental health, mental and physical component scale	0-100	Higher scores indicate greater HRQoL
EuroQoL (EQ-5D-5L) (28,29)	Utility / global health rating	6	mobility, self-care, usual activities, pain/discomfort, and anxiety/ depression (utility) visual analogue scale (VAS)	0-1 (index) 0-100 (VAS)	Higher scores indicate greater utility/health rating
Visual Functioning Questionnaire (VFQ-25) (30)	Visual functioning	25	Overall, near/distance vision difficulties, social functioning/ role limitations, dependency on others, mental health symptoms due to vision, future expectations for vision, driving difficulties, pain and discomfort around the eyes, peripheral and color vision	0-100	Higher scores indicate greater visual functioning
Anterior Skull Base Nasal Inventory-12 (ASK nasal-12) (32)	Nasal morbidity	12	None (mean score of all items)	0-5	Higher scores indicate greater nasal morbidity
Sino-nasal outcome test (SNOT-22) (33)	Nasal morbidity	22	Rhinologic, extra-nasal rhinologic or ear/facial symptoms, psychological or sleep dysfunction	0-110	Higher scores indicate greater nasal morbidity
Short Form-Health and Labor Questionnaire (SF-HLQ) (31)	Work status	24	None (for this study)	-	-
Statistics Netherlands (CBS) comorbidity questionnaire (19)	Comorbidities	29	None (for this study)	-	-

Supplementary table 2. Percentage of missing items per questionnaire and time-point

Name	Number of Items (N)	Preoperative (%)	2 days (%)	5 days (%)	6 weeks (%)	6 months (%)
LBNQ-Pituitary	27	0.5		4.4	4.0	8.0
SF-36	36	0.1			2.9	5.4
EQ-5D	6	0.2	1.9	1.9	2.9	5.0
VFQ-25	25	1.9		2.8	3.0	4.3
ASK nasal-12	12	0.7		2.0	3.1	4.6
SNOT-22	22	1.1		3.2	3.0	4.2

LBNQ-Pituitary (Leiden Bother and Needs Questionnaire - Pituitary), SF-36 (Short form-36), EQ-5D (EuroQoL), VFQ-25 (Visual functioning Questionnaire-25), ASK nasal-12 (anterior skullbase nasal inventory), SNOT-22 (Sino-nasal outcome test)

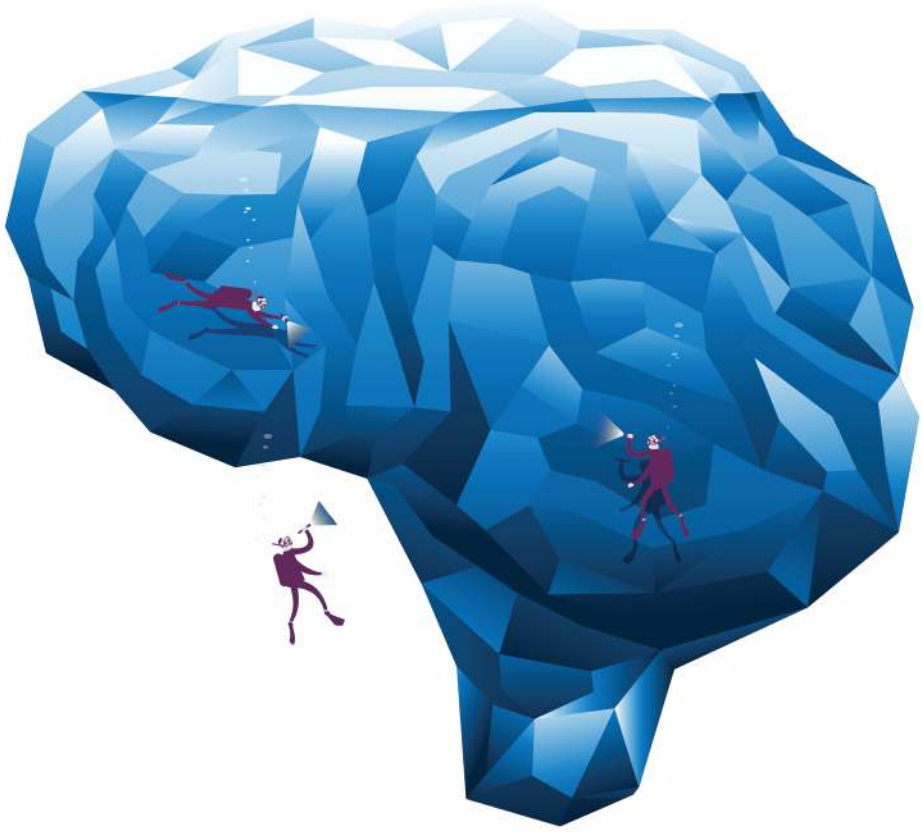
Supplementary table 3. Literature overview of studies describing clinical and patient-reported outcomes before and after surgery of a pituitary tumor

Author, year	Country	Tumor types	PROMS assessed	Domain	N	Measurements
Ye et al. 2016 (8)	Vancouver, Canada	CD	SF-36	Generic HRQoL	51	Baseline and 1st 2 postoperative visits (mean 2.4 and 7.4 months)
Jalessi et al. 2016 (9)	Teheran, Iran	Skull base patients (85% NFA, ACRO, CD)	SNOT-22, 9Q	Nasal morbidity	106	Baseline, 1, 3, 6, 12 months
Lindsay et al. 2006 (35)	Maryland, USA	CD	SF-36R, MOS cognitive scale	Generic HRQoL, morbidity	23	Baseline and 6 months
Little et al. 2015 (10)	Multiple, USA	All	ASK nasal-12, SF-8, EQ-5D	Generic HRQoL, nasal morbidity	218	Baseline, 2 weeks, 3, 6 months
McCoul et al. 2012 (11)	NY, USA	NFA, hypersecreting	ASBQ, SNOT-22	Disease-specific HRQoL, nasal morbidity	81	Baseline, 3, 6, 12 weeks, 6, 12 months
Milian et al. 2013 (12)	Tuebingen, Germany	Sellar lesions (88.7% adenomas, NFA, ACRO, CD, PRL, other (e.g. RCC/ colloid cysts).	SF-36, SCL-90-R	Generic HRQoL, psychopathologic	106	Baseline (n=106), 3 months (n=78), 12 months (n=65)
Okamoto et al. 2010 (13)	Tokyo, Japan	NFA, ACRO, CD, PRL, TSH	VFQ-25, SF-36	Visual functioning, generic HRQoL	74	Baseline-3 months
Pledger et al. 2016 (14)	Virginia, USA	NFA	SNOT-20, NOSE, SF-36, headache scale.	Nasal morbidity, generic HRQoL	82 (47 endoscopic)	Baseline, 1-2d, 2, 4, 8 weeks, 1 year
Rioja et al. 2016 (15)	Barcelona, Spain	Various (adenoma (5), meningioma (5), cranio (3), RCC (1), chordoma (3)	SF-36, RSOM, VAS	Nasal morbidity, generic HRQoL	55	Baseline, 12 months
Schreiber et al. 2019 (16)	Brescia, Italy	NFA, GH, CUSH, PRL, RCC, Meningioma	SF-36, ASK-12, SNOT-22	Nasal morbidity, generic HRQoL	34	Baseline, 6 months
Tanemura et al. 2012 (17)	Nagoya, Japan	NFA (nadruk op visual field deficits)	SF-36, GHQ, NRS	generic HRQoL	30	Baseline, 1, 6 months

Supplementary table 3. Literature overview of studies describing clinical and patient-reported outcomes before and after surgery of a pituitary tumor (continued)

Author, year	Country	Tumor types	PROMS assessed	Domain	N	Measurements
Current study	Leiden, The Netherlands	NFA, ACRO, CD, PRL, cranio, RCC	LBNQ-Pituitary, SF-36, EQ-5D, ASK nasal-12, SNOT-22, VFQ-25, SF-HLQ, comorbidity questionnaire	Generic HRQoL, disease-specific, nasal morbidity, visual functioning, work, comorbidity	103	Baseline, 2, 5 days

N (Number of patients), NFA (non-functioning adenoma), ACRO (acromegaly), CD (cushing's disease), PRL (prolactinoma), cranio (craniopharyngioma), RCC (rathke's cleft cyst), ASK nasal-12 (Anterior skull base nasal inventory), SNOT-22 (Sinonasal outcome test), MOS (Morbidity outcome scale), SCL-90-R (Symptom Checklist 90-Revised), QLS-H (Questions on Life Satisfaction-Hypopituitarism), AcroQoL (Acromegaly Quality of Life Questionnaire), NOSE (The short form of the Nasal Obstruction Symptom Evaluation), RSOM (Rhinosinusitis outcome measure), BAST-24 (Barcelona smell test-24), GHQ (General health questionnaire), NRS (Numerical rating scale of pain), pa-KPS (Patient-assessed Karnofsky performance scale)



6

Feasibility, safety, and outcomes of a stratified fast-track care trajectory in pituitary surgery

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ABSTRACT

Objective

Discharge policies concerning hospitalization after endoscopic pituitary tumor surgery are highly variable. A few studies support fast-track discharge; however, this is not commonplace. Our goal was to report the transition to and evaluate the feasibility, safety, clinical- and patient-reported outcomes and costs of fast-track care in pituitary surgery.

Methods

This observational study included 155 patients undergoing pituitary surgery between December 2016 and December 2018. Fast-track care consisted of planned discharge 2–3 days after surgery, followed by daily surveillance by a case manager. All outcomes were compared with patients not eligible for fast-track discharge. The total group (fast-track and non-fast-track) was compared with historic controls ($N = 307$).

Results

A total of 79/155 patients (51%) were considered eligible for fast-track discharge, of whom 69 (87%) were discharged within 3 days. The total group was discharged more often within 3 days compared with historic controls (49 vs. 20%, $p < 0.001$), the total length of stay did not differ (5.3 vs. 5.7 days, $p = 0.363$). Although the total group had more readmissions compared with historic controls (17 vs. 10%, $p = 0.002$), no life-threatening complications occurred after discharge. On average, clinical- and patient-reported outcomes improved over time, both in the fast-track and non-fast-track groups. The mean overall costs within 30 days after surgery did not differ between the total group € 9992 (SD € 4562) and historic controls € 9818 (SD € 3488) ($p = 0.649$).

Conclusion

A stratified fast-track care trajectory with enhanced postoperative outpatient surveillance after pituitary tumor surgery is safe and feasible. As expected, costs of the fast-track were lower than the non-fast-track group, however we could not prove overall cost-effectiveness compared with the historic controls.

INTRODUCTION

Transsphenoidal surgery is the primary treatment option for most pituitary tumors [1–4] and over the past one to two decades the surgical technique of this procedure has shifted from a microscopic to an endoscopic approach in many centers [5], with reduced complication rates [6–8]. Careful monitoring of potential neurosurgical and endocrine complications is key, since they may still occur even in uneventful surgery. Patients remain in-hospital mainly for the monitoring of water and electrolyte imbalances caused by diabetes insipidus (DI) and/or delayed hyponatremia. Importantly, patients remain at risk for delayed hyponatremia, the primary reason for readmissions, for up to 14 days after pituitary tumor surgery [9, 10]. Effective management of postoperative water and electrolyte disturbances and awareness of hyponatremia symptoms is one of the main clinical challenges after pituitary tumor surgery both at an in- and outpatient setting [11].

In line with trends in general surgical care, fast-track care trajectories are applied in some centers that treat pituitary tumors. Common practice, however, is highly variable and many centers keep patients admitted for 5–8 days after uneventful surgery. The results from a limited number of studies support the concept that early discharge, e.g. discharge 2–3 days postoperatively, is feasible and safe [12–14]. However, sample sizes in the available studies were small (N < 50) and the occurrence of water and electrolyte disturbances during the immediate postdischarge period, as well as patients' experiences were not evaluated. Length of stay (LOS) is an important measure, however, it is insufficient by itself to measure success of the surgery and studies should encompass patient-relevant outcomes [15, 16]. Furthermore, there is limited data on how to transition towards a fast-track discharge care trajectory, e.g. how to stratify patients regarding estimated date of discharge beforehand, how to perform home monitoring, and when to reconsider scheduled discharge.

In our tertiary referral center, part of the endoERN reference network, the general policy was to discharge patients 5 days after pituitary tumor surgery and we did not stratify patients on anticipated LOS. Through an innovation project we introduced a fast-track protocol with such a preoperative stratification and with daily outpatient monitoring after discharge. This predefined protocol was based on a literature-based risk evaluation [17]. The aim of the present study was to systematically and comprehensively evaluate the feasibility, safety, patient perspective, and costs of this fast-track care in pituitary tumor surgery, including pre- and postoperative risk assessments of potential complications. Results from this evaluation will provide important information for healthcare providers considering short-stay after surgery, which is necessary for expectation management surrounding the perioperative care trajectory.

METHODS

Study design

This prospective cohort study was performed among a consecutive group of pituitary tumor patients treated endoscopically between December 2016 and December 2018 in a tertiary reference center. There were two reference groups: the first consisted of all pituitary tumor patients operated in the same period but were not considered eligible for fast-track discharge; the second was a retrospective cohort consisting of patients treated endoscopically prior to the intervention between January 2010 and November 2016 (historic controls). The Ethical Committee of the Leiden University Medical Center approved the prospective part prior to the study (p16.091). Consent was obtained from each patient after full explanation of the purpose and nature of all procedures used. For the historic control group, the same ethical committee approved a waiver of medical ethical review (G19.011).

Study population

All patients were diagnosed with a pituitary tumor and underwent endoscopic transsphenoidal resection between January 2010 and December 2018 at our tertiary referral center, the Leiden University Medical Center in the Netherlands. From December 2016 onwards, patients were preoperatively assessed for eligibility for fast-track discharge. The systematic assessments were based according to a literature-based clinical protocol during a weekly pituitary multidisciplinary team meeting. Predefined reasons for ineligibility for the fast-track group were: need for emergency surgery (e.g. apoplexy), Cushing's disease (CD), giant adenoma, craniopharyngioma, living far from the hospital, inadequate support network, and/or cognitive deficits. Directly after surgery, re-evaluation of the eligibility for fast-track discharge as well as an estimation of complication risks was performed by the treating neurosurgeon. Discharge was based on clinical grounds and only when deemed safe by the treating physician. This was reassessed on a daily basis after surgery. Patients in the historic control group received care as usual.

Interventions: fast-track care trajectory and usual care

Patients considered eligible for the fast-track care trajectory were instructed to actively participate in their own postoperative care by means of a standardized checklist which they had to report to the case manager on a daily basis after discharge. This checklist was composed to support patients to keep track of their fluid balance, weight, and relevant clinical signs and symptoms (Supplementary Table 1). Patients were instructed to report results digitally during the first 10–14 days after surgery. Those not capable of complying with our electronic surveillance were monitored through telephone consultation. The duration of the surveillance was dependent on the clinical judgment of the case

manager and could be extended if deemed clinically necessary. Patients not eligible for fast-track discharge received care as usual up to December 2017, but along the way were also included in the outpatient monitoring after discharge. The surgical procedure has previously been published and was in line with existing guidelines [18–20]. All patients received low-dose perioperative corticosteroids (hydrocortisone) until postoperative confirmation of adequate pituitary–adrenal axis function was performed through dynamic testing or a fasting cortisol. Postoperative sodium levels were determined on POD7 for all patients and/or in case of symptoms of hyponatremia.

Assessments

All data, with the exception of the prediction of complications, were obtained in the context of routine care and gathered by means of review of the medical records and questionnaires. Questionnaires could be filled in either digitally or on paper, both shown to provide equivalent results [21]. The treating neurosurgeon was asked to report his assessment on a case report form, directly after surgery.

Disease-specific and sociodemographic characteristics

These included age sex, comorbidities, tumor type, date of diagnosis, pituitary function, visual functioning, and cerebral nerve deficits. Comorbidities were categorized into diabetes mellitus, neurovascular, cardiovascular, pulmonary, ophthalmologic disease, or malignancies. Tumor types included: nonfunctioning pituitary adenoma, acromegaly (ACRO), CD, prolactinoma (PRL), TSH-producing adenoma, Rathke's cleft cyst, or craniopharyngioma (Cranio). Pituitary function was defined as: (1) no deficits, (2) single hormone deficiency, (3) single hormone deficiency plus DI, (4) multiple hormone deficiencies, (5) multiple hormone deficiencies plus DI, and (6) DI alone. Visual functioning was defined as the presence of visual field deficits, or not. Prior treatments were described as: (1) no treatment, (2) prior medical (tumor) treatment, (3) prior surgery, and (4) prior radiotherapy.

Outcome parameters

Primary outcomes were feasibility, safety, ability to predict postoperative complications, patient-reported experience, and costs. Patient-reported outcomes were secondary outcomes.

Feasibility

Feasibility was defined as the proportion of patients allocated to the fast-track group, who were discharged 2–3 days after surgery and not readmitted within the fifth postoperative day (POD), which was often the date of discharge prior to the implementation of the protocol. Furthermore, adherence to the fast-track surveillance protocol was

registered by means of the length of surveillance and the frequency and duration of fluid balance interventions.

Safety

Safety was defined as the occurrence of a severe complication after discharge (Clavien–Dindo grade III or higher) [22]. Complications of interest were readmission within 30 days (general), transient DI/permanent DI/delayed hyponatremia/new pituitary deficiencies (endocrine complications) and postoperative CSF leak/epistaxis/intracranial hemorrhage (neurosurgical complications). Transient DI was defined as necessity of treatment (desmopressin) up to 6 months after surgery. Permanent DI was defined as treatment for more than 6 months. CSF leaks during surgery with prompt closure were not considered a postoperative complication and were not a contraindication for early discharge. For readmissions, the primary reason of readmission, duration of readmission in days, and postoperative date of readmission were recorded.

Ability to predict postoperative complications

The estimated risk of complications was evaluated immediately after surgery by the neurosurgeons to investigate whether this would help to differentiate between patients at risk of complications and those who were not. The likelihood of complications included transient DI, permanent DI, new onset of pituitary deficiencies, epistaxis, postoperative CSF leak, and intracranial hemorrhage. The likelihood of complications was dichotomized into not likely and possible, from which the sensitivity and specificity were calculated.

Patient-reported outcome measures (PROMs)

A comprehensive set of PROMs was administered at baseline (preoperatively) and 6 weeks after surgery. Changes in PROMs were calculated as between group differences corrected for baseline. Disease bother was measured through the Leiden Bother and Needs Questionnaire-pituitary (LBNQ-Pituitary) [23], which was modified in order to make it suitable for perioperative repeated measurements. The total score ranges from 0 to 100, with higher scores indicating a greater disease bother or need for help. Health-related quality of life (HRQoL) was measured using the short form-36, from which physical and mental component scores can be calculated. These range from 0 to 100, with higher scores indicating better HRQoL [24]. Health status was assessed using the five-level EQ-5D index (Dutch tariff, anchored at 0 (as bad as death) and 1 (perfect health)), and the EQ-5D VAS (ranging from 0 to 100) [25, 26]. Higher scores indicate a better perceived health status. Visual functioning was assessed through the visual functioning questionnaire-25 (range 0 to 100), and higher scores indicate better visual functioning [27].

Patient-reported experience measures (PREMs)

Patient-reported experiences were measured 4 weeks after surgery among patients in the fast-track group by means of a self-designed questionnaire and included experience of delivered care, sense of safety at home during the first 3 days at home, as well as the period after (day 4 through day 7). This questionnaire also assessed the self-perceived patient empowerment on a five-point Likert scale (range: “not at all” to “completely”) and the self-perceived optimal discharge date (range: −2 to +4 days).

Costs

Costs were estimated from a healthcare perspective, at price level 2019. Hospital care included the initial admission (regardless of duration) and all subsequent hospital care up to 30 days after surgery (including readmission, emergency room visits, outpatient clinic visits, e-mail, and telephone contacts). All healthcare use was assessed from patient records, except for outpatient clinic visits in the non-fast-track and historic cohort, which was set at two visits, unless hospitalization lasted for more than 30 days. Costs for surgery were derived from the Dutch Healthcare Authority [28, 29], and all other costs from Dutch reference prices designed to standardize economic evaluations (Supplementary Table 2) [30].

Statistical analysis

All statistical analyses were performed with SPSS 25.0 software (SPSS Inc., Armonk, NY, USA). Nominal variables are presented as frequencies with percentages, numerical variables as means and standard deviations (SD), or medians with interquartile ranges (IQR). Comparisons were made between the fast-track and non-fast-track groups, as well as between the historic group and the total group (fast-track and non-fast-track). Comparisons were performed through one-way ANOVA, Chi-square analyses, Fisher’s exact test, or general linear mixed models (GLM), where applicable. The sensitivity (Se) and specificity (Sp) were used to calculate the discriminative ability of the predictions, as approximated by ½(Se + Sp) [31]. Longitudinal analysis was performed via GLM analysis and results are presented as means with corresponding standard errors. For all analyses, the level of significance was set at $p < 0.05$ (two-sided). Missing data on the validated questionnaires were handled by parcel summary imputation [32].

The historic control group comprised of all patients surgically treated between January 2010 and December 2016, including those with diagnoses that were not considered eligible for fast-track surgery. In an attempt to compare the fast-track group with representative patients from our historical cohort, all comparisons were repeated after exclusion of patients with CD, Cranio, giant adenomas, and acute apoplexy (sensitivity analysis).

RESULTS

Between December 2016 and December 2018, a total of 155 patients were surgically treated for a pituitary tumor. Patients had a mean age of 48.4 years (SD 16.9) and 54% were female. Most patients had an NFA (45%), followed by ACRO and PRL (both 16%), CD (14%), and other tumors (9%). Among the historic cohort, surgical treatment was performed among 307 patients, with a mean age of 51.5 years (SD 16.9). Of these, 53% were female and most patients also had an NFA (45%), followed by CD (17%), ACRO (16%), PRL (10%), and other tumors (12%) (Table 1).

Feasibility

Of the 155 patients, 79 patients (51%) were preoperatively considered eligible for fast-track discharge. Of these, 69 patients (87%) were discharged 2–3 days after surgery as planned (POD2: N = 37, POD3: N = 32) and three of these patients (4%) needed to be readmitted within POD5. Among the patients eligible for fast-track discharge that required a stay of more than 3 days (range 4–17 days), one was readmitted within the fifth POD. In addition, among patients not considered eligible at preoperative counseling, 7 (9%) were successfully discharged after 2–3 days after surgery (POD2: N = 1, POD3: N = 6). In comparison, in the historic cohort, only 61 patients (20%) were discharged 2–3 days after surgery (POD2: N = 17, POD3: N = 44).

Among patients in the fast-track group, reasons for delaying discharge were uncontrolled DI in seven patients (9%) and a postoperative CSF leak in three patients (4%). The three most frequent reasons for a priori non-eligibility were CD (N = 20, 26%), emergency surgery (N = 11, 14%), and due to various comorbidities (N = 10, 13%) (Figs. 1 and 2a). Adherence to the fast-track surveillance protocol is depicted in Fig. 2. Surveillance by the case manager was stopped on average on POD14 (IQR 11–15) (Fig. 2b). Reasons for extending the period of surveillance beyond the initially planned 14 days were a prescheduled sodium check on POD15 (N = 8), fluctuating fluid balance/uncontrolled DI (N = 9), persisting physical complaints (N = 2), and a previous readmission (N = 2). During follow-up, 24 patients received a fluid restriction, which started on average 7.3 days (SD 1.1) after surgery and lasted for a mean of 4.6 days (SD 2.4) (Fig. 2c). All but five patients were able to provide daily evaluations digitally and were monitored through telephone consultation.

Length of stay

Patients in the fast-track group had a significantly shorter LOS compared with the non-fast-track group (3.0 vs. 7.6 days, $p < 0.001$), however the overall LOS of the total group was not significantly lower compared with the historic cohort (5.3 vs. 5.7 days, $p = 0.363$) (Table 2).

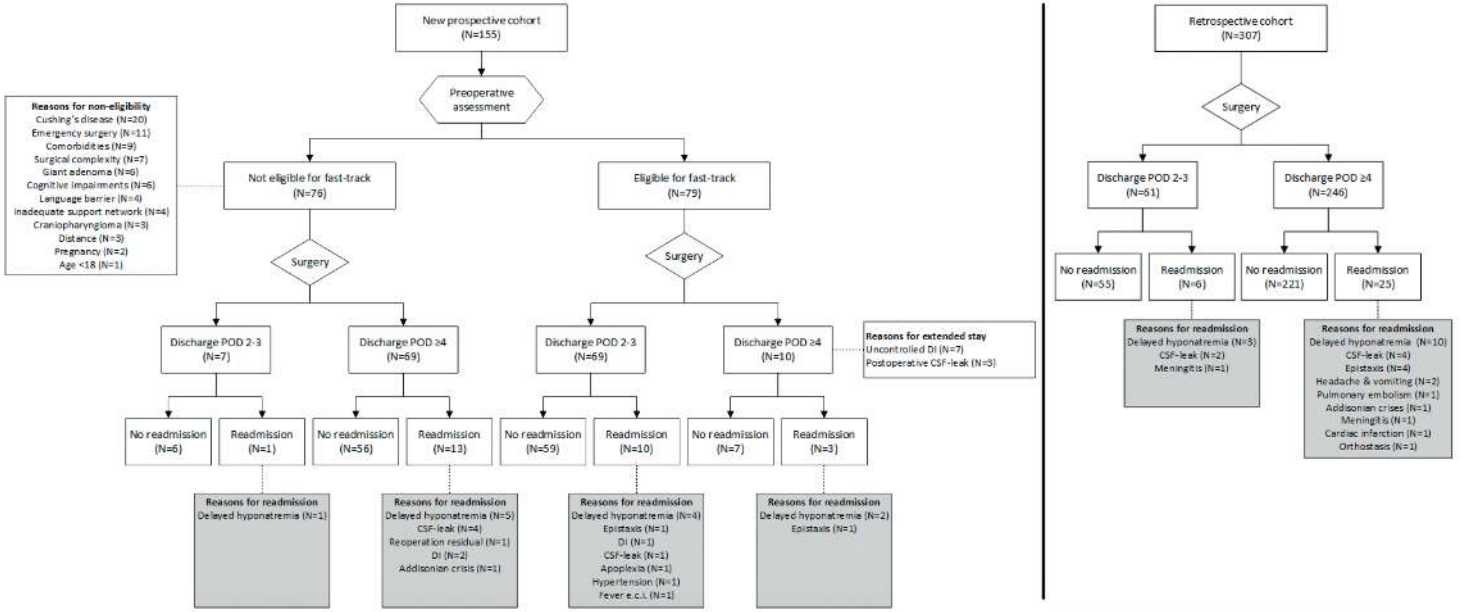

Figure 1. Flow-chart of patients surgically treated for a pituitary tumor

* For patients readmitted more than once, the reason of first readmission is shown

Table 1. Baseline characteristics of patients with a pituitary tumor

	Fast-track	Non-fast-track	*p* value*	Total	Historic cohort	*p* value**
	(*N* = 79)	(*N* = 76)		(*N* = 155)	(*N* = 307)	
Sociodemographic characteristics						
Female gender, *N* (%)	43 (54.4)	40 (52.6)	0.873	83 (53.5)	163 (53.1)	1.000
Age in years, mean (SD)	47.2 (16.0)	49.7 (17.9)	0.368	48.4 (16.9)	51.5 (16.9)	0.069
Comorbidities, *N* (%)						
Diabetes mellitus	3 (3.8)	12 (15.8)	0.014	15 (9.7)	38 (12.4)	0.442
Neurovascular disease	11 (13.9)	10 (13.2)	1.000	21 (13.5)	36 (11.7)	0.653
Cardiovascular disease	17 (21.5)	40 (52.6)	<0.001	57 (36.8)	121 (39.4)	0.614
Malignancies	8 (10.1)	3 (3.9)	0.211	11 (7.1)	33 (10.7)	0.242
Pulmonary disease	1 (1.3)	5 (6.6)	0.112	6 (3.9)	27 (8.8)	0.057
Ophthalmologic disease	15 (19.0)	15 (19.7)	1.000	30 (19.4)	55 (17.9)	0.705
Disease-specific characteristics						
Tumor type, *N* (%)						
NFA	40 (50.6)	30 (39.5)		70 (45.2)	137 (44.6)	
ACRO	15 (19.0)	10 (13.2)		25 (16.1)	50 (16.3)	
CD	0 (0.0)	21 (27.6)		21 (13.5)	53 (17.3)	
PRL	20 (25.3)	5 (6.6)		25 (16.1)	30 (9.8)	
RCC	4 (5.1)	0 (0.0)		4 (2.6)	13 (4.2)	
Cranio	0 (0.0)	9 (11.8)		9 (5.8)	19 (6.2)	
TSH-oma	0 (0.0)	1 (1.3)	<0.001	1 (0.6)	5 (1.6)	0.433
Tumor size, *N* (%)						
Micro	19 (24.1)	20 (26.3)		39 (25.2)	64 (20.8)	
Macro	60 (75.9)	45 (59.2)		105 (67.7)	226 (73.9)	
Giant	0 (0.0)	11 (14.5)	0.001	11 (7.1)	16 (5.2)	0.374

Table 1. Baseline characteristics of patients with a pituitary tumor (continued)

	Fast-track	Non-fast-track	*p* value*	Total	Historic cohort	*p* value**
	(*N* = 79)	(*N* = 76)		(*N* = 155)	(*N* = 307)	
Cavernous sinus invasion, *N* (%)	12 (15.2)	11 (14.5)	1.000	23 (14.8)	72 (23.5)	0.041
Time since diagnosis in years, median (IQR)	1.1 (0.2–5.2)	0.2 (0.0–1.7)	0.002	0.4 (0.1–3.9)	0.5 (0.1–3.6)	0.483
Prior treatments, *N* (%)						
No treatment	40 (50.6)	45 (59.2)	0.334	85 (54.8)	185 (60.3)	0.273
Medication	31 (39.2)	25 (32.9)	0.504	56 (36.1)	75 (24.4)	0.009
Surgery	11 (13.9)	15 (19.7)	0.393	26 (16.8)	62 (20.2)	0.384
Radiotherapy	0 (0.0)	1 (1.3)	0.490	1 (0.6)	7 (2.3)	0.277
Apoplexy, *N* (%)	4 (5.1)	16 (21.1)	0.004	20 (12.9)	24 (7.8)	0.093
Preoperative endocrine status, *N* (%)						
No deficits	40 (50.6)	33 (44.0)		73 (47.4)	152 (49.8)	
Single hormone deficiency	15 (19.0)	10 (13.3)		25 (16.2)	34 (11.1)	
Single hormone deficiency + DI	0 (0.0)	1 (1.3)		1 (0.6)	0 (0.0)	
Multiple hormone deficiencies	24 (30.4)	28 (37.3)		52 (33.8)	118 (38.7)	
Multiple hormone deficiencies + DI	0 (0.0)	2 (2.7)		2 (1.3)	1 (0.3)	
DI alone	0 (0.0)	1 (1.3)	0.308	1 (0.6)	0 (0.0)	0.095
Preoperative visual status, *N* (%)						
No deficits	51 (64.6)	32 (42.1)	0.041	83 (53.5)	159 (52.0)	1.000
Cranial nerve palsy, *N* (%)	2 (2.5)	10 (13.2)	0.017	12 (7.7)	13 (4.2)	0.128
Completed questionnaire, *N* (%)	65 (82.3)	42 (55.3)		107 (69.0)	16 (5.2)	

Due to rounding, not all percentages of the categorical variables add up to 100%

N number, *SD* standard deviation, *IQR* interquartile range, *NFA* nonfunctioning pituitary adenoma, *ACRO* acromegaly, *CD* Cushing's disease, *PRL* prolactinoma, *RCC* Rathke's cleft cyst, *Cranio* craniopharyngioma, *TSH* thyroid-stimulating hormone

Bold values indicate statistical significance $p < 0.05$

*Fast-track vs. non-fast-track; **Total vs. historic cohort

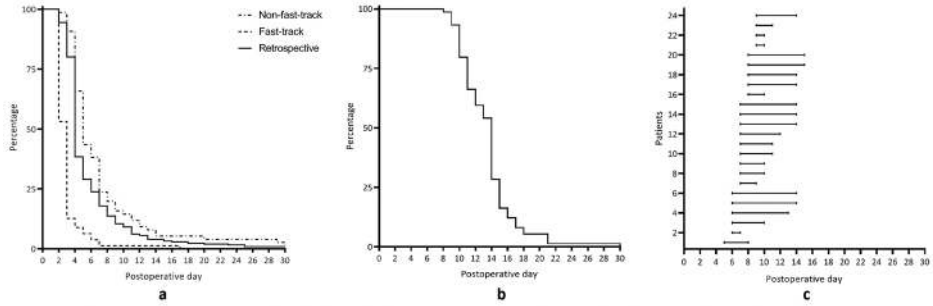

Figure 2. Survival curve of duration of date of discharge (a); active surveillance after surgery (b); onset and duration of fluid restrictions per patient (c)

Safety

No life-threatening complications occurred after discharge (Clavien–Dindo grade IV), in particular not in the period between fast-track discharge and "regular" discharge. However, two patients (2.5%) were readmitted for the surgical treatment of an epistaxis late after fast-track discharge (grade III, POD12 and 21). In the fast-track discharge group, a total of 13 patients (16%) were readmitted after discharge, on average 8.5 days (SD 6.0) after surgery. This was most frequently due to delayed hyponatremia (N = 6, 43%) and did not differ with the non-fast-track group, among which 14 (18%) were readmitted (p = 0.747). Patients readmitted among the non-fast-track group were readmitted on average 13.2 days (6.2 SD) after surgery and also most frequently due to delayed hyponatremia (N = 6, 43%). In the historic cohort group, there were significantly fewer readmissions compared with the total group (N = 31, 10% vs. N = 27, 17%, p = 0.03). In the total group, the reason for readmission was most frequently due to delayed hyponatremia (N = 13, 42%) (Fig. 3, Table 2).

Ability to predict postoperative complications

On average, the ability to predict complications after surgery was low. For all complications, a high specificity was combined with a low sensitivity or vice versa. The discriminative ability ranged from 45 to 62%, showing that it was difficult to predict which patients are at risk of complications after surgery (Table 3).

Patient-reported experience

Among the fast-track group, the overall patient satisfaction about the delivered care after discharge was a 7.9 (SD 1.5, scale 1–10), which was significantly lower among patients readmitted after discharge compared with those who were not readmitted (8.1 vs. 7.0, p = 0.04). The mean overall sense of safety at home during the first 3 days after discharge was 6.7 (SD 2.5, scale 1–10), which was not statistically different between patients who were not readmitted compared with those who were (mean 6.9 vs. 5.3, p = 0.08). After the

Table 2. Surgical outcomes and costs among 462 surgically treated patients with a pituitary tumor stratified according to cohort

	Fast-track (*N* = 79)	Non-fast-track (*N* = 76)	*p* value*	Total (*N* = 155)	Historic cohort (*N* = 307)	*p* value**
Length of stay, mean (SD) Complications	3.0 (1.9)	7.6 (8.6)	<0.001	5.3 (6.6)	5.7 (4.9)	0.363
Number of readmitted patients, *N* (%)	13 (16.5)	14 (18.4)	0.747	27 (17.2)	31 (10.1)	0.025
Length of stay of all readmissions, mean (SD)	3.6 (2.7)	4.3 (4.2)	0.647	4.0 (3.5)	4.1 (3.4)	0.917
Any complication, *N* (%)	38 (48.1)	46 (60.5)	0.147	84 (54.2)	179 (58.3)	0.427
Transient DI, *N* (%)	20 (25.3)	28 (36.8)	0.165	48 (31.0)	53 (17.3)	0.001
Permanent DI, *N* (%)	3 (3.8)	7 (9.2)	0.204	10 (6.5)	17 (5.5)	0.834
Delayed hyponatremia, *N* (%)	9 (11.4)	14 (18.4)	0.262	23 (14.8)	31 (10.1)	0.167
New onset pituitary deficiency, *N* (%)	4 (5.1)	9 (11.8)	0.148	13 (8.4)	22 (7.2)	0.709
Postoperative CSF leak, *N* (%)	3 (3.8)	8 (10.5)	0.126	11 (7.1)	25 (8.2)	0.719
Epistaxis, *N* (%)	10 (12.7)	2 (2.6)	0.032	12 (7.7)	29 (9.4)	0.606
Postoperative intracranial hemorrhage, *N* (%)	0 (0.0)	1 (1.3)	0.490	1 (0.6)	3 (1.0)	1.000
Hospital costs (in euro's)						
Admission, mean (SD)	7249 (1318)	10394 (5868)	<0.001	8791 (4488)	9127 (3306)	0.363
Readmission, mean (SD)	438 (1221)	608 (1759)	0.486	521 (1506)	323 (1287)	0.141
Emergency room visits, mean (SD)	42 (108)	50 (153)	0.677	46 (132)	25 (85)	0.039
Outpatient clinic visits, mean (SD)	55 (102)	332 (68)	<0.001	191 (164)	343 (34)	<0.001
E-mail contacts, mean (SD)	626 (284)	0 (0)	<0.001	319 (373)	0 (0)	<0.001
Telephone contacts, mean (SD)	242 (184)	0 (0)	<0.001	123 (178)	0 (0)	<0.001
Total hospital costs, mean (SD)	8652 (1748)	11,384 (5974)	<0.001	9992 (4562)	9818 (3488)	0.649

N number, *SD* standard deviation, *IQR* interquartile range, *DI* diabetes insipidus, *CSF* cerebrospinal fluid Bold values indicate statistical significance $p < 0.05$

*Fast-track vs. non-fast-track; **Total vs. historic cohort

initial period at home (3 days), the mean overall sense of safety improved to a mean of 7.7 (SD 1.8, scale 1–10), which was significantly lower among patients readmitted compared with those who were not (6.0 vs. 8.0, p = 0.001). Over half of the patients (54%) perceived themselves as very/completely empowered, which did not differ between both groups (p = 1.00). Nearly 40% of patients (N = 23/58), however, would have preferred to stay admitted one or more days longer, which was significantly higher among readmitted patients (p = 0.02) (Table 4). This was not assessed in the non-fast-track group, nor in the historical controls.

Table 3. Postoperative evaluation of complication risks by treating neurosurgeon among fast-track patients (*N* = 64)

Total		Unlikely	Possible	Sensitivity	Specificity	Discriminative ability
Transient DI	*N*					
Yes	14	0	14			
No	50	12	38	100%	24%	62%
Permanent DI, *N*						
Yes	3	3	0			
No	61	54	7	0%	89%	44%
New onset pituitary deficiency, *N*						
Yes	4	2	2			
No	60	27	33	50%	45%	48%
CSF leak, *N*						
Yes	3	2	1			
No	61	39	22	33%	64%	49%
Epistaxis, *N*						
Yes	7	1	6			
No	55	19	36	86%	35%	60%
Postoperative hemorrhage, *N*						
Yes	0	0	0			
No	64	47	17	–	73%	–

N number, *DI* diabetes insipidus, *CSF* cerebrospinal fluid

Costs

The mean costs of perioperative treatment were € 8652 (SD € 1748) for patients in the fast-track group, which was significantly lower compared with patients in the non-fast-track group (€ 11,384; SD € 5974, p < 0.001). There was no significant difference in costs between the total group (€ 9992; SD € 4562) and the historic cohort (€ 9818; SD € 3488, p = 0.649) (Table 2).

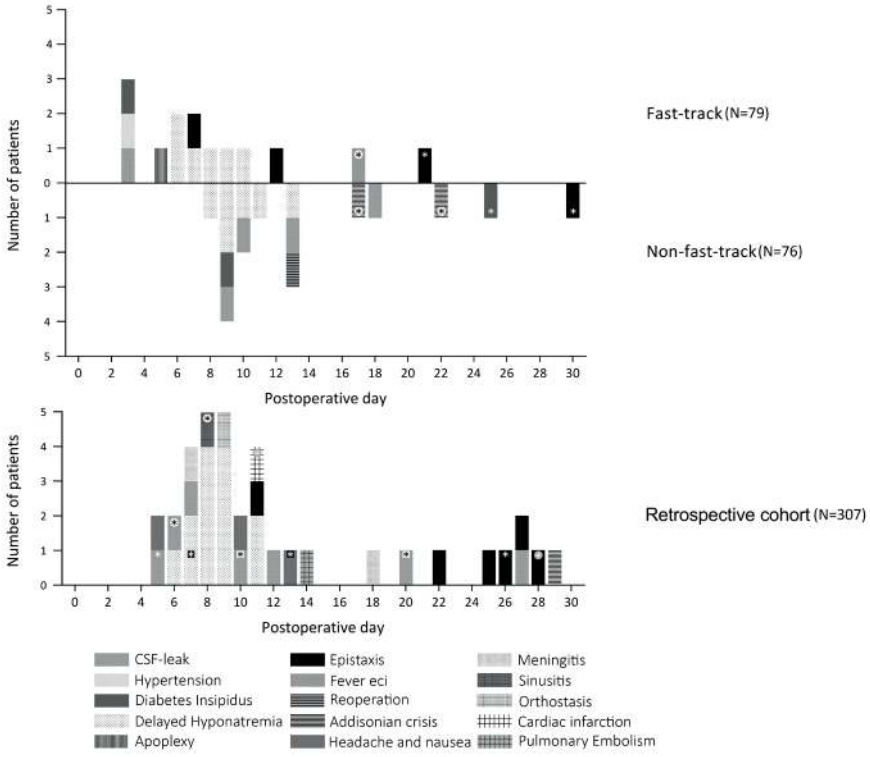

Figure 3. Readmissions per day and reasons for readmission among all patients

Patient-reported outcomes

In general, the disease burden decreases among patients after surgery compared with prior to surgery; HRQoL improves, nasal morbidity decreases, and visual functioning improves after surgery irrespective of whether a patient is in the fast-track or non-fast-track group, nor were there any differences between the total group and the historic controls (Supplementary Table 3).

Sensitivity analysis

Excluding patients with diagnoses not considered eligible for fast-track from the historic control group yielded a selection of 213 patients. Both groups (fast-track and selected historic cohort) were grossly comparable (Supplementary Table 4). Among the fast-track group, we found a shorter LOS (mean 3.0 vs. 5.1 days, $p < 0.001$), but higher occurrence of transient DI (25 vs. 15%, $p = 0.036$). The costs in the fast-track group were significantly lower than in the selected historic control group (€ 8652 vs. € 9266 $p = 0.021$) (Supplementary Table 5).

Table 4. Patient-perceived satisfaction, sense of safety, and perceived optimal discharge date among patients eligible for fast-track

	Total (*N* = 79)	No readmission (*N* = 69)	Readmission (*N* = 10)	*p* value
Completed questionnaire, *N* (%)	58 (73.4)	49 (71.0)	9 (90.0)	
Delivered care after discharge, mean (SD)	7.9 (1.5)	8.1 (1.5)	7.0 (1.4)	0.044
Sense of safety at home: day 1–3 (scale 1–10), mean (SD)	6.7 (2.5)	6.9 (2.4)	5.3 (2.9)	0.078
Sense of safety at home: after 3 days (scale 1–10), mean (SD)	7.7 (1.8)	8.0 (1.6)	6.0 (1.9)	0.001
Sense of self-empowerment, *N* (%)				
Not at all	1 (1.7)	1 (2.0)	0 (0.0)	
Slightly	3 (5.2)	3 (6.1)	0 (0.0)	
Moderately	22 (37.9)	18 (36.7)	4 (44.4)	
Very	16 (27.6)	13 (26.5)	3 (33.3)	
Completely	16 (27.6)	14 (28.6)	2 (22.2)	1.00
Patient-perceived optimal date of discharge, *N* (%)				
1 day earlier	3 (5.2)	3 (6.1)	0 (0.0)	
Exact the same day	32 (55.2)	29 (59.2)	3 (33.3)	
1 day later	8 (13.8)	8 (16.3)	0 (0.0)	
2 or more days later	15 (25.9)	9 (18.4)	6 (66.7)	0.023

N number, *SD* standard deviation, (bold) $p < 0.05$

DISCUSSION

This study shows that fast-track discharge after pituitary surgery is feasible and can be safely implemented when incorporated in a well-defined care trajectory with stratification. For a select group of patients, we were able to decrease the overall LOS by including the patient as an active participant, while being under surveillance of a dedicated case manager. Early discharge was possible in 87% of preoperatively identified cases, and in an additional 9% of the non-eligible cases. It remains difficult, however, to adequately predict complications and readmissions and therefore we advocate that all patients require monitoring up to at least 14 days postoperatively. After the reported evaluation period we implemented the described protocol in our practice. It is likely that with increasing experience, more patients can be stratified towards the fast-track discharge group. Restriction of early postoperative vasopressin use and earlier institution of fluid restrictions may reduce the number of readmissions. It is furthermore probably possible to reduce the number of contact moments without compromising patient safety. Readmissions appeared relatively high (16%) in the fast-track discharge, as well as the non-fast-track discharge group (18%) compared with historical controls (10%). Since this was mainly due to SIADH and the protocol was directed to detect patients at risk at an early stage, it is likely that we were more aware of diagnosing and treating

this complication at an early stage. Importantly, no life-threatening complications occurred in the home setting. So, we conclude that the high readmission rate most likely reflects the intense attention to postoperative complications combined with our low threshold for readmittance. Results shown in this study provide useful information that will facilitate better expectation management, improve water and electrolyte imbalance protocols, decrease the occurrence of delayed hyponatremia, and subsequent readmissions.

Even though there are more centers that discharge patients at POD2 or even sooner, the feasibility and safety has only been scarcely evaluated [12–14]. In the postoperative phase, the risk of delayed hyponatremia remains an important problem. This study confirms previous data that patients are at risk for readmission due to delayed hyponatremia, for which reported peak incidence ranges from POD4 to POD7 [10, 11, 33, 34]. Our study adds to this that late complications do occur even up to 30 days after surgery. Our study provides practical tips for those who consider the transition to fast-track care. It will allow a shift from inpatient general nursing care to an extended period of daily outpatient care by a specialized case manager, dedicated to treat both endocrinological and neurosurgical aspects.

One of the main reasons to initiate this fast-track protocol was the impression that our patients thought that postoperative hospitalization was only for complication surveillance, not for actual needed care. An unanticipated result is the lower than expected overall sense of safety at home during the first 3 days as perceived by patients discharged early after surgery. Control data of experienced safety in the first days after discharge are not available for pituitary surgery, so we do not know if this is uncommon or not. Furthermore, the majority of our patients indicated afterwards that they were content with the day of discharge. Based on obtained patients' experiences, we doubt whether further shortening the admission period, albeit commonplace in some centers, would be desired by patients. Patients who were readmitted reported a lower perceived safety at home, which might be explained in part by the fact that patients who experience adverse events after discharge often have lower evaluations of care [35]. So, patient education, expectation management, and additional strategies to improve the sense of safety are warranted.

There are several recent publications regarding standardized fluid restrictions in the short-term postoperative phase [36–39]. Benefits from this standardized fluid restriction approach are the low-threshold of application of fluid restrictions and the specific targeting of patients at risk for delayed hyponatremia. Even though delayed hyponatremia is the most frequent reason for readmission, this approach is less suitable for

management of other complications, since patients guided through a standardized fluid restriction protocol are not followed as strictly and the adaptability is lower compared with our fast-track protocol. The results from these fluid restriction studies, in combination with our fast-track results, might suggest that a combined approach, consisting of daily contact in combination with low threshold fluid restrictions, should be considered. In this context, it is also important to consider a restriction of intraoperative fluids for early discrimination between DI and perioperative fluid overload.

The size, comprehensiveness, and prospective nature are the main strengths of this study. Previous studies had smaller sample sizes (up to 47 patients) compared with our study. By comparing results from the fast-track group with the non-fast-track group, as well as with the historic cohort group, we have provided more accurate reference data from which we drew our conclusions regarding the outcomes of our fast-track protocol. Ideally, we would have performed a randomized controlled trial or a cluster randomized trial, however due to the rarity of the disease, the heterogeneity of the population, and the odds of contamination of the non-surveillance group, these methods were deemed not feasible [40].

Also, by presenting and comparing the results of these three groups we have attempted to provide insight into the possible occurrence of selection bias. The differences in terms of costs appear to be small, but promising, if only those patients from the historic cohort are considered that meet eligibility criteria for fast-track. Nevertheless, results of the sensitivity analysis should be interpreted with caution, since it is unknown what direction the results of the historic cohort would go towards when the selection of patients would have been performed like that of the fast-track group. We potentially introduced recall bias, which was introduced by asking patients to recollect their initial sense of safety several weeks after discharge instead of on the actual date itself.

Another limitation of this study is the standardization of costs for the retrospective and non-fast-track group. This might have resulted in lower overall costs for these groups of patients and future research should focus more on the cost aspect of the intervention. Preferably this should be done through a time-driven-activity-based-costing approach, which is advocated within the model of value-based healthcare [41]. Also, further evaluation of optimal transition towards a fast-track care trajectory, as well as evaluation of differences between patient evaluations and how to optimally empower patients is necessary to optimize this care trajectory.

CONCLUSION

Discharging selected patients 2–3 days after transsphenoidal surgery through a well-defined fast-track care trajectory appears feasible and safe. Although the overall costs of the fast-track group were lower compared with the non-fast-track group, the overall costs between the total group and the historic group did not differ, while a specialized case manager provided prolonged daily monitoring. Since the prediction of complications remains difficult and readmissions do occur, monitoring is needed also after uneventful surgery. With this approach we did not encounter any life-threatening situations by expediting the date of discharge in a large group of patients. Additional patient education and expectation management are needed to improve the reassurance about the safety of early discharge.

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Supplementary table 1. Daily questionnaire after pituitary surgery

1. What was your fluid balance during the previous 24 hours?	
In: ml	Out: ml

2. What was your weight after awakening this morning?
Kilograms

3. Did you have a fever during the previous 24 hours (temperature of >38.5°C)?	
☐	Yes → Take a double dosage of hydrocortisone and contact the case manager
☐	No → No further action required

4. How are you feeling today?		
☐	Not good	→ Fill in the rest of the questionnaire
☐	Reasonably well	→ Fill in the rest of the questionnaire
☐	Good	→ No further action required

4b. How are you feeling compared to yesterday?		
☐	Worse compared to yesterday	→ Fill in the rest of the questionnaire
☐	Unchanged	→ Fill in the rest of the questionnaire
☐	Better compared to yesterday	→ No further action required
☐	I don't have any complaints	→ No further action required

5. Are you increasingly tired and/or are you feeling washed-out?		
☐ Yes	→ it's getting worse	→ Take a double dosage of hydrocortisone and contact the case manager
	→ it's about the same	→ No further action required
	→ it's improving	→ No further action required
☐ No	→ No further action required	

6. Have you had complaints of nausea and/or did you vomit in the previous 24 hours?	
☐ Yes	→ Take a double dosage of hydrocortisone and contact the case manager
☐ No	→ No further action required

7. Have you lost your appetite?		
☐ Yes	→ Worse compared to before	→ Contact the case manager
	→ Unchanged	→ No further action required
	→ Better compared to before	→ No further action required
☐ No	→ No further action required	

8. Do/Did you have a headache?		
☐ Yes	→ Worse compared to before	→ Contact the case manager
	→ Unchanged	→ No further action required
	→ Better compared to before	→ No further action required
☐ No	→ No further action required	

9. Do you have any physical complaints at the moment?	
☐ Yes	→ Please report your complaints
☐ No	→ No further action required

10. Do you have unquenchable thirst despite drinking?	
☐ Yes	→ Take a double dosage of hydrocortisone and contact the case manager
☐ No	→ No further action required

11. Do you feel like you have to urinate more than usual?	
☐ Yes	→ Contact the case manager
☐ No	→ No further action required

12. Is there leakage of fluid out of your nose (not: old blood or fluid from the nasal douche)?	
☐ Yes	→ Contact the case manager
☐ No	→ No further action required

13. How is your vision since the surgery?	
☐ It's getting worse	→ Contact the case manager
☐ Unchanged	→ No further action required
☐ It's improving	→ No further action required

→ In case all questions have resulted in the answer "No further action required" we request you to send your answers to the case manager before 10:00 a.m.
→ In case of a fever, severe fatigue, nausea, vomiting, we urge you to take a double dosage of hydrocortisone and contact the case manager or on-call endocrinologist immediately.

Supplementary table 2. Unit prices in euros (€)

	Price (€)	*Year*	*Source*	*Remark*
Cost of surgery	4551	2019	Open DIS[1]	Per operation
Inpatient care	679	2019	Guideline[2]	Per day
Telephone consultation / e-consultation	87	2019	Guideline[3]	Per consultation
Outpatient care	173	2019	Guideline[2]	Per visit
Emergency care	274	2019	Guideline[2]	Per visit

[1] National average costs for comparable medical treatments, excluding hospital days
[2] Dutch guidelines for healthcare cost calculation
[3] Consistent with GP consultations, specialist telephone consultations were valued at 50% of face-to-face consultations

Supplementary Table 3. Patient-reported outcomes before and 6 weeks after surgery among patients treated for a pituitary tumor (after August 2016)

	Fast-track (N=65/79)		**Non-fast-track (N=42/78)**		**p-value***	**Total group (N=107/155)**		**Historic cohort (N=16/313)**		**p-value****
LBNQ-Pituitary index, mean (SE)[1]										
at baseline	22.88	(2.28)	24.00	(2.70)		23.32	(1.74)	27.40	(4.10)	
after 6 weeks	16.41	(2.01)	18.10	(2.30)	.650	17.07	(1.52)	15.38	(2.59)	.120
SF-36 MCS, mean (SE)[2]										
at baseline	44.33	(1.53)	43.36	(1.99)		43.95	(1.21)	43.75	(3.93)	
after 6 weeks	47.51	(1.38)	48.55	(1.51)	.384	47.92	(1.03)	49.93	(2.33)	.356
SF-36 PCS, mean (SE)[2]										
at baseline	43.70	(1.28)	39.73	(1.59)		42.14	(1.02)	40.22	(2.74)	
after 6 weeks	41.00	(1.08)	38.30	(1.23)	.498	39.94	(0.82)	38.44	(2.53)	.434
EQ-index, mean (SE)[2]										
at baseline	0.886	(0.01)	0.866	(0.02)		0.878	(0.01)	0.869	(0.02)	
after 6 weeks	0.886	(0.02)	0.875	(0.02)	.929	0.882	(0.01)	0.900	(0.02)	.372
EQ-VAS, mean (SE)[2]										
at baseline	72.45	(2.04)	66.58	(3.38)		70.15	(1.84)	68.25	(4.42)	
after 6 weeks	67.72	(2.96)	68.51	(3.30)	.463	68.03	(2.23)	65.44	(5.82)	.747
ASK nasal-12, mean (SE)[2]										
at baseline	0.80	(0.11)	0.58	(0.08)		0.71	(0.07)	0.60	(0.16)	
after 6 weeks	1.10	(0.12)	0.97	(0.12)	.926	0.94	(0.19)	0.94	(0.19)	.778
SNOT-22, mean (SE)[2]										
at baseline	25.70	(2.75)	22.92	(2.32)		24.61	(1.91)	25.94	(4.87)	
after 6 weeks	26.51	(2.69)	27.43	(3.02)	.412	26.87	(2.04)	25.03	(3.75)	.524
VFQ-25, mean (SE)[2]										
at baseline	84.37	(1.94)	76.63	(2.75)		81.33	(1.64)	84.01	(3.22)	
after 6 weeks	91.08	(1.27)	86.16	(1.65)	.095	89.15	(1.04)	91.33	(1.88)	.545

* fast-track versus non-fast-track (corrected for baseline), ** total versus historic cohort (corrected for baseline)
LBNQ-Pituitary (Leiden bother and needs questionnaire-pituitary), SF-36 (short form-36), MCS (mental component scale), PCS (physical component scale), EQ-5D (EuroQoL), VAS (visual analog scale), ASK-12 (anterior skullbase nasal inventory-12), SNOT-22 (sino-nasal outcome test-22), VFQ-25 (visual functioning questionnaire-25), SE (standard error)
[1] Higher scores indicate better HRQoL, health status, visual functioning and increased nasal morbidity
[2] Lower scores indicate lower disease burden
(bold) p<0.05

Supplementary table 4. Baseline characteristics of patients with a pituitary tumor

	Fast-track (N=79)	Selection of historic cohort (N=213)	P-value
Sociodemographic characteristics			
Female gender, N (%)	43 (54.4)	105 (49.3)	.510
Age in years, mean (SD)	47.2 (16.0)	52.0 (16.7)	**.030**
Comorbidities, N (%)			
Diabetes mellitus	3 (3.8)	20 (9.4)	.145
Neurovascular disease	11 (13.9)	26 (12.2)	.843
Cardiovascular disease	17 (21.5)	69 (32.4)	.083
Malignancies	8 (10.1)	22 (10.3)	1.000
Pulmonary disease	1 (1.3)	20 (9.4)	**.019**
Ophthalmologic disease	15 (19.0)	39 (18.3)	.867
Disease-specific characteristics			
Tumor type, N (%)			
NFA	40 (50.6)	119 (55.9)	
ACRO	15 (19.0)	47 (22.1)	
CD	0 (0.0)	0 (0.0)	
PRL	20 (25.3)	29 (13.6)	
RCC	4 (5.1)	13 (6.1)	
Cranio	0 (0.0)	0 (0.0)	
TSH-oma	0 (0.0)	5 (2.3)	.158
Tumor size, N (%)			
Micro	19 (24.1)	28 (13.1)	
Macro	60 (75.9)	185 (86.9)	
Giant	0 (0.0)	0 (0.0)	**.031**
Cavernous sinus invasion, N (%)	12 (15.2)	52 (24.5)	.152
Time since diagnosis in years, median (IQR)	1.1 (0.2-5.2)	0.6 (0.1-3.8)	.199
Prior treatments, N (%)			
No treatment	40 (50.6)	127 (59.6)	.184
Medication	31 (39.2)	61 (28.6)	.090
Surgery	11 (13.9)	36 (16.9)	.595
Radiotherapy	0 (0.0)	3 (1.4)	.566
Apoplexy, N (%)	4 (5.1)	12 (5.6)	1.000
Preoperative endocrine status, N (%)			
No deficits	40 (50.6)	108 (50.7)	
Single hormone deficiency	15 (19.0)	27 (12.7)	
Single hormone deficiency + DI	0 (0.0)	0 (0.0)	
Multiple hormone deficiencies	24 (30.4)	78 (36.6)	
Multiple hormone deficiencies + DI	0 (0.0)	0 (0.0)	

Supplementary table 4. Baseline characteristics of patients with a pituitary tumor (continued)

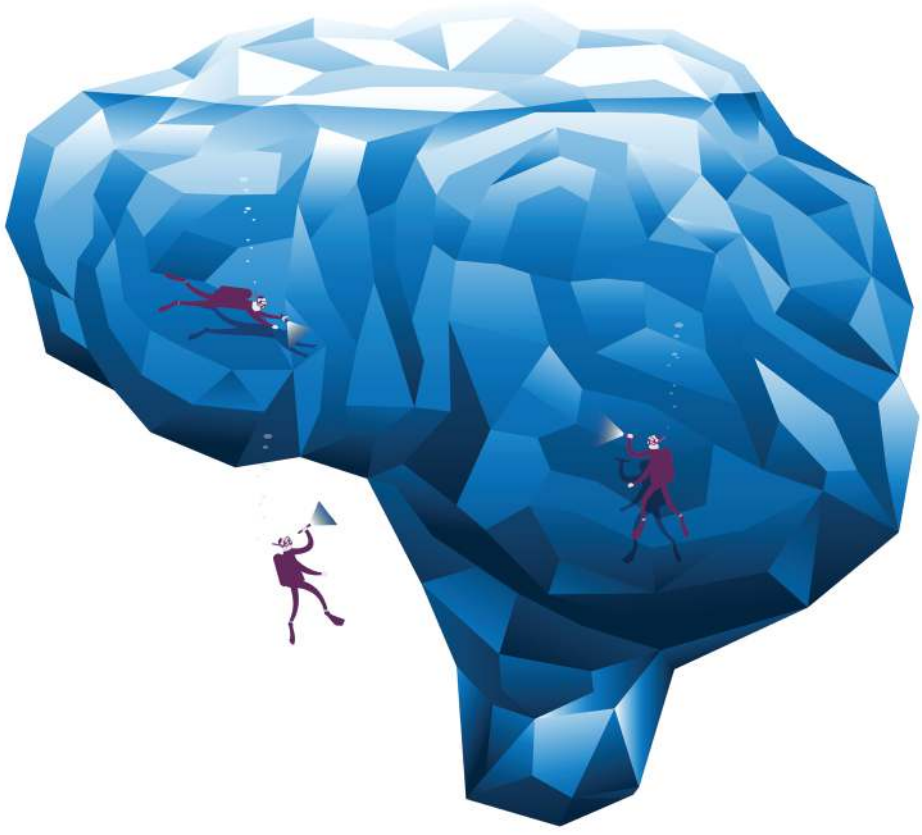
	Fast-track (N=79)	Selection of historic cohort (N=213)	P-value
DI alone	0 (0.0)	0 (0.0)	.327
Preoperative visual status, N (%)			
No deficits	51 (64.6)	106 (54.9)	.102
Cranial nerve palsy, N (%)	2 (2.5)	4 (1.9)	.661

N (number), SD (standard deviation), IQR (interquartile range), NFA (non-functioning pituitary adenoma), ACRO (acromegaly), CD (Cushing's disease), PRL (prolactinoma), RCC (Rathke's cleft cyst), Cranio (craniopharyngioma), TSH (thyroid-stimulating hormone)
Due to rounding, not all percentages of the categorical variables add up to 100%

Supplementary table 5. Surgical outcomes and costs among 292 surgically treated patients with a pituitary tumor stratified according to cohort

	Fast-track (N=79)	Selection of historic cohort (N=213)	p-value
Length of stay, mean (SD)	3.0 (1.9)	5.1 (3.2)	**<.001**
Complications			
Number of readmitted patients, N (%)	13 (16.5)	22 (10.3)	.160
Length of stay of all readmissions, mean (SD)	3.6 (2.7)	4.5 (3.6)	.605
Any complication, N (%)	38 (48.1)	118 (55.4)	.292
Transient DI, N (%)	20 (25.3)	31 (14.6)	**.036**
Permanent DI, N (%)	3 (3.8)	11 (5.2)	.765
Delayed hyponatremia, N (%)	9 (11.4)	24 (11.3)	1.000
New onset pituitary deficiency, N (%)	4 (5.1)	18 (8.5)	.456
Postoperative CSF leak, N (%)	3 (3.8)	15 (7.1)	.416
Epistaxis, N (%)	10 (12.7)	22 (10.3)	.536
Postoperative intracranial haemorrhage, N (%)	0 (0.0)	1 (0.5)	1.000
Hospital costs (in euro's)			
Admission, mean (SD)	7249 (1318)	8660 (2203)	**<0.001**
Readmission, mean (SD)	438 (1221)	338 (1256)	.541
Emergency room visits, mean (SD)	42 (108)	26 (84)	.188
Outpatient clinic visits, mean (SD)	55 (102)	346 (0)	**<0.001**
E-mail contacts, mean (SD)	626 (284)	0 (0)	**<0.001**
Telephone contacts, mean (SD)	242 (184)	0 (0)	**<0.001**
Total hospital costs, mean (SD)	8652 (1748)	9266 (2540)	**.021**

N (number), SD (standard deviation), IQR (interquartile range), DI (diabetes insipidus), CSF (cerebrospinal fluid)
(bold) p<0.05



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How non-functioning pituitary adenomas can affect health-related quality of life: a conceptual model and literature review

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ABSTRACT

After treatment for a non-functioning pituitary adenoma (NFA) health-related quality of life (HRQoL) improves considerably. However, the literature about the normalization of HRQoL after treatment is inconclusive. Some researchers described a persistently decreased HRQoL compared to reference data, while others did not. Considering this variety in observed HRQoL outcomes, the aim of the present review was to provide a literature overview of health outcomes in patients with an NFA, using a conceptual HRQoL model. A concrete conceptualization of the health outcomes of patients with an NFA can be helpful to understand the observed variety in HRQoL outcomes and to improve clinical care and guidance of these patients. For this conceptualization, the Wilson and Cleary model was used. This model has a biopsychosocial character and has been validated in several patient populations. In the present review, health outcomes of patients with an NFA were described at each stage of the model e.g. biological and physiological variables, symptom status, functional status, general health perceptions and overall HRQoL. The Wilson–Cleary model elucidates that elements at each stage of the model can contribute to the impairment in HRQoL of patients with an NFA, which explains the reported variety in the literature. Furthermore, by applying the model, potential interventions targeting these elements can be identified. While optimal biomedical treatment has always been the focus, it is clearly not sufficient for good HRQoL in patients with an NFA. Further improvement of HRQoL should be supported by a pituitary specific care trajectory, including psychosocial care (e.g. self-management training), to beneficially affect characteristics of the patient and the (healthcare) environment, with the utmost goal to optimize HRQoL in patients after treatment.

BACKGROUND

Pituitary adenomas are benign tumors, with an estimated prevalence of 78–94 cases per 100,000 individuals, and an incidence of four cases per 100,000 individuals [1]. Ten percent of all pituitary adenomas are non-functional adenomas (NFAs) [2]. NFAs commonly occur during adulthood with a median age at diagnosis of 51.5 years (range 19–79 years) [3]. At time of diagnosis, tumor size is relatively large compared to functioning tumors, since hormone excesses are absent, and therefore mainly manifest via compression of surrounding tissues, predominantly compression on the optic chiasm. Primary treatment consists of surgical resection of the tumor to relieve mass effects. Conventional radiotherapy may be used in case of tumor growth or when surgical resection is not an option due to the localization [2]. After treatment, patient reported health-related quality of life (HRQoL) improves considerably (Fig. 1) [4], however, the evidence about normalization of HRQoL is inconclusive. While some researchers described a persistent decreased HRQoL compared to healthy controls and reference data [5, 6], others did not [7, 8].

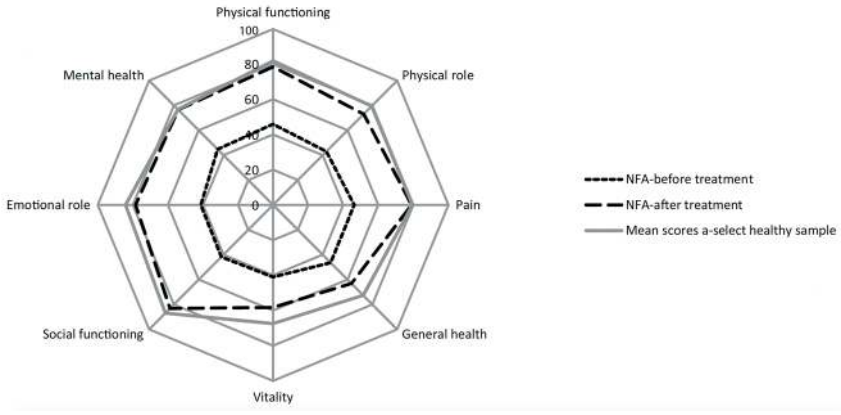

Figure 1. HRQoL scores of patients with an NFA (Short Form 36 scores), figure derived from [4]. Higher scores indicate better HRQoL

Furthermore, the cause of the persistent impairments in HRQoL seems to be multifactorial and several contributing factors have been reported, including visual function, type of surgery (craniotomy vs. transsphenoidal), hypopituitarism, and the need for hormone replacement therapy [4].

The aim of the present review was to provide an overview of health outcomes of patients with an NFA using a conceptual HRQoL model i.e. the Wilson and Cleary model [9]. A concrete conceptualization of the health outcomes of patients with an NFA will be help-

ful in the understanding of the observed variety in HRQoL outcomes, the identification of potential interventions, and can be used for further improvement of the clinical care trajectory and somatic and psychosocial guidance of these patients.

Health-related quality of life

Over the past decade, alongside the improved treatment options, the scope of relevant outcomes has expanded from primary outcomes, such as mortality and morbidity, towards the evaluation of functional status and HRQoL. Although it is established that HRQoL should cover physical-, psychological-, and social well-being (in accordance with the biopsychosocial model) [10], a single concrete definition of HRQoL is lacking, which results in major challenges for the evaluation and interpretation of HRQoL [11]. A commonly used definition is that HRQoL is "the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient" [12]. For the assessment of HRQoL several measures have been developed and validated, and it is recommended that a generic measure (covering general HRQoL domains) is combined with a disease-specific measure (covering HRQoL aspects relevant for a specific disease) [11]. Unfortunately, a disease-specific HRQoL questionnaire for NFA is currently lacking.

THE WILSON–CLEARY MODEL OF HRQOL

A model that is frequently used to conceptualize HRQoL, which validity is supported by empirical evidence over the years [13], and has been widely applied to different patient populations [14–16], is the conceptual model proposed by Wilson and Cleary (1995) [9]. This model establishes the biopsychosocial model [10] by integrating the clinical paradigm (i.e. the biomedical paradigm), and the quality of life model (i.e. social science paradigm). Where the biomedical paradigm focusses on biological, physiological, and clinical outcomes, the social science paradigm focusses on dimensions of functioning and overall wellbeing. The Wilson and Cleary model states that health can be considered as a continuum of increasing biological, psychological and social complexity, with pure biological measures on the left side of the model, and measures of general health perceptions on the right (Fig. 2). It clarifies the proposed dominant causal relationships (bold) and mediating factors. From left to right, it goes from cell-level to the individual, to the interaction of the individual in its social context. The arrows used in Fig. 2 do not imply that there are no reciprocal relations, just as the absence of arrows does not imply that there are no such relationships. Furthermore, it should be noted that the relation between symptom status and biological and physiological variables is rather complex. In other words, biological and physiological variables can be profoundly abnormal with-

out the patient perceiving symptoms, or the other way around. In the next paragraphs the Wilson and Cleary model will be elaborated for patients with an NFA.

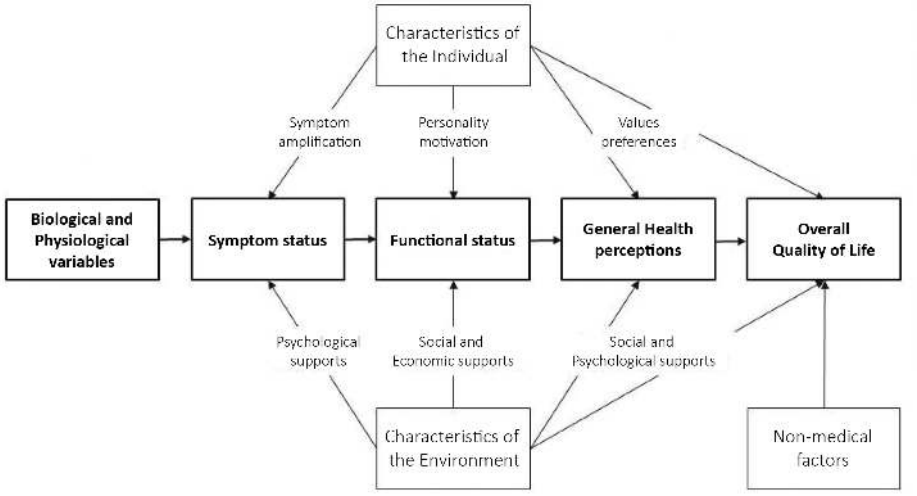

Figure 2. Wilson–Cleary model of HRQoL [9]. Biological and physiological variables: function of cell, organs, and organ systems e.g. diagnoses, laboratory values, measures of physiological function, and physical examination findings. Symptom status: a patient's perception of an abnormal physical, emotional or cognitive state.
Functional status: ability of the individual to perform particular tasks. The main domains of functioning are physical functioning, social functioning, role function, and psychological function. General health perceptions: subjective rating of health, and represent and integrates all the previous health concepts.

Biological and physiological variables

Pituitary dysfunction may occur in all pituitary adenomas due to a variety of causes e.g. mass effect of the tumor, surgical treatment, or radiotherapy. Severe hormone deficits, (pan)hypopituitarism, is diagnosed by blood sampling for gonadotropin, thyroid stimulating hormone, and prolactin, and dynamic stimulation tests for adrenocorticotrope hormone (ACTH), cortisol and growth hormone, and measurement of urine production for vasopressin deficiency [17]. Mild hypopituitarism can be difficult to diagnose, due to individual set-points, hormone sensitivity, and circadian variability. Nevertheless, also mild hypopituitarism may affect end organ function. Therefore, the majority of the patients with hypopituitarism need lifelong hormone replacement therapy, aiming to mimic the physiology of end organ hormones as good as possible. Replacement therapy for adrenal insufficiency is of particular relevance, since too low cortisol levels can lead to a potentially life threatening acute adrenal crisis (i.e. Addison's crisis). Contrary to this, when replacement therapy exceeds supra-physiological cortisol levels, it can result in Cushing's syndrome like symptoms. Therefore, adequate replacement therapy in adrenal insufficiency as well as, adaptation of the dose during stress, is crucial [18]. In clinical practice, endocrine diseases are followed by evaluating clinical signs and hor-

mone measurements. Serum, plasma, salivary, or urinary hormone concentrations are currently the best tools for clinicians to classify disease status in (chronic) care. It has been acknowledged that the currently available physiological measures do not always reliably represent the clinical situation. The assessment of cortisol levels in scalp hair is a relatively new method to assess cortisol exposure over longer time periods and has been evaluated in patients with primary and secondary adrenal insufficiency [19]. Furthermore, it was examined whether hair cortisol levels correlated with patient reported HRQoL, and it appeared that HRQoL correlates slightly with hair cortisol levels [20]. These results are not surprising, considering the Wilson–Cleary model with biological and physiological variables on the one end, and HRQoL on the other end with patient- and environmental characteristics influencing this continuum. These observations support the idea that HRQoL is not only determined by biological disease status, but by a multidimensional underlying mechanism.

Symptom status

When changes in biological and physiological variables occur, an individual might perceive this via symptoms. Symptom status is defined by Wilson and Cleary as a patient's perception of an abnormal physical, emotional, or cognitive state [9]. As was mentioned previously, NFAs are usually relatively large at time of diagnosis, giving either compression on the pituitary or the optic chiasm, resulting in headaches, hypopituitarism, visual loss, third nerve palsy, pituitary apoplexy, tiredness, decreased libido, and sometimes even galactorrhea [3]. These symptoms tend to improve after surgery, however, extensive longitudinal literature of perioperative HRQoL is limited. Wolf et al. demonstrated that headache severity and vision related HRQoL improved significantly up to 6 months after transsphenoidal surgery [21]. Furthermore, patients may suffer from impaired olfactory function as a complication of the transsphenoidal surgery. Little et al. showed an initial decrease of sinonasal HRQoL after (both microscopic and endoscopic) surgery, which improved at later follow-up [22]. Wang et al. demonstrated a decrease in the ability to detect odors up to 4 months after surgery [23]. Although symptoms improve after biomedical treatment, persistent symptoms are reported after long-term remission. During focus group conversations with patients in a chronic state of their disease, patients reported physical pain, sleeping problems, changes in physical appearance (i.e. weight changes), cognitive problems (i.e. problems in concentration, short-term memory, and executive functioning), decreased libido, physical sexual dysfunction, depressive symptoms, melancholy, mood swings, worries, increased sensitivity to stress, fear of tumor recurrence, decreased self-esteem, loneliness, anger, difficulties in communication about the disease, and a lack of empathy from the environment. The reported sleep problems were characterized by sleeping in blocks of 2–3 h [24]. Sleep characteristics have also been quantitatively examined, showing sleep alterations in patients treated

for an NFA, including decreased subjective sleep quality, disturbed distribution of sleep stages and disturbances in diurnal rhythmicity [6, 25]. Although it can be postulated that these sleeping problems can be explained by imperfections in hormone replacement therapy (i.e. hydrocortisone replacement) [26], there is increasing evidence that these problems are caused by hypothalamic dysfunction [27]. Joustra et al. examined sleep characteristics in patients treated for an NFA and patients with primary adrenal insufficiency treated with hydrocortisone replacement therapy and demonstrated that patients with primary adrenal insufficiency have normal sleep characteristics in contrast to patients with an NFA. These results provided evidence that sleeping problems might be caused by hypothalamic dysfunction [28]. Furthermore, sleep disturbances and daytime sleepiness were also associated with increased impairment in HRQoL [6, 29].

Functional status

This refers to the ability of the patient to perform particular defined tasks [9]. The symptom status largely determines whether patients perceive issues in their functioning. In accordance, the previously described symptoms result into impairments in several functional domains. During the focus group conversations patients reported problems in physical functioning, cognitive functioning, sexual functioning, psychological functioning, and social functioning. For instance, work related problems, such as diminished ability to function, to cooperate and to concentrate. As a result patients lost their job or were (partly) rejected [24]. The cognitive complaints reported by patients have also been examined through neuropsychological tests. Previous studies demonstrated that patients treated for NFA had a worse performance on verbal memory and executive functioning compared to healthy matched controls and references values [30, 31]. Interestingly, some reported the negative effect of additional radiotherapy on cognitive functioning [17, 30, 32], while others did not [33, 34].

Characteristics of the individual

These individual characteristics (or patient characteristics) as formulated in the Wilson–Cleary model cover factors such as personality, motivation, values, and preferences. Patients' preferences or values refer to the value patients attach to a particular consequence of their disease. For instance, a patient can experience a symptom as a burden, while the same symptom does not bother another patient. The way patients perceive their illness and its treatment are also known as 'illness perceptions' and 'beliefs about medication'.

Illness perceptions and beliefs about medication

Illness perceptions and beliefs about medication are formulated by the extended Common-Sense Model of Self-Regulation (CSM) and can be categorized into values and

preference in the Wilson–Cleary model. These preferences and values play an important role at several points of the Wilson–Cleary model and are particularly important in the understanding of general health perceptions and overall HRQoL, which is in accordance with the extended CSM, since this model also states that illness perceptions and beliefs about medication correlate with HRQoL [35]. During the focus group conversations patients reported negative illness perceptions, such as the chronic time course of their disease, and concerns about potential side effects of their medication (i.e. hydrocortisone) [24].

Coping strategies

Furthermore, following the extended CSM, illness perceptions and beliefs about medicines influence coping behavior. During the focus group conversations patients reported less efficient coping strategies, such as withdrawal, and overdoing activities [24]. Coping strategies were also quantitatively assessed by Tiemensma et al. as they demonstrated that patients with pituitary disease use less effective coping strategies compared to an a-select sample of the Dutch population, including performing less active coping, seeking less social support, and using more avoidant coping strategies [36].

Personality

A changed personality, another characteristic of the individual, is considered a problem by patients. Sievers et al. quantitatively examined personality traits in patients with an NFA, and demonstrated that compared to a normal population control group, patients with an NFA reported more neuroticism, social desirability, anticipatory worries, pessimism, fear of uncertainty, fatigability, and asthenia [37]. Individual demographic characteristics have also been found to play a role in HRQoL in patients with an NFA, since female sex and older age were found to negatively influence HRQoL [5, 7, 33].

Characteristics of the environment

Economical-, psychological-, and social support are environmental characteristics. The latter two play an important role in general health perception and overall quality of life. During the focus group conversations patients reported unmet needs regarding care and guidance they had perceived. For instance, they would have received more information about adverse effects of medication, physical-, psychological-, and cognitive complaints and issues regarding sexual functioning. Furthermore, they would have preferred more recognition for certain complaints. These unmet needs can be categorized into characteristics of the individual (i.e. patient characteristics), since they can be influenced by personal factors. On the other hand, unmet needs can also be influenced by characteristics of the environment (e.g. availability of healthcare facilities). For example, patients reported dissatisfaction with other aspects of medical care i.e. stress-management training, lifestyle recommendations, physiotherapists, dietitians, medical

sports experts, and psychologists. For instance, these unmet needs can be caused by limitations in economic support or inadequate referrals. Some types of support (e.g. psychological-, social support) are less well developed for a rare disease such as pituitary disease compared to more prevalent (chronic) diseases.

Tools to meet unmet healthcare needs

Recently, a disease-specific patient reported outcome measure (PROM) was developed and validated by our research group, that assesses to which extent patients with pituitary disease are bothered by certain complaints, as well as their needs for support from healthcare professionals, i.e. the *Leiden Bother and Needs Questionnaire for Pituitary disease* (*LBNQ-Pituitary)*). This PROM covers five subscales i.e. mood problems, negative illness perceptions, issues in sexual functioning, physical and cognitive complaints, issues in social functioning [38]. This PROM can help healthcare professionals to address the unmet needs experienced by patients.

Besides professional environmental factors (i.e. healthcare facilities), there are also personal environmental factors. Often the single most important person in a patient's social network is their spouse or partner. Focus group conversations with partners of patients with a pituitary condition revealed that partners were worried about the complaints of the pituitary disease, had negative beliefs about medication, and perceived coping challenges, relationship issues, social issues, and unmet needs regarding care [39]. These observations clearly demonstrate that chronic care for patients with pituitary disease is not limited to just the patient. In order to support patients and their partners in coping with the consequences of the pituitary disease, a self-management program was developed for patients with pituitary disease and their potential partners i.e. *Patient and Partner Education Program for Pituitary disease* (*PPEP-Pituitary*). This program aims to (at least partly) fulfil the unmet needs regarding support for psychological and social issues. PPEP-Pituitary was based on a standardized Patient and Partner Education Program initially developed for patients (and partners) with Parkinson's disease [40]. A multicenter randomized-controlled trial revealed that patients reported more self-efficacy after PPEP-Pituitary which was still present after 6 months. Self-efficacy is described in the 'Social Cognitive Theory' of Bandura [41] and is defined as the person's beliefs in his or her own capabilities and skills to perform a certain action, in a certain situation. Following this theory, behavior is directly influenced by goals and self-efficacy beliefs. In accordance, several studies showed that self-efficacy beliefs influences self-management behavior [42, 43]. Patients also reported to be less bothered by mood problems directly after PPEP-Pituitary, however this returned to baseline levels 6 months later. Partners reported an increase in vitality, a decrease in depressive symptoms and an increase in treatment control after PPEP-Pituitary. This persisted at follow-up after 6 months [44]. It can be

postulated that offering this program as standard clinical care will improve the quality of the (healthcare) environment, and ultimately the patient and partner reported HRQoL.

General health perceptions and HRQoL

In accordance to the Wilson–Cleary model, the domains described in the preceding paragraphs all contribute to patient perceived HRQoL. This increase in interest in HRQoL has led to an increase in the number of HRQoL studies in patients with an NFA and these studies show some diversity regarding HRQoL outcomes. Johnson and colleagues reported HRQoL impairments in patients with an untreated NFA, especially in physical and mental functioning during active disease [45]. Some confirmed this decreased HRQoL in patients treated for an NFA compared to reference values and healthy controls [5, 6], however others did not report any differences [7, 8, 46]. Furthermore, some studies demonstrated the negative effect of tumor recurrence [7], hypopituitarism [5, 47] and radiotherapy [48] on HRQoL, while other did not (pituitary deficiency [46], radiotherapy [33, 46]). In addition, no differences in HRQoL were found between patients surgically treated for an NFA and patients treated with mastoid surgery [48]. No differences were found while comparing patients with growth hormone deficiency (GHD) due to an NFA compared to traumatic brain injury [49, 50]. Male patients with GHD due to an NFA, compared to patients with GHD due to a craniopharyngioma, reported a better HRQoL, whereas female patients with an NFA reported a worse HRQoL [51]. Intervention studies reported that HRQoL of patients with an NFA improved after transsphenoidal surgery [47, 52]. Furthermore, patients treated with craniotomy reported more HRQoL impairments compared to patients treated with transsphenoidal surgery [8]. There have been several systematic reviews on endoscopic and microscopic transsphenoidal surgery, describing comparable or better clinical results after endoscopic surgery [53]. Furthermore, a qualitative study performed by Lwu et al. described that patients perceived less burden after endoscopic surgery compared to microscopic surgery [54]. However, there is limited knowledge about the long-term outcomes of endoscopic vs. microscopic surgery in terms of HRQoL. Intervention studies about the effect of growth hormone replacement therapy in patients treated for NFA with GHD all reported a positive effect on HRQoL [49–51, 55–57]. On the other hand, a cross-sectional study of Capatina et al. demonstrated that non-replaced GHD was an independent predictor of a better score in bodily pain, general health perception and energy/vitality [7].

CONCLUSION

The present review emphasizes that although patients may be in a stable medical condition, health issues are present at each level of the Wilson–Cleary model (Fig. 3). Applica-

tion of the Wilson–Cleary model to patients with an NFA enables to observe that persistent impairments in HRQoL might be explained by issues at each stage of this model. This also provides further insight into why there is such a variety in clinical outcomes, and why some patients experience severe problems, while others experience either no or only mild problems. This emphasizes that improvement in overall HRQoL in patients with pituitary disease requires optimal biomedical treatment initiating a cascade of improvement in health outcomes starting with a better symptom status. Nevertheless, this model also clarifies that besides the currently available biomedical interventions (i.e. surgery, radiotherapy, hormone replacement therapy) targeting biological and physiological variables, interventions are needed that pay attention to other (psychosocial) elements of the model e.g. cognitive functioning, sexuality/intimacy, psychological well-being, social functioning, coping behavior, self-efficacy beliefs, illness perceptions, medication beliefs, quality of the partner relationship, and the social network/ support. Therefore, further improvement of HRQoL should be supported by a pituitary specific care trajectory, including psychosocial care (e.g. self-management training), in order to beneficially affect characteristics of the patient and the (healthcare) environment, with the utmost goal to optimize HRQoL in patients after treatment for an NFA.

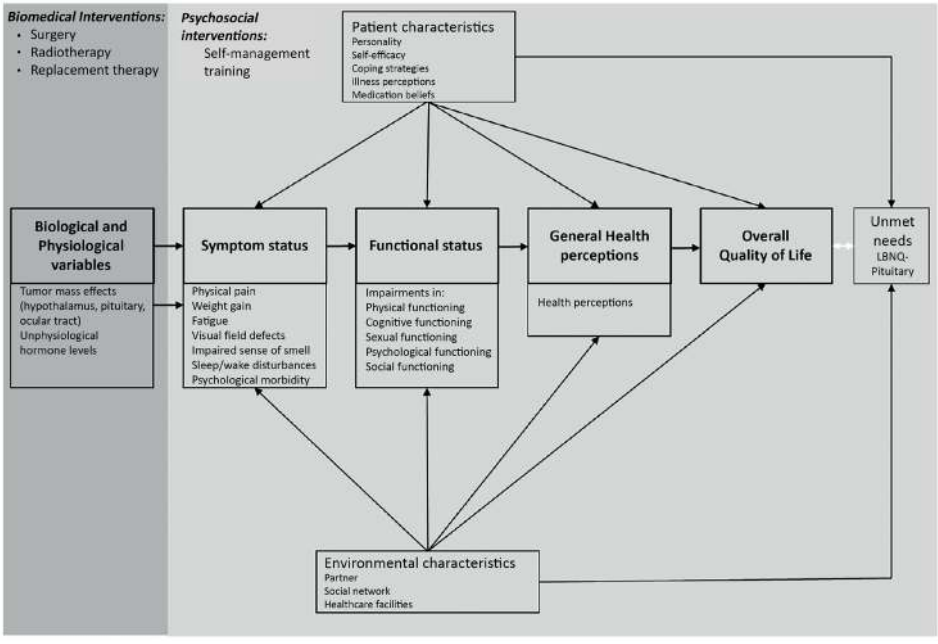

FIgure 3. Wilson–Cleary model of HRQoL elaborated for NFA

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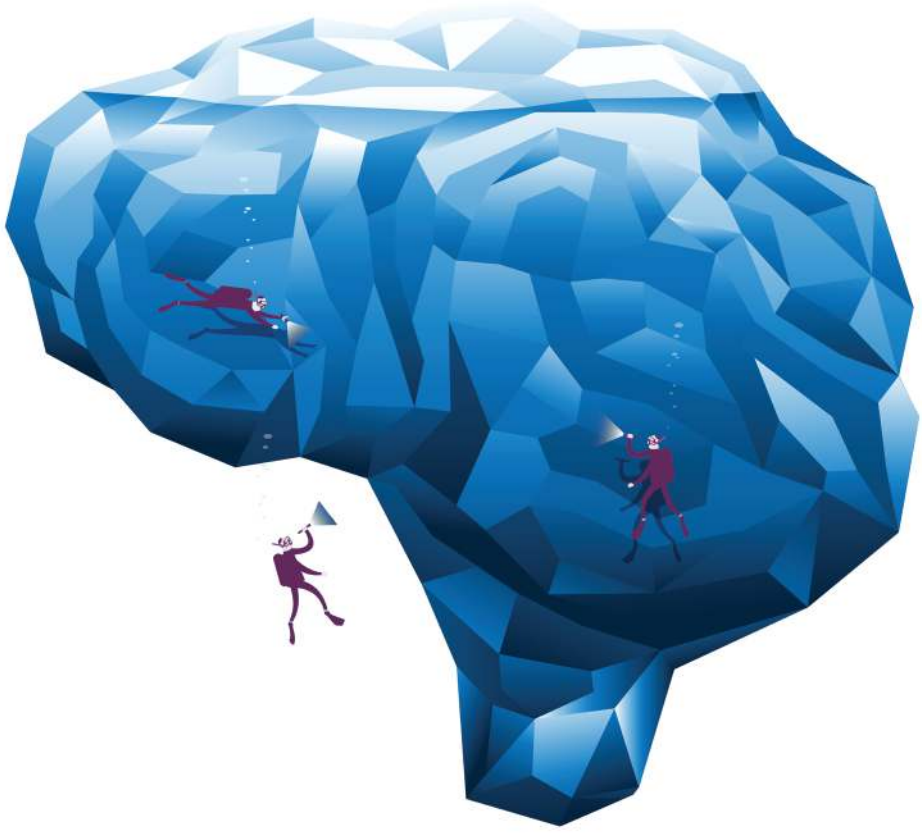

8

Work disability and its determinants in patients with pituitary tumor-related disease

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ABSTRACT

Introduction

Pituitary tumors may have a considerable impact on patients' functional status, including paid employment, yet research in this area is sparse.

Objective

To describe work disability and its determinants in patients treated for a pituitary tumor.

Methods

Cross-sectional study including patients treated for a pituitary tumor in the working age (18–65 years), who completed five validated questionnaires assessing work disability [Short Form-Health and Labor Questionnaire, Work Role Functioning Questionnaire 2.0 (WRFQ)], health-related quality of life (HRQoL) and utility (Short Form-36, EuroQoL) and disease burden (Leiden Bother and Needs Questionnaire-Pituitary). Additional data were extracted from the medical records (age, gender, tumor type, treatment, date of diagnosis) and self-reports (marital status, education, endocrine status). Associations of disease-specific and sociodemographic characteristics, HRQoL, and disease burden with (not) having a paid job were examined through multivariate logistic regression.

Results

We included 241 patients (61% female, median age 53 years, median time since diagnosis 11 years), of whom 68 (28%) were without a paid job. Patients who had acromegaly, Cushing's disease, (pan)hypopituitarism, radiotherapy, were single, less educated, lower HRQoL, and increased disease burden were more often without a paid job ($p < 0.05$). Among those with paid jobs, 41% reported health-related absenteeism in the previous year. The three work incapacitating problems reported by the largest proportion of patients were within the mental and social domain (WRFQ).

Conclusion

Work disability among patients treated for a pituitary tumor is substantial. As impact on social functioning is high, it is strongly advised to incorporate work disability during clinical guidance of patients.

INTRODUCTION

Even long after multimodality treatment of pituitary tumors, many patients report impairments in health-related quality of life (HRQoL) [1–3]. An important, but relatively underinvestigated domain of HRQoL is the impact of pituitary tumors on societal participation, with special regard to having or maintaining a paid job.

Our recent focus group study in patients addressing the patient's perspective on disease burden and needs for support indicated that chronic pituitary conditions have a significant impact on work and financial status [4]. In that qualitative study, several patients expressed experiencing a lack of understanding by employers, medical specialists, and occupational physicians. Some patients feared losing their jobs and therefore refrained from informing their employers/ co-workers about their disease or from mentioning it during job interviews. Furthermore, a number of patients reported not being able to continue their jobs because they could not perform the same tasks they used to do [4].

Quantitative studies on the extent of work disability in terms of having a paid job or not in this disease area are scarce. Rates of patients without a paid job vary between 36 and 74% [5–9]; however, these studies report a variety of pituitary conditions [7–9], and/or do not exclusively comprise of patients of working age [5, 6, 8, 9], therefore affecting these rates. Determinants of having a paid job or not have not been studied extensively.

Work disability, however, not only comprises having paid employment or not; sick leave (absenteeism) or not being productive while at work (presenteeism, in some countries defined as hidden absenteeism) are also important aspects. Previous studies have reported absenteeism rates varying between 19.8 and 40.2 days per year [5, 10–12], while presenteeism and perceived problems at work have never been addressed in patients with pituitary tumors. More insight into the perceived problems may help patients and healthcare providers, including occupational physicians, in guiding patients.

The objectives of this current study were to investigate (1) the rates of patients with and without a paid job treated for a pituitary tumor and of working age; (2) determinants of not having a paid job in this group; (3) loss of productivity in patients with a paid job defined as absenteeism and presenteeism; and (4) patients' perceived problems at work.

PATIENTS AND METHODS

Study design

This cross-sectional survey study among a cohort of patients treated for a pituitary tumor in a chronic care setting was performed between September 2016 and March 2017 at a tertiary referral center, the Leiden University Medical Center (LUMC) in the Netherlands. Institutional medical ethical review board approval was obtained prior to the start of the study (p12.067).

Study population

Patients included in this study were part of a larger cross-sectional cohort (N = 400) on long-term outcomes among patients treated for a pituitary tumor, including all patients diagnosed with a pituitary tumor (non-functioning pituitary adenoma (NFPA), acromegaly (ACRO), Cushing's disease (CD), prolactinoma (PRL) or Rathke's cleft cyst (RCC)), with sufficient Dutch language skills, more than 6 months of treatment, and currently under active follow-up. A subset of this study, patients between the ages of 18 and 65, was eligible for the present study. Patients were identified through the hospital registries. Diagnosis was confirmed prior to invitation by means of review of the medical record by DJL. Eligible patients were invited by a written letter to participate in this study; after written informed consent was obtained, a questionnaire was sent to all participants. In case of non-response, patients were re-approached by regular mail or by telephone.

Assessments

A set of 5 validated questionnaires was administered, including measures on work status and productivity [Short-Form-Health and Labor Questionnaire (SF-HLQ)], work-related difficulties [work role functioning questionnaire 2.0 (WRFQ)], HRQoL and utility [Short Form-36 (SF-36) and EuroQoL (EQ-5D)], and perceived bother and needs for support [Leiden Bother and Needs for Support Questionnaire for pituitary patients (LBNQ-Pituitary)], and questions on current medication usage, as well as visits to an occupational physician. The questionnaires could be filled in either digitally or on paper, both shown to provide equivalent results [13].

Disease-specific and sociodemographic characteristics

The disease-specific and sociodemographic characteristics were collected from the digital medical records (tumor type, date of diagnosis) and self-reports (educational level, marital status, endocrine status). This included age, sex, and hormonal status (with hypopituitarism defined as replacement of ≥ 1 endocrine deficits, and panhypopituitarism as ≥ 2 plus hydrocortisone replacement). Treatment was categorized arbitrarily into 4 categories: (1) no treatment (including patients with discontinued medication),

(2) ongoing medical (tumor) treatment (including those with prior surgery and/or radiotherapy), (3) postoperative patients (excluding ongoing medical treatment and irradiated patients), (4) a history of radiotherapy (including prior surgery and/or discontinued medication). The categorization among patients with multimodality treatment was done according to the supposed largest ongoing impact in the current chronic setting: (1) ongoing medication (greatest impact), (2) radiotherapy, (3) past surgical intervention, (4) no therapy or temporary medical treatment (least impact). A detailed description of the treatment algorithm, which was in line with existing guidelines, has previously been published [14–16]. Level of education was categorized into low, intermediate or high, based on the guidelines of Statistics Netherlands (CBS) [17], which correspond with the International Standard Classification of Education Fields of Training and Education 2013 of the UNESCO [18].

Work status

Work status was assessed through two questionnaires: a selection of the *SF-HLQ* was used to obtain information about employment, absenteeism and presenteeism over the past 12 months. Employment was divided into two categories: (1) having a paid job, which included part-time paid jobs, some combined with other duties such as education, taking care of the household or receiving a work disability pension; (2) not having a paid job, including engagement in any non-paid duties, education, taking care of the household, voluntary and involuntary unemployment, or early pension. The questionnaire did not differentiate whether voluntary and involuntary unemployment/early pension was due to the illness or due to other reasons. Absenteeism was defined as the number of days on sick leave over the past 12 months, presenteeism as reduced productivity while at work, and assessed by means of a question on the self-perceived performance at work on a scale of 1–10 [19].

The *WRFQ* assesses work disabilities and consists of 27 questions, divided into four subcategories including: work scheduling and output demands (WSOD), physical demands (PD), mental & social demands (MSD), and flexibility demands (FD) from which an index score was calculated. Items were scored on a 5-point rating scale: (1) all the time (100%), (2) most of the time, (3) half of the time (50%), (4) some of the time, (5) completely not (0%). All items included the option “not applicable to my job” [20]. Higher scores indicate less self-perceived work disabilities.

Health-related quality of life and utility

The *SF-36* is a 36-item questionnaire which covers eight domains: physical function, physical role, bodily pain, general health, vitality, social function, emotional role, and

mental health. These subscales range from 0 to 100, from which the physical and mental component score can be calculated. Higher scores indicate better HRQoL [21].

The *EQ-5D* (5-level) consists of 5 domains: mobility, self-care, usual activities, pain/ discomfort, and anxiety/ depression, from which utility (range 0–1) can be calculated (EQ-5D index). The EQ-5D also includes a visual analog scale (VAS), which records self-reported health status (range 0–100). Higher scores indicate a better perceived health status [22].

Perceived bother and needs for support

The LBNQ-Pituitary is a disease-specific questionnaire, which was developed through focus group interviews with patients [23]. For this study, the LBNQ-Pituitary consisted of 26 items divided into five subscales: mood problems, negative illness perceptions, issues in sexual functioning, physical and cognitive complaints, and issues in social functioning, from which an index score can be calculated (range 0–100). A detailed description of how the items are scored has been previously published. Higher scores indicate a greater bother [23]. For this study we added a question on the usage of and number of visits to an occupational physician.

Statistical analysis

Data entry and control was performed through an online survey platform. All statistical analyses were performed with SPSS 23.0 software (IBM SPSS Inc., Armonk, USA). Numerical variables are presented as means and standard deviations (SD) or medians with interquartile ranges (IQR), nominal variables as frequencies with percentages.

For the univariate analysis, a Chi square test was performed for categorical variables, student's *T* test or Mann–Whitney *U* tests for numerical variables where applicable. Logistic regression analysis was used to determine the relationship between work status (paid job/no paid job) as a dependent factor and all possible contributing factors (i.e., disease-specific characteristics, sociodemographic characteristics, HRQoL). To control for confounding, variables associated with both the determinant and the outcome and not in the causal pathway of the relationship of interest were used as covariates in the multivariate analysis [24]. All determinants were corrected for age and gender, depending on the determinant also for tumor type, treatment and/or QoL. For the work disability analysis, variables were compared between tumor types via AN(C)OVA, corrected for age and gender where applicable. For all analyses, the level of significance was set at $p < 0.05$ (two-sided) and associations are expressed as odds ratios (ORs) with the corresponding 95% confidence interval (CI). Missing data on the questionnaires was handled by complete case analysis due to the low amount of missings (< 5%).

RESULTS

Study population

A total of 1667 patients were identified from the hospital registry. After exclusion of ineligible patients, letters were sent to 772 patients (including patients > 65 years), enrolling a total of 400 (51.8%) patients of whom 241 (60.2%) patients between 18 and 65 years of age (figure 1).

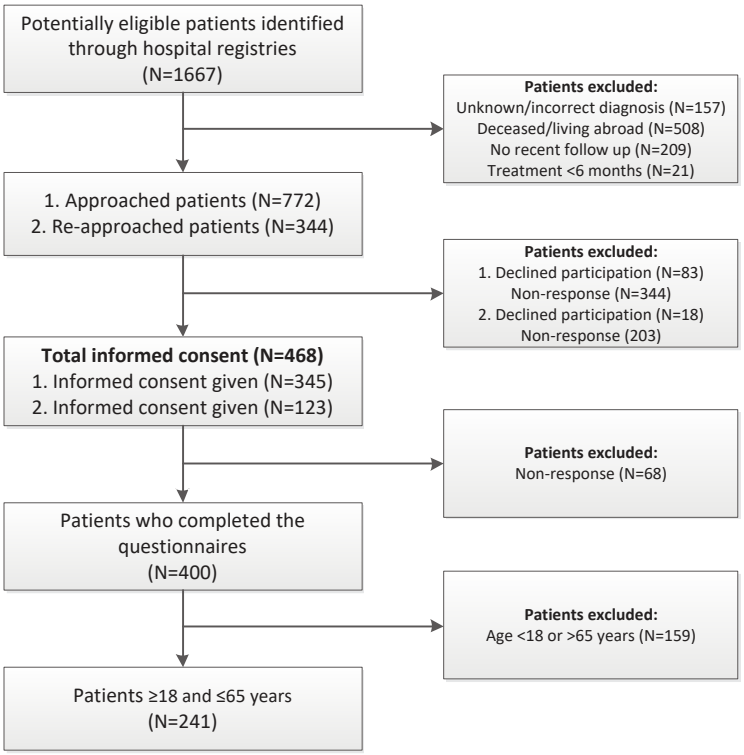

Figure 1. Flow chart of in-/exclusion of patients with a pituitary tumor

Patient characteristics

The 241 patients (61% female) included in the study had a median age of 53.0 (IQR 45.0–59.5) years. Median time since diagnosis was 11.4 (IQR 5.2–20.5) years and almost half of the patients were highly educated (48%). Tumor type was: (1) NFPA in 65 patients (27%), (2) ACRO in 41 patients (17%), (3) CD in 32 patients (13%), (4) PRL in 97 patients (40%), and (5) RCC in 6 patients (3%). Many patients had undergone multimodality treatment, with most patients in the surgical group (40%), followed by ongoing medical therapy (31%). (Pan)hypopituitarism was present in 129 (54%) of patients (table 1).

Table 1. Characteristics of 241 patients with a pituitary tumor and of working age and comparisons between those working and not working

	Total (N = 241)	No paid job (N = 68)	Paid job (N = 173)	P-value
Sociodemographic characteristics				
Female gender, N (%)	147 (61.0)	44 (32.0)	103 (68.0)	0.459
Age in years, median (IQR)	53.0 (45.0–59.5)	54.7 (45.6–60.7)	52.4 (44.9–59.2)	0.114
Marital status, N (%)				
Relationship/married	190 (79.2)	48 (70.6)	142 (82.6)	**0.040**
Education, N (%)				
Low	65 (27.0)	27 (39.7)	38 (22.0)	< **0.001**
Intermediate	60 (24.9)	22 (32.4)	38 (22.0)	
High	115 (47.7)	19 (27.9)	96 (55.5)	
Disease-specific characteristics				
Tumor type, N (%), % per tumor type				
NFPA	65 (27.0)	15 (23.1)	50 (76.9)	**0.021**
ACRO	41 (17.0)	16 (39.0)	25 (61.0)	
CD	32 (13.3)	15 (46.9)	17 (53.1)	
PRL	97 (40.2)	20 (20.6)	77 (79.4)	
RCC	6 (2.5)	2 (33.3)	4 (66.7)	
Time since diagnosis in years, median (IQR)	11.4 (5.2–20.5)	10.8 (5.1–19.0)	13.7 (6.6–23.8)	0.204
Treatment, N (%)				
No treatment/discontinued medication	36 (14.9)	6 (8.8)	30 (17.3)	**0.022**
Ongoing medication	75 (31.1)	17 (25.0)	58 (33.5)	
Surgery	96 (39.8)	29 (42.6)	67 (38.7)	
Radiotherapy	34 (14.1)	16 (23.5)	18 (10.4)	
Endocrine status, N (%)				
No deficits	112 (46.5)	18 (26.5)	94 (54.3)	< **0.001**
Hypopituitarism	84 (34.9)	34 (50.0)	50 (28.9)	
Panhypopituitarism	45 (18.7)	16 (23.5)	29 (16.8)	
HRQoL and disease bother				
EQ-5D score, mean (SD)a	0.908 (0.08)	0.862 (0.12)	0.926 (0.06)	< **0.001**
EQ-5D VAS, mean (SD)a	73.32 (20.7)	63.88 (19.1)	77.02 (20.1)	< **0.001**
SF-36 PCS, mean (SD)a	46.53 (10.5)	39.91 (11.5)	49.13 (8.9)	< **0.001**
SF-36 MCS, mean (SD)a	47.84 (12.0)	44.41 (13.3)	49.19 (11.1)	**0.005**
LBNQ-Pituitary total score, mean (SD)b	17.37 (18.9)	25.99 (20.8)	13.98 (17.0)	< **0.001**

Due to rounding, not all percentages of the categorical variables add up to 100% Bold — $p < 0.05$

NFPA non-functioning pituitary adenoma, *ACRO* acromegaly, *CD* Cushing's disease, *PRL* prolactinoma, *RCC* Rathke's cleft cyst, *N* number, *SD* standard deviation, *IQR* interquartile range, *EQ-5D* EuroQoL, *SF-36* short form-36, *LBNQ-Pituitary* Leiden bother and needs questionnaire- pituitary, *VAS* visual analogue scale, *MCS* mental component scale, *PCS* physical component scale

[a]Higher scores indicate better HRQoL

[b]Lower scores indicate lower disease burden

Work status

Sixty-eight (28%) patients did not have a paid job. This proportion was highest in patients with Cushing's disease (15/32, 47%) and lowest in patients with a prolactinoma (20/97, 21%). Those without a job did not differ with respect to age [median age of 54.7 (45.6–60.7) years] compared to those with a job [median age of 52.4 (44.9–59.2) years], however, there was a tendency to a lower education level (40% vs. 22% low education, intermediate 32% vs. 22%), and more endocrine deficits (74% vs. 46%) (Table 1). The following reasons were reported for not having a paid job: 1) being a scholar/student (3%), taking care of the household (31%), receiving an early pension (9%), having a (partial) disability pension (41%) or another reason [i.e. involuntary unemployment or performing charity work (16%)] (Supplementary Fig. 1). Of those with a (partial) disability pension, 21 out of 28 received full-disability pensions (80–100% disability) (table 1).

Determinants for having a paid job or not

After correcting for relevant confounders, patients diagnosed with Cushing's disease (range OR 2.9–3.3) or acromegaly (OR 2.5–2.7) were more often without a paid job, compared to patients with a NFPA or prolactinoma; had undergone radiotherapy more often compared to no current treatment (OR 3.9); or had one or more endocrine deficits compared to patients without any deficits (OR 2.9–3.6). Furthermore, patients not currently in a relationship were more often without a paid job (OR 2.3), as well as patients with a low or intermediate education (OR 3.0–3.4). When correcting for HRQoL, the relationship between the determinants low education, Cushing's disease, endocrine status and having a job or not remained significant (table 2).

Working problems among patients with a paid job

Patients with a pituitary tumor and a paid job report a median number of 36 working hours per week (IQR 26.0–40.0), which was not significantly different between various tumor types. In total, 41% of patients with a paid job reported to have missed on average 27.1 (SD 54.5) days during the previous year due to illness (absenteeism) and 39% of patients reported being bothered by health-related problems during work (range per tumor type: 29–50%). Among those bothered, there was a significant difference between tumor types regarding performance at work despite health-related problems (presenteeism: mean 6.8, range per tumor type 6.3–8.5, $p = 0.03$). Only 21 patients (12%) were under treatment of an occupational physician during the previous year (table 3). The highest percentage of patients reported problems with mental and social demands (i.e. concentrating on work tasks and working without losing train of thought) (Supplementary Table 3, Fig. 2).

Table 2. Univariate and multivariate analysis of determinants for not having a paid job among pituitary tumors of working age

	Crude			Adjusted for disease-specific and sociodemographic characteristics			Adjusted for disease-specific, sociodemographic characteristics and QoL		
Determinant	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Female gender	1.25	.696-2.231	.460	-	-	-	-	-	-
Age	1.02	.990-1.047	.218	-	-	-	-	-	-
Marital status (ref: Relationship/married)[a] single/divorced/widow	**1.97**	**1.03-3.79**	**.042**	**2.27**	**1.15-4.49**	**.019**	1.77	.80-3.87	.157
Education (ref: high)[a]									
Intermediate	**3.59**	**1.79-7.21**	**<.001**	**3.43**	**1.70-6.93**	**.001**	2.13	.96-4.75	.064
Low	**2.93**	**1.42-6.01**	**.003**	**2.99**	**1.45-6.17**	**.003**	**3.31**	**1.48-7.42**	**.004**
Tumor type (ref: PRL)[a]									
NFA	1.16	.54-2.47	.710	1.11	.50-2.44	.803	.84	.35-2.04	.698
ACRO	**2.46**	**1.11-5.47**	**.027**	**2.73**	**1.19-6.29**	**.018**	1.96	.77-4.99	.161
CD	**3.40**	**1.45-8.00**	**.005**	**3.25**	**1.38-7.67**	**.007**	**2.86**	**1.10-7.45**	**.032**
RCC	1.93	.33-11.27	.468	1.68	.28-9.97	.566	.97	.13-7.34	.979
Time since diagnosis[b]	1.02	.99-1.05	.154	1.00	.96-1.03	.860	1.02	.98-1.05	.375
Treatment (ref: no treatment)[c]									
Ongoing Medication	1.47	.52-4.10	.467	1.35	.45-4.00	.594	1.25	.37-4.22	.716
Surgery	2.16	.81-5.76	.122	1.55	.50-4.77	.445	1.43	.41-5.05	.576
Radiotherapy	**4.44**	**1.47-13.42**	**.008**	**3.87**	**1.11-13.45**	**.033**	3.04	.74-12.51	.123
Endocrine status (ref: no deficits)[b]									
Hypopituitarism	**3.55**	**1.82-6.92**	**<.001**	**3.76**	**1.84-7.68**	**<.001**	**3.97**	**1.77-8.88**	**.001**
Panhypopituitarism	**2.88**	**1.31-6.36**	**.009**	**2.87**	**1.16-7.12**	**.023**	**2.94**	**1.06-8.17**	**.039**

Included for HRQoL: EQ-index, MCS, PCS, LBNQ-P index Bold— $p < 0.05$

Ref reference category, *OR* odds ratio, *CI* confidence interval

[a]Adjusted for age, gender (HRQoL), [b]Adjusted for age, gender, tumor type, treatment (HRQoL), [c]Adjusted for age, gender, tumor type (HRQoL)

Table 3. Patient and work characteristics among 173 patients of working age with a pituitary tumor and a paid job, stratified per tumor type

	Total (N=173)	NFPA (N=50)	ACRO (N=25)	CD (N=17)	PRL (N=77)	RCC (N=4)	p-value
SF-HLQ							
Working hours/week, median (IQR)	36.0 (24.0-40.0)	36.0 (28.0-40.0)	40.0 (32.0-40.0)	32.0 (22.0-40.0)	32.0 (24.0-40.0)	39.0 (29.0-45.0)	.211[b]
Bothered by health-related problems during work, N (%)	68 (39.3)	22 (44.0)	9 (36.0)	5 (29.4)	30 (39.0)	2 (50.0)	.608[b]
Performance at work despite health-related problems, mean among those bothered (SD) (scale 1-10)	6.8 (1.7)	6.3 (1.6)	7.9 (1.4)	7.6 (1.5)	6.6 (1.7)	8.5 (0.7)	**.025**[b]
Absence from work during the past year due to health-related problems, N (%)	70 (40.5)	25 (50.0)	7 (28.0)	8 (47.1)	27 (35.1)	3 (75.0)	.104[b]
Days absent during previous year, median days (IQR)	5.0 (4.0-28.0)	10.0 (4.0-30.0)	10.0 (5.0-35.0)	5 (4.5-5.0)	5 (3.0-30.0)	10 (3.0-130.0)	.424[b]
Medical consumption							
Contact with occupational physician, N (%)	21 (12.1)	8 (16.0)	3 (12.0)	1 (5.9)	8 (10.4)	1 (25.0)	.706
WRFQ 2.0 (scale 0-100)							
Work scheduling and output demands, mean (SD)[a]	78.0 (28.7)	77.0 (28.3)	81.8 (27.0)	84.1 (29.5)	76.8 (28.8)	63.3 (52.7)	.714[b]
Physical demands, mean (SD)[a]	84.3 (27.1)	83.7 (28.6)	87.2 (25.2)	83.9 (24.1)	84.5 (26.6)	68.3 (54.8)	.849[b]
Mental demands and social demands, mean (SD)[a]	75.6 (31.2)	85.2 (24.8)	84.0 (28.0)	76.6 (28.6)	60.7 (52.9)	77.9 (29.2)	.380[b]
Flexibility demands, mean (SD)[a]	79.8 (29.1)	76.1 (30.3)	86.3 (25.2)	84.1 (27.9)	79.6 (29.0)	68.3 (50.6)	.563[b]
Index score, mean (SD)[a]	78.6 (28.1)	77.2 (28.6)	83.1 (26.5)	85.7 (25.4)	77.8 (27.1)	50.4 (51.3)	.179[b]

NFPA non-functioning pituitary adenoma, ACRO acromegaly, CD Cushing's disease, PRL prolactinoma, RCC Rathke's cleft cyst, N number, SD standard deviation, IQR interquartile range, SF-HLQ short form-health and labor questionnaire, WRFQ work role functioning questionnaire 2.0
Bold—$p < 0.05$
a Higher scores indicate better performance at work
b Corrected for age and gender

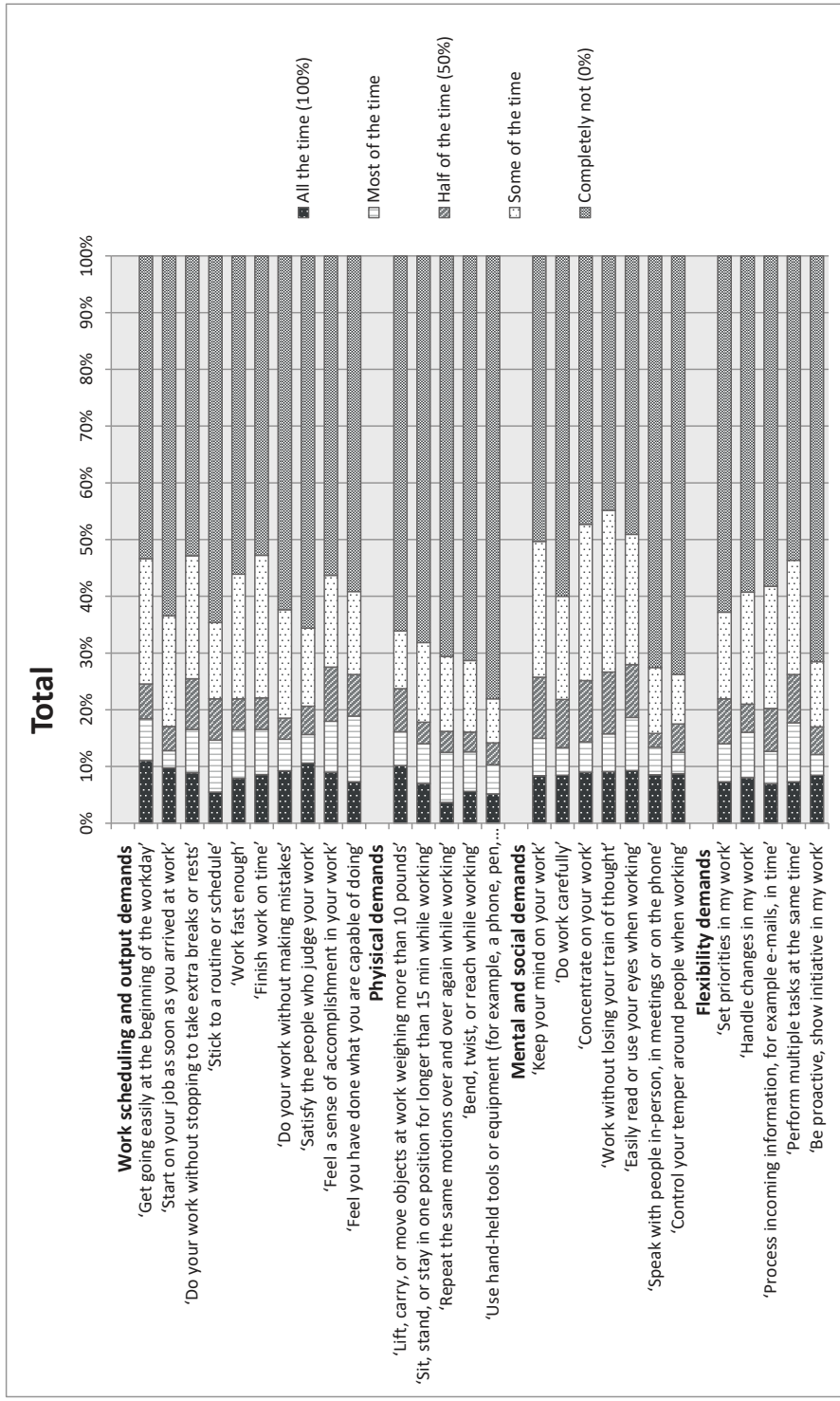

Figure 2. Difficulties experienced at work among patients with a paid job

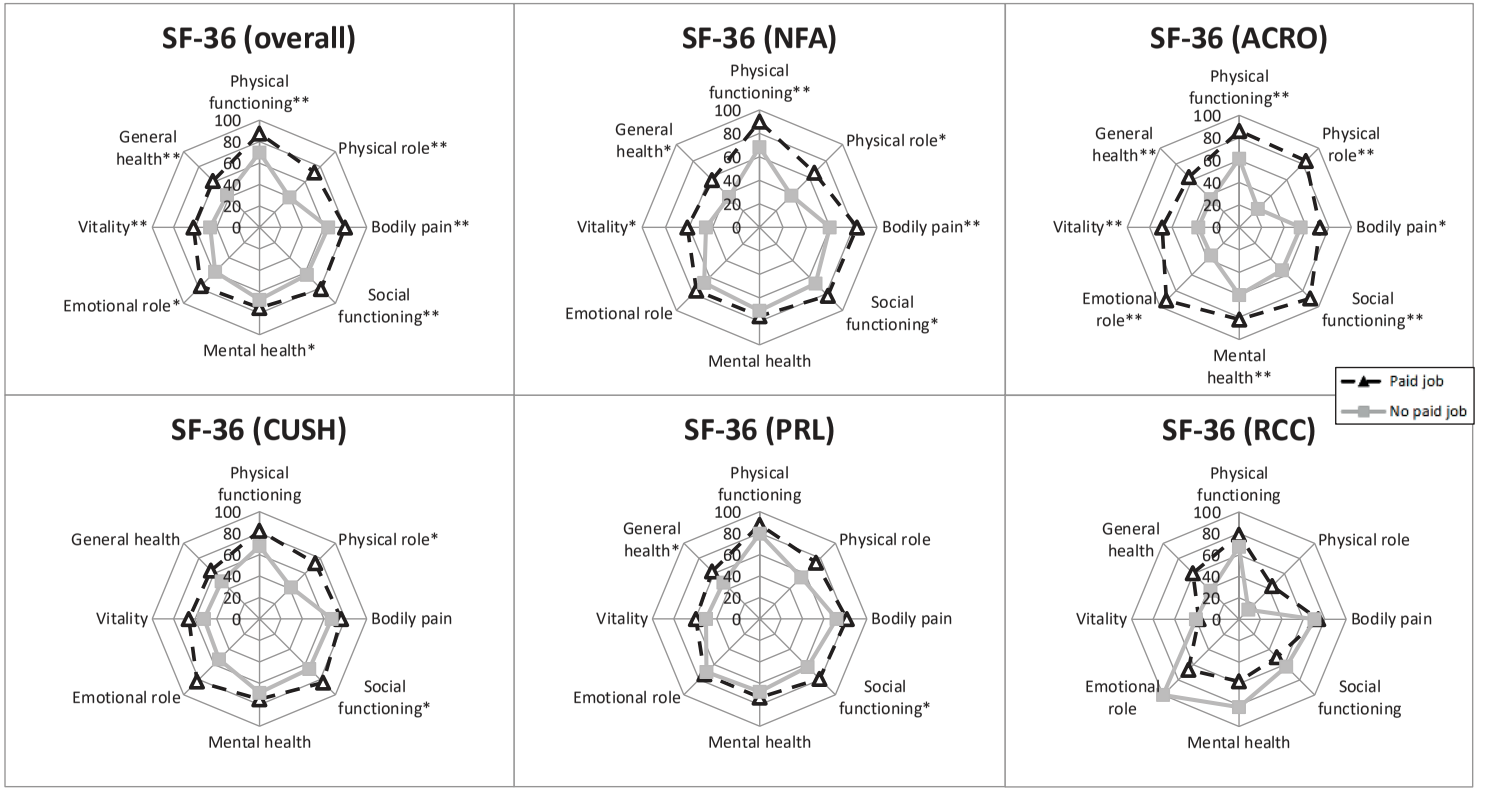

Figure 3. SF-36 scores in patients with a paid job compared to those without a paid job

* p<.05 / ** p<.001

† Higher scores indicate better HRQoL

Quality of life

In general, HRQoL was significantly higher among patients with a paid job compared to those without a paid job on all domains of the SF-36 (range mean difference 7.6–32.8, $p< 0.05$). This was confirmed among patients with acromegaly in a subgroup analysis between patients with and without a paid job, however could only be confirmed for some, but not all domains for patients with other tumor types (NFPA, CD, PRL) (figure 3).

DISCUSSION

This large cross-sectional study in patients treated for a pituitary tumor and of working age reveals that 28% of patients do not have a paid job. We found an increased risk of not having a paid job among patients with Cushing's disease, acromegaly, (pan) hypopituitarism and/or those patients that had undergone radiotherapy. In addition, well-known general determinants such as being single or lower education are also valid in this condition. Of those with a paid job, relatively many reported having missed work due to illness during the past year (41%) or not performing up to their self-perceived maximum potential (39%). The most common problems reported by patients concerned mental and social demands of work. This study is the first to look at determinants of (not) having a paid job in patients with a pituitary tumor. Furthermore, to the best of our knowledge, this study represents the largest study to date that looks at work disability and the relationship between job status and HRQoL in this population.

Rates of patients with a paid job

Data on work disability among patients with a history of a pituitary disease are scarce. The overall rate of 72% of patients with a paid job found in our study could not be verified in other studies, however, it is lower when compared to the general Dutch population (78.6%) (matched for age, gender and education) [25]. Two studies reported lower rates of patients with a paid job. Van Roijen et al. studied a cohort of 129 patients with hypopituitarism and found that only 26% of patients had a paid job [5]. While they did not report data within the same age range, the study also took place in 1989, further limiting comparability. Likewise, Brod et al. showed that 56% of adult patients with growth hormone deficiency had a paid job, however their results should be interpreted with caution, since they present data of a heterogeneous group of 39 patients, including patients with short stature, brain tumors, and trauma [9].

Among patients with functioning tumors, the reported rates were more comparable to ours. Wagenmakers et al. prospectively studied 123 Dutch patients in remission of CD of whom 51% had a paid job [8]. While these results are indeed in line with our findings

among patients with CD (53%), the study lacked information exclusively on patients aged 18–65. Short-term outcomes, on the other hand, as found by Pikkarainen et al., were higher (66% with a paid job), however the population represented patients with Cushing's syndrome (26 adrenal and 48 pituitary adenomas) and data was collected retrospectively, both limiting interpretability [7].

In contrast to the long-term outcomes, Jahangiri et al. looked at rates prior to diagnosis/treatment, and did not find significant differences between 18 patients with apoplexia compared to 117 patients without apoplexia [26]. These results were also collected retrospectively, had many missing data and lacked long-term results, therefore also limiting comparability of results.

Determinants for not having a paid job

This study is the first to study determinants for not having a job in a chronic setting of patients with pituitary tumors. We found tumor type, treatment, endocrine status (disease-specific), marital status, and education level (sociodemographic) to increase the risk of not having a paid job. The disease-specific and sociodemographic determinants found in the present study are in agreement with those affecting HRQoL [1, 27–29] in pituitary and other diseases [30, 31]. In the short-term, Jahangiri et al. did not find a difference between patients with apoplexia and without apoplexia regarding having a paid job or not [6]. A history of apoplexia is probably of less importance in the chronic phase, as well as in functioning tumors.

As anticipated, patients with (pan)hypopituitarism were significantly more often without a paid job compared to those without endocrine deficits. In our analysis hypopituitarism patients performed worse than those with panhypopituitarism. The variable composition of number and severity of the number of deficiencies and replacement status limits the exact interpretation of this finding.

Absenteeism, problems experienced at work and HRQoL

We found a relatively high percentage of patients (41%) with absence from work due to health-related reasons during the past year. Regarding the magnitude of absenteeism, our data were skewed, with the median being 5 days per year, whereas the mean was 27.1 days. The latter was considerably higher than that of the average Dutch population (8.8 days per year) (matched for age, gender) [32], however, unfortunately could not be compared to matched controls. In line with our findings, Jonsson et al. found increased sick leave in patients with NFPA (mean leave 40.2 days) compared to age-matched controls (24.0 days) [10], and other studies reported means varying between 19.8 and 38.4 days per year [5, 11, 12].

The highest percentage of patients without a paid job was among patients with ACRO/CD. The difference in HRQoL between patients with and without a paid job was largest among patients with ACRO (Fig. 3), perhaps indicating the presence of a mild and severe phenotype of patients with ACRO. Previous studies have endorsed these thoughts on various subtypes of acromegaly [33–35], however none incorporated the long-term outcomes (as depicted in Tier 3 of the value-based healthcare model [36]) on social participation and sustainability of health, such as work disability. Prior to the study we had anticipated finding lower overall work functioning scores as measured with the WRFQ, particularly for patients with ACRO and CD. In the total cohort, we indeed found lower average scores compared to those of a large selection of Dutch employees [20], and found scores comparable to those of Dutch cancer survivors [37], which emphasizes the impact of having a pituitary tumor. Unexpectedly, however, the overall WRFQ score showed a non-significant higher score among patients with ACRO and CD compared to patients with PRL and NFPA, indicating a trend towards better functioning at work. This seems at odds with the fewer paid jobs among patients with ACRO/CD. Even though it can be postulated that this is due to the smaller numbers, it can also be hypothesized that when patients with ACRO/CD are able to maintain their work, they appreciate their work more and therefore experience fewer work-related problems compared to patients with NFPA/PRL. We also found that the largest proportion of pituitary tumor patients were bothered at work by problems in the mental and social domains, which is in line with difficulties experienced by cancer survivors [38] and patients with rheumatoid arthritis [39].

A notable finding was the relatively low percentage of patients visiting an occupational physician (12%), despite the fact that quite a lot of patients (40%) in our study reported being bothered by health-related issues at work during the previous year. In the Netherlands, the occupational physician has the role of case manager to guide patients back to work. While patients in our cohort were in a chronic care setting, potentially explaining the minimal number of visits, this might be a potential target for future interventions.

Strengths and weaknesses

A clear strength of this study is the large sample of participating patients, enabling comparison between various types of pituitary tumors. A recent study performed by van Lier et al. showed that the use of self-reported information on absenteeism and presenteeism was considered the best way to measure sick leave, quantity and quality of work [40], therefore supporting the results presented here.

The limitations of our study are mostly based on limitations of a cross-sectional cohort study. The non-longitudinal nature of the study leads to unanswered questions whether work disability in patients with pituitary tumors is due to the pituitary tumor or has a

different nature, and on the interplay between productivity and quality of life. Another limitation is the single center setting of the study. Since the study took place in the Netherlands, which has relatively high work participation and high social security benefits, the generalizability to other countries might be an issue. The social security benefits in the Netherlands are not the same as but can be compared to systems in Scandinavia and Germany [41]. Due to the high social security benefits in the Netherlands, it could be that we observed higher rates of patients without a paid job compared to countries with lower benefits. This might also lead to more severe work problems in countries with lower social security benefits since these patients are unable to afford losing their jobs, and therefore work beyond their capacity, even though they are actually unable to keep it up.

An additional limitation is the distribution of the education level among participants in our study. Even though we invited all patients with a pituitary tumor, there was a high proportion of highly educated patients among our participants. This might decrease the generalizability of our study and the interpretation of our results, since in general, higher education reduces health-related working problems. Furthermore, the low amount of patients with a RCC patients is a limitation. However, after conducting a sensitivity analysis (excluding RCC from the analysis), no different effect was found.

Though quality of life and functioning are influenced by one's ability to work and vice versa, these aspects are often overlooked in current care. A healthcare provider is not always aware of a patient's employment status, and if so, it is generally difficult for the treating physician to help a patient to improve functioning at work. This emphasizes the relevance of our study and it remains important to realize that the impact of a pituitary tumor on work functioning is high. It is therefore necessary to increase awareness among all healthcare providers involved, including occupational physicians, and use targeted interventions in an effort to reduce work disability/prevent unemployment. Regarding interventions aimed at the problems perceived while being at work, these should focus on mental and social demands of the job in relation to the person's capabilities.

CONCLUSION

We have shown that work disability among patients with a pituitary tumor is substantial. Not only are they relatively often without a paid job, sick leave is considerable among those who work, and many patients encounter difficulties at work, mostly regarding the mental and social sphere. The determinants and difficulties at work found in this study could potentially be used for further research and we advise healthcare professionals to take these results into consideration in the clinical guidance of patients.

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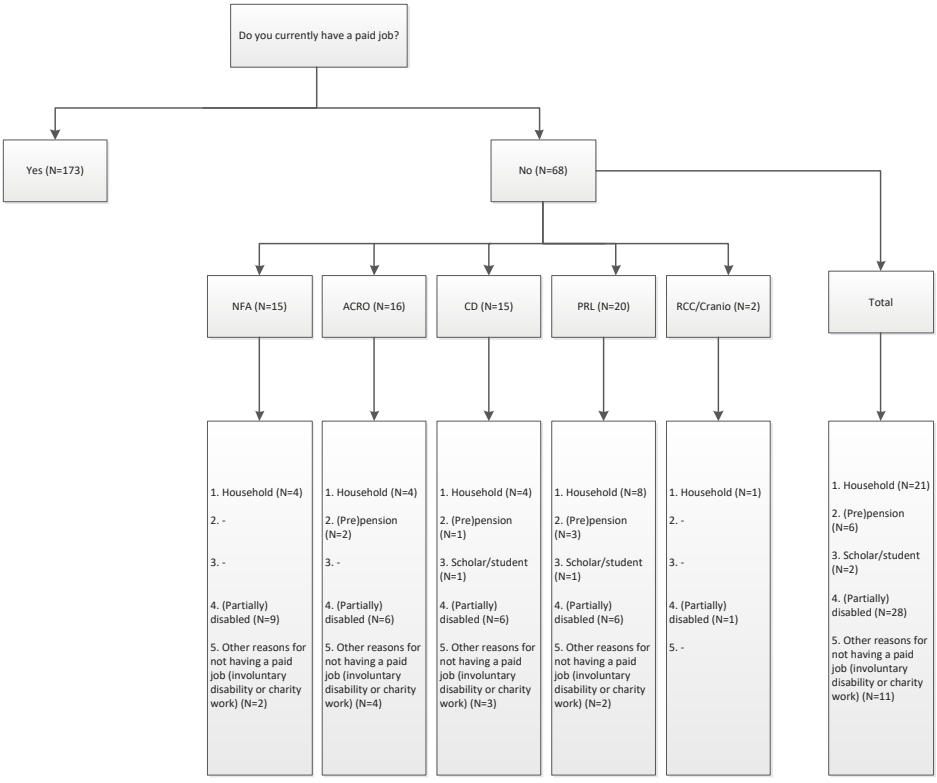
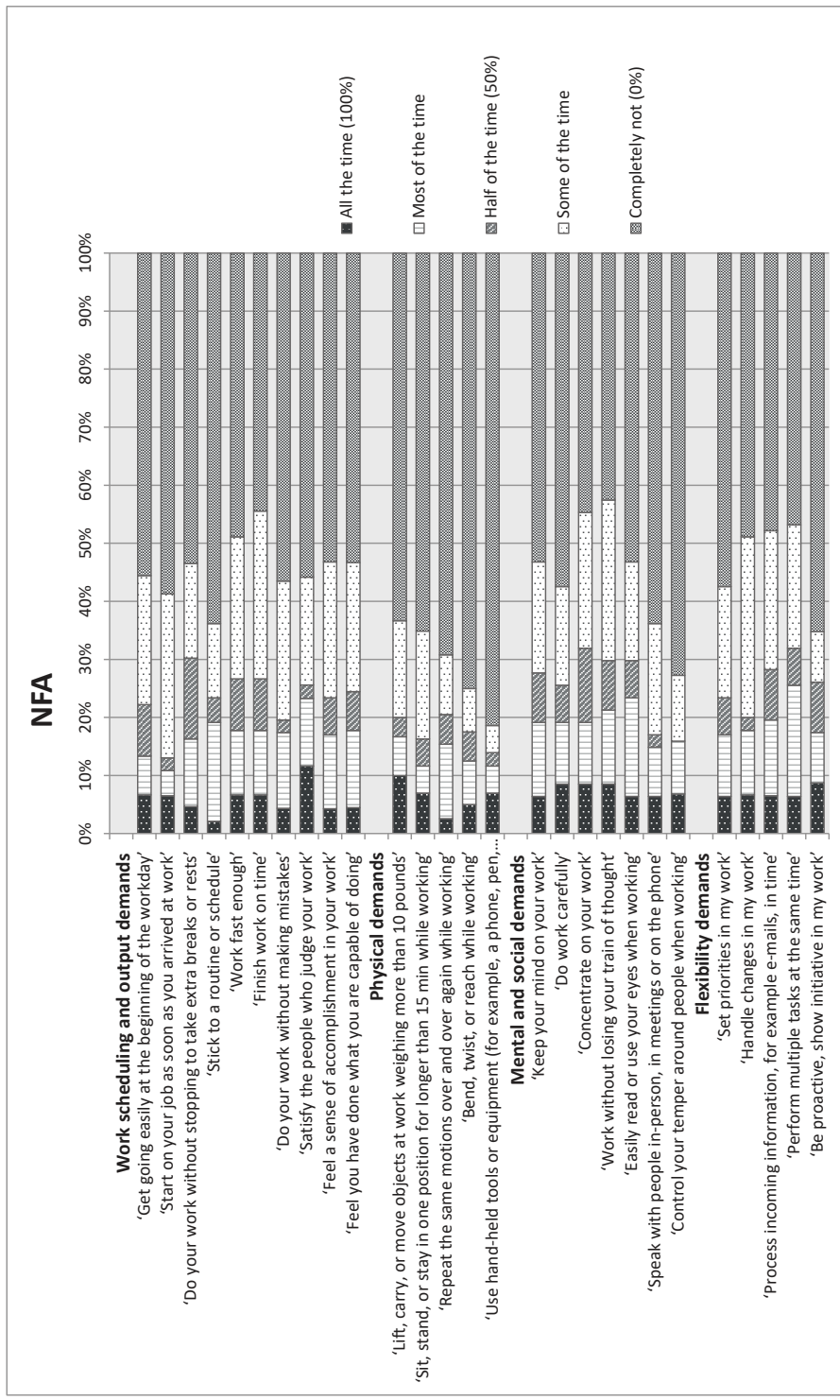
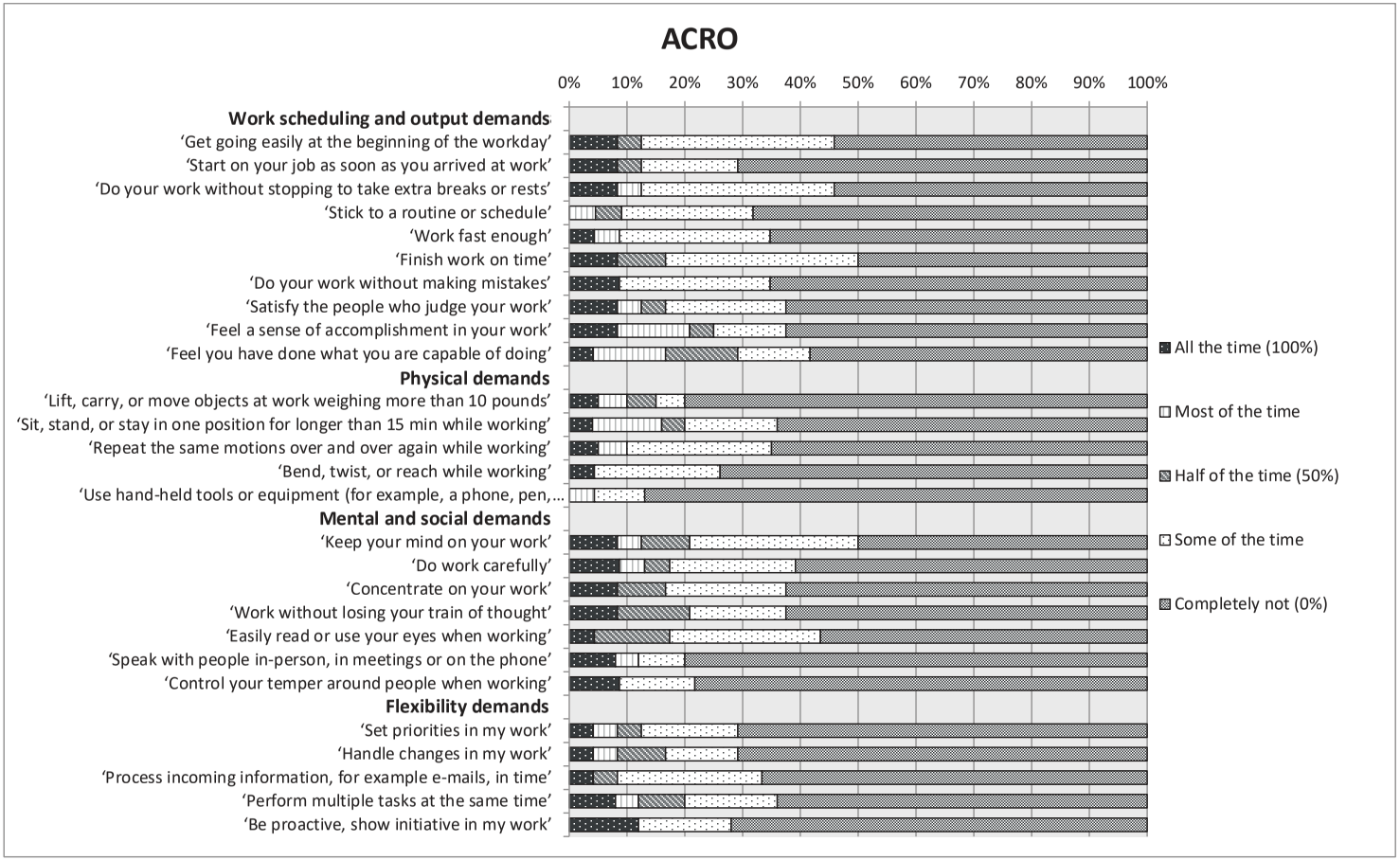


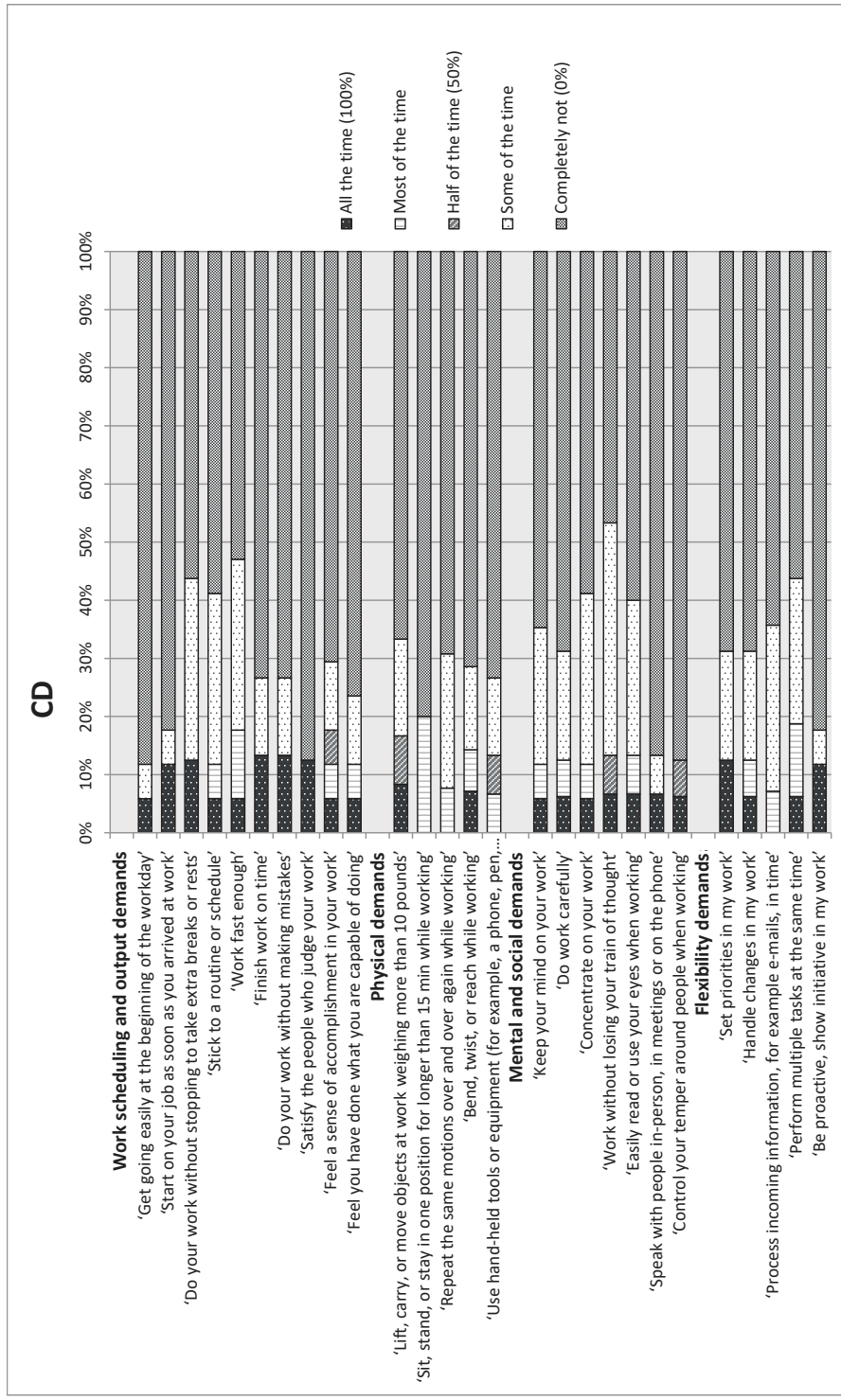
Supplementary figure 1. Flow chart of employment status in patients with a pituitary tumor of working age



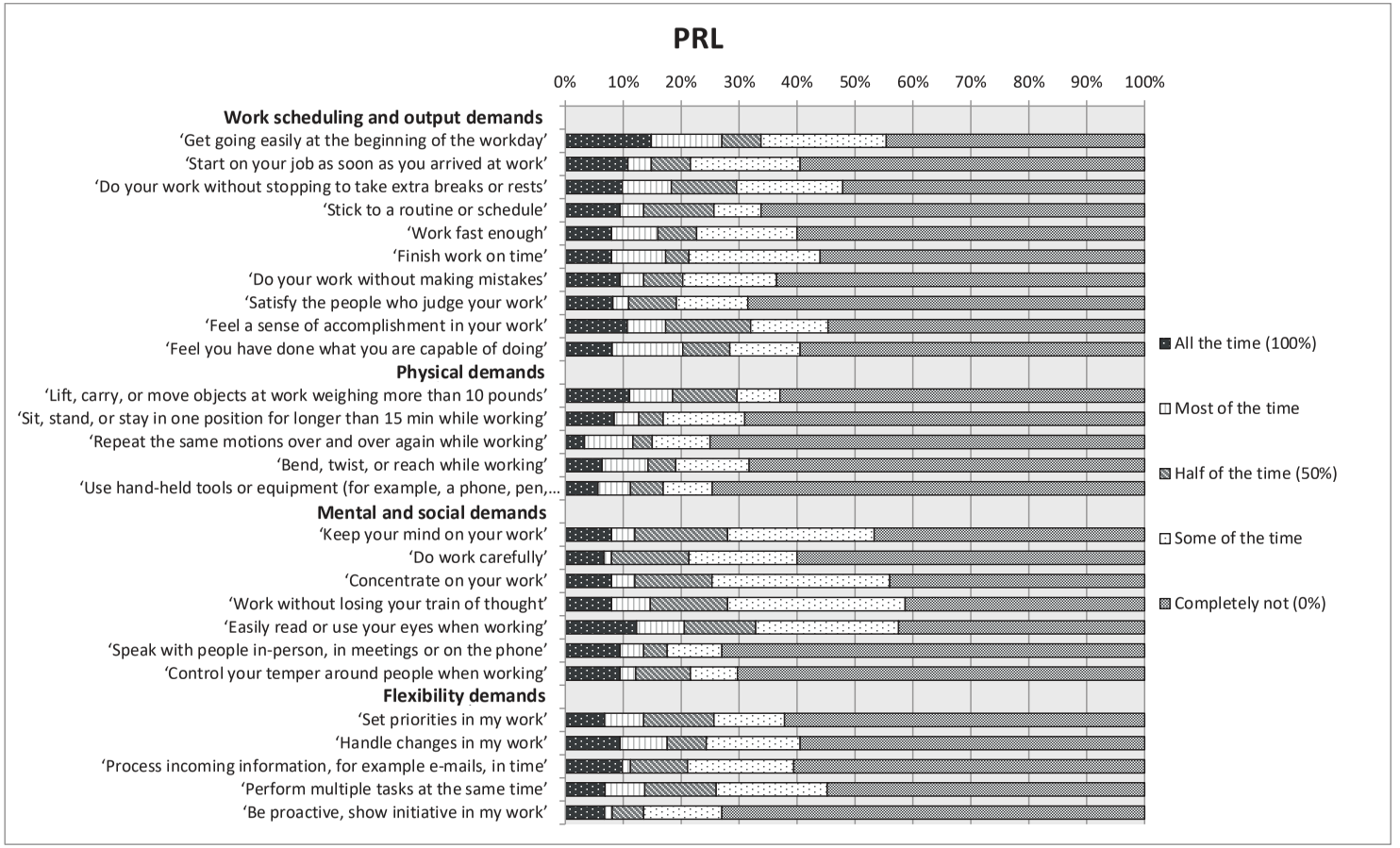
Supplementary figure 2. Difficulties experienced at work among patients with a paid job (per tumor type and endocrine status)



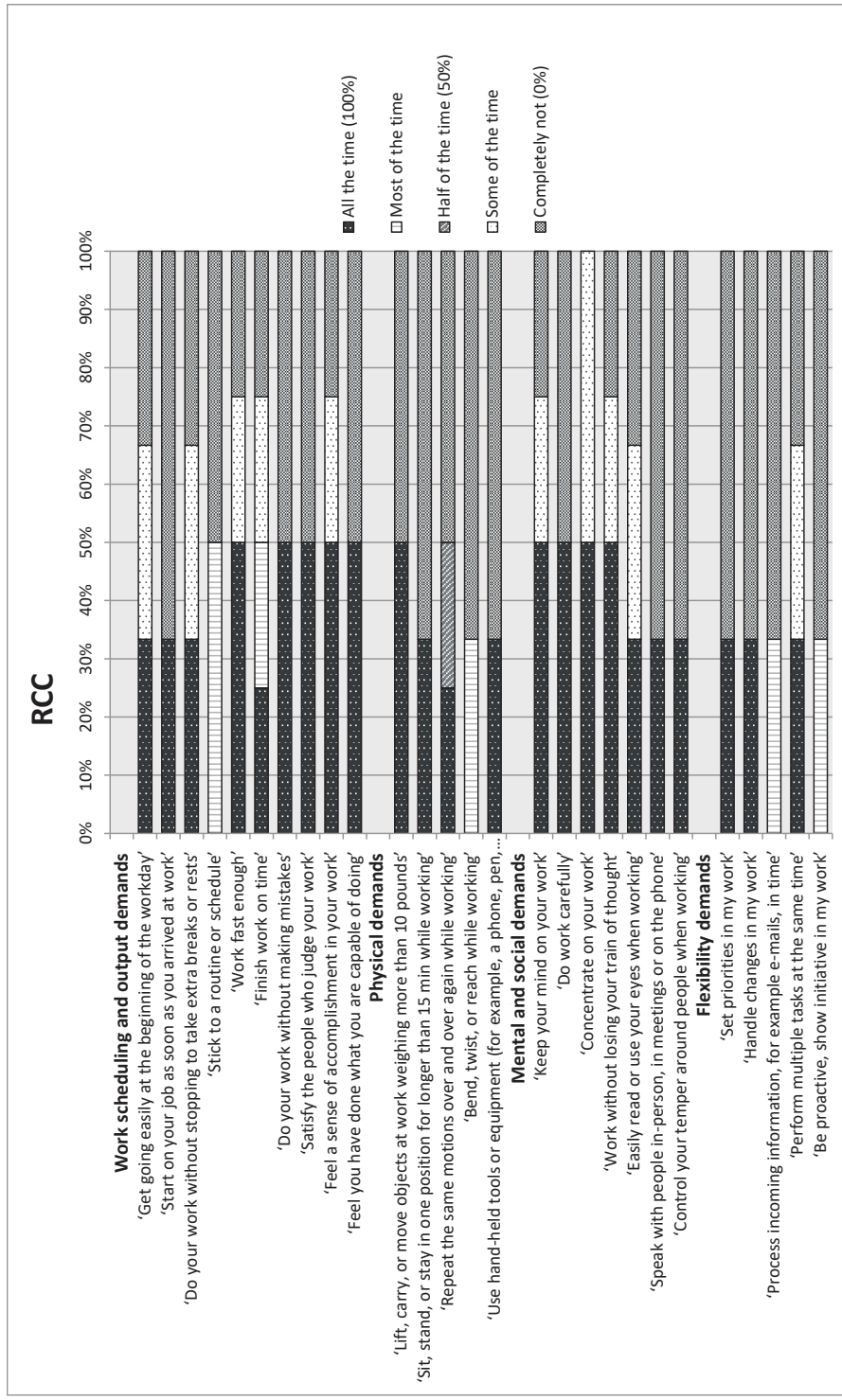
Supplementary figure 2. Difficulties experienced at work among patients with a paid job (per tumor type and endocrine status) (continued)



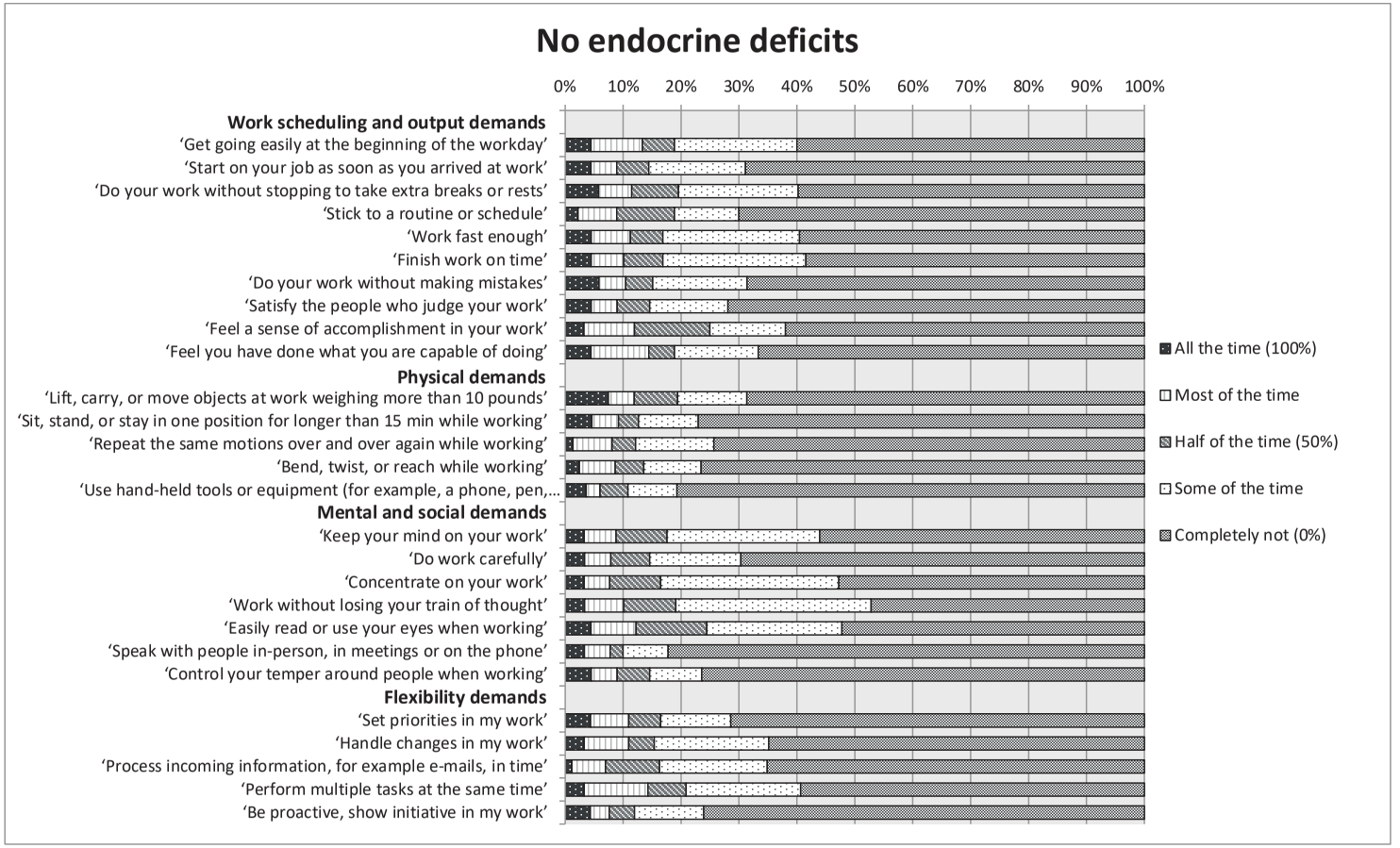
Supplementary figure 2. Difficulties experienced at work among patients with a paid job (per tumor type and endocrine status) (continued)



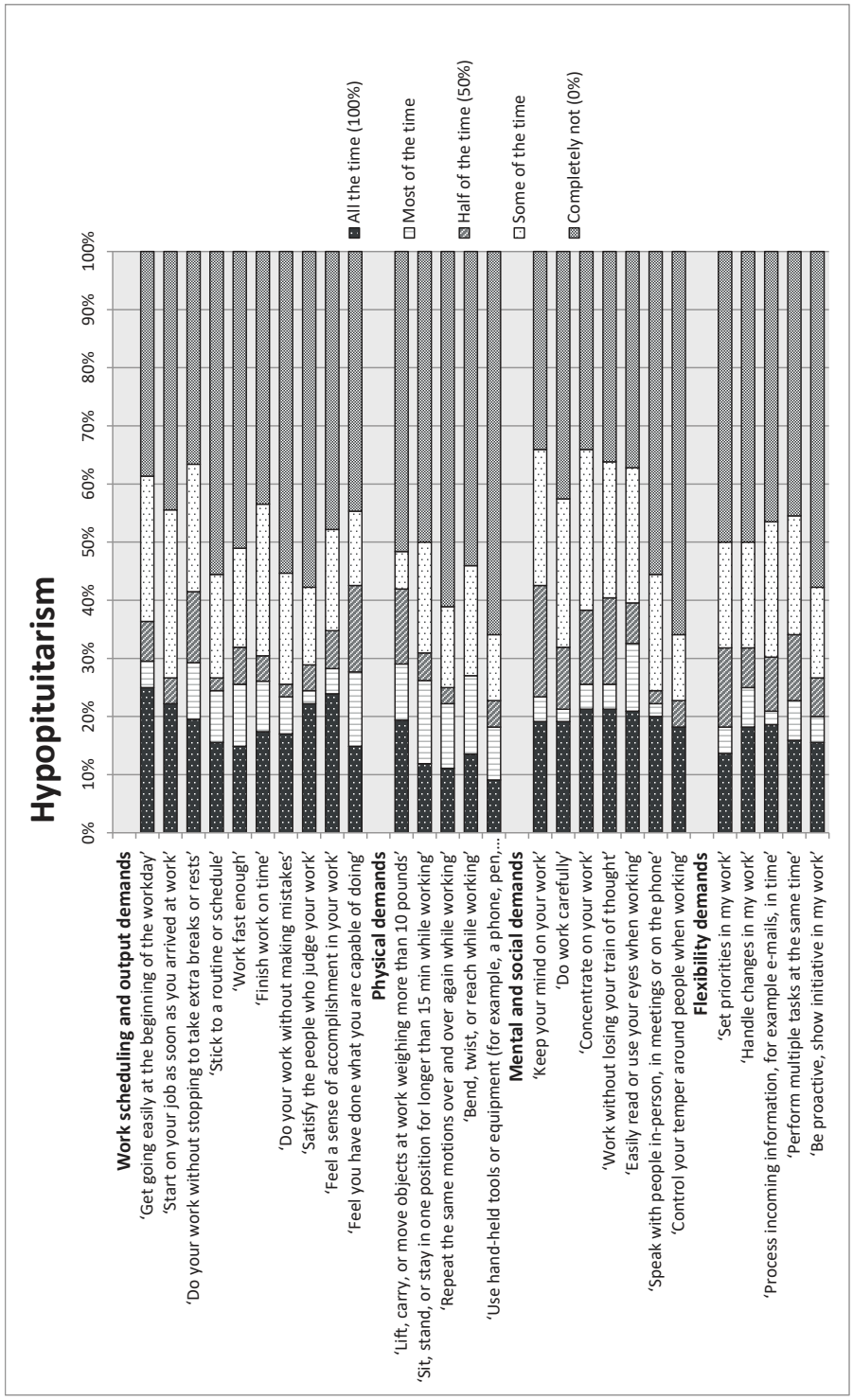
Supplementary figure 2. Difficulties experienced at work among patients with a paid job (per tumor type and endocrine status) (continued)



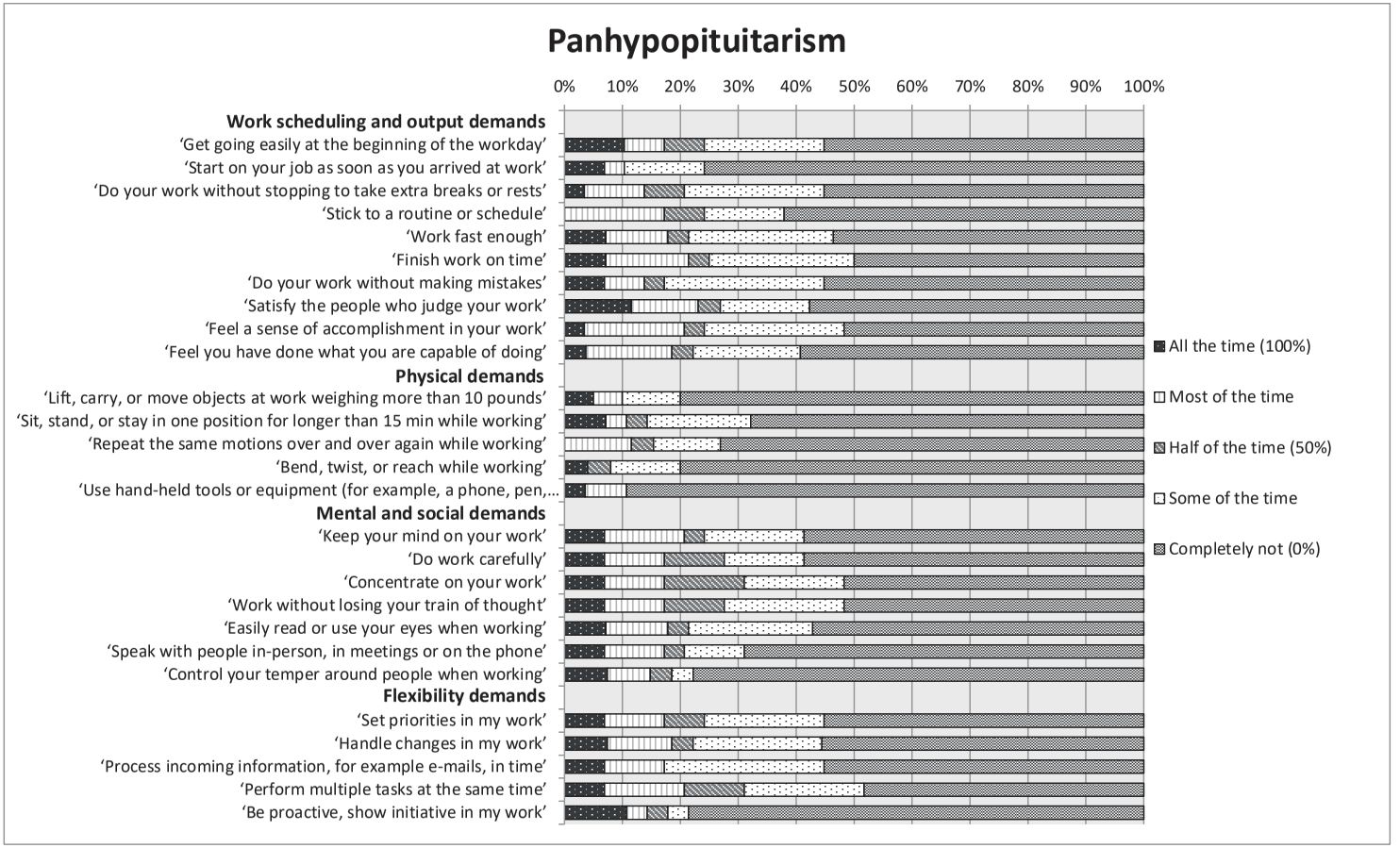
Supplementary figure 2. Difficulties experienced at work among patients with a paid job (per tumor type and endocrine status) (continued)



Supplementary figure 2. Difficulties experienced at work among patients with a paid job (per tumor type and endocrine status) (continued)



Supplementary figure 2. Difficulties experienced at work among patients with a paid job (per tumor type and endocrine status) (continued)



Supplementary figure 2. Difficulties experienced at work among patients with a paid job (per tumor type and endocrine status) (continued)

Supplementary table 1. Treatment patterns of 241 patients with a pituitary tumor categorized per tumor type

	Total (N=241)	NFA (N=65)	ACRO (N=41)	CD (N=32)	PRL (N=97)	RCC (N=6)
Treatment, N (%)						
No treatment / discontinued medication						
No treatment	9 (3.7)	5 (7.7)	0 (-)	0 (-)	3 (3.1)	1 (16.7)
Discontinued medication	27 (11.2)	2 (3.1)	0 (-)	0 (-)	24 (24.7)	1 (16.7)
Ongoing medication						
Medication only	49 (20.3)	1 (1.5)	0 (-)	0 (-)	48 (49.5)	0 (-)
Prior surgery	18 (7.5)	2 (3.1)	10 (24.4)	1 (3.1)	5 (5.2)	0 (-)
Prior surgery and radiotherapy	8 (3.3)	0 (-)	6 (14.6)	2 (6.2)	0 (-)	0 (-)
Surgery						
Surgery only	64 (26.6)	30 (46.2)	11 (26.8)	19 (59.4)	0 (-)	4 (66.7)
Prior medication	32 (13.3)	6 (9.2)	9 (22.0)	5 (15.6)	12 (12.4)	0 (-)
Radiotherapy						
Prior medication	1 (0.4)	0 (-)	0 (-)	0 (-)	1 (1.0)	0 (-)
Prior surgery	25 (10.4)	19 (29.2)	1 (2.4)	3 (9.3)	2 (2.1)	0 (-)
Prior medication and surgery	8 (3.3)	0 (-)	4 (9.8)	2 (6.3)	2 (2.1)	0 (-)

NFA (non-functioning pituitary adenoma), ACRO (acromegaly), CD (Cushing's disease), PRL (prolactinoma), RCC (Rathke's cleft cyst), N (number)
Due to rounding, not all percentages of the categorical variables add up to 100%

Supplementary table 2. Patient and work characteristics among 173 patients of working age with a pituitary tumor and a paid job, stratified per endocrine status

	Total (N=173)	No deficits (N=94)	Hypopit (N=50)	Panhypopit (N=29)	p-value
SF-HLQ					
Working hours/week, median (IQR)	36.0 (24.0-40.0)	32.0 (24.0-40.0)	36.0 (27.0-40.0)	38.0 (31.0-40.0)	.566†
Bothered by health-related problems during work, N (%)	68 (39.3)	30 (34.5)	22 (46.8)	16 (55.2)	.113†
Performance at work despite health-related problems, mean (SD) (scale 1-10)*	6.8 (1.7)	7.0 (1.5)	6.4 (1.7)	7.0 (2.0)	.579†
Absence from work during the past year due to health-related problems, N (%)	70 (40.5)	27 (28.7)	15 (30.0)	18 (62.1)	**.011**†
Days absent during previous year, median days (IQR)	5.0 (4.0-28.0)	5.0 (3.0-30.0)	10.0 (3.0-55.0)	8.5 (5.0-20.0)	**.017**†
Medical consumption					
Contact with occupational physician, N (%)	21 (12.1)	10 (10.6)	9 (18.0)	2 (6.8)	.279
WRFQ 2.0 (scale 0-100)					
Work scheduling and output demands, mean (SD)*	78.0 (28.7)	82.9 (24.3)	68.3 (34.4)	78.3 (28.9)	**.016**†
Physical demands, mean (SD)*	84.3 (27.1)	88.5 (21.3)	73.0 (35.5)	88.6 (24.3)	**.006**†
Mental demands and social demands, mean (SD)*	75.6 (31.2)	82.9 (24.1)	67.9 (34.5)	77.8 (31.8)	**.019**†
Flexibility demands, mean (SD)*	79.8 (29.1)	84.3 (24.7)	71.0 (34.6)	79.1 (28.7)	**.042**†
Index score, mean (SD)*	78.6 (28.1)	83.9 (22.6)	67.6 (34.3)	79.2 (28.7)	**.003**†

(bold) p<0.05

* Higher scores indicate better performance at work

† corrected for age and gender

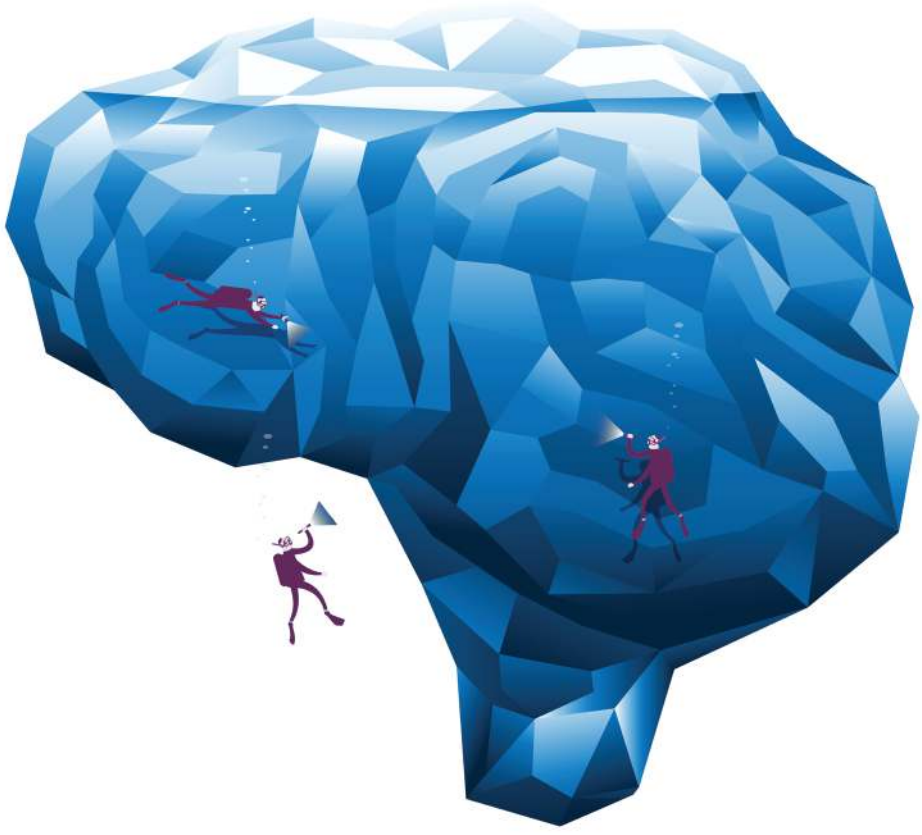
NFA (non-functioning pituitary adenoma), ACRO (acromegaly), CD (Cushing's disease), PRL (prolactinoma), RCC (Rathke's cleft cyst), N (number), SD (standard deviation), IQR (interquartile range), SF-HLQ (short form-health and labor questionnaire), WRFQ 2.0 (work role functioning questionnaire 2.0)

Supplementary table 3. Percentages of perceived work-related difficulties at work per tumor type in patients with a pituitary tumor and a paid job

Difficulty with….
Work scheduling and output demands
Get going easily at the beginning of the workday
Start on your job as soon as you arrived at work
Do your work without stopping to take extra breaks or rests
Stick to a routine or schedule
Work fast enough
Finish work on time
Do your work without making mistakes
Satisfy the people who judge your work
Feel a sense of accomplishment in your work
Feel you have done what you are capable of doing
Physical demands
Lift, carry, or move objects at work weighing more than 0 pounds
Sit, stand, or stay in one position for longer than 5 min while working
Repeat the same motions over and over again while working
Bend, twist, or reach while working
Use hand-held tools or equipment (for example, a phone, pen, keyboard, computer mouse, drill, hairdryer or sander)
Mental and social demands
Keep your mind on your work
Do work carefully
Concentrate on your work
Work without losing your train of thought
Easily read or use your eyes when working
Speak with people in-person, in meetings or on the phone
Control your temper around people when working
Flexibility demands
Set priorities in my work
Handle changes in my work
Process incoming information, for example e-mails, in time
Perform multiple tasks at the same time
Be proactive, show initiative in my work

(bold) ≥50% of patients experience problems with item at work (only considering NFA, ACRO, CD, PRL based on the low number of patients with a RCC)
NFA (non-functioning adenoma), ACRO (acromegaly), CD (Cushing's disease), PRL (prolactinoma), RCC (Rathke's cleft cyst)
The 5-point rating scale is categorized into three categories: 1) completely not (0%), 2) sometimes ("some of the time" and "half of the time (50%)") and 3) frequently ("most of the time" and "all the time" (100%))

Total (N=173)		NFA (N=50)		ACRO (N=25)		CD (N=17)		PRL (N=77)		RCC (N=4)	
Sometimes (1-50%) % of patients	Frequently (50-100%) % of patients	Sometimes (1-50%) % of patients	Frequently (50-100%) % of patients	Sometimes (1-50%) % of patients	Frequently (50-100%) % of patients	Sometimes (1-50%) % of patients	Frequently (50-100%) % of patients	Sometimes (1-50%) % of patients	Frequently (50-100%) % of patients	Sometimes (1-50%) % of patients	Frequently (50-100%) % of patients
28.2	18.4	31.1	13.3	37.5	8.3	5.9	5.9	28.4	27.0	33.3	33.3
23.8	12.8	30.4	10.9	20.8	8.3	5.9	11.8	25.7	14.9	0.0	33.3
30.6	16.6	30.2	16.3	33.3	12.5	31.3	12.5	29.6	18.3	33.3	33.3
20.7	14.6	17.0	19.1	27.3	4.5	29.4	11.8	20.3	13.5	0.0	50.0
27.4	16.5	**33.3**	**17.8**	26.1	8.7	29.4	17.6	24.0	16.0	25.0	50.0
30.7	16.6	**37.8**	**17.8**	**41.7**	**8.3**	13.3	13.3	26.7	17.3	25.0	50.0
22.8	14.8	26.1	17.4	26.1	8.7	13.3	13.3	23.0	13.5	0.0	50.0
18.8	15.6	20.9	23.3	25.0	12.5	0.0	12.5	20.5	11.0	0.0	50.0
25.7	18.0	29.8	17.0	16.7	20.8	17.6	11.8	28.0	17.3	25.0	50.0
22.0	18.9	28.9	17.8	25.0	16.7	11.8	11.8	20.3	20.3	0.0	50.0
17.8	16.1	20.0	16.7	10.0	10.0	25.0	8.3	18.5	18.5	0.0	50.0
17.8	14.0	23.3	11.6	20.0	16.0	0.0	20.0	18.3	12.7	0.0	33.3
16.9	12.5	15.4	15.4	25.0	10.0	23.1	7.7	13.3	11.7	25.0	25.0
16.1	12.6	12.5	12.5	21.7	4.3	14.3	14.3	17.5	14.3	0.0	33.3
11.6	10.3	7.0	11.6	8.7	4.3	20.0	6.7	14.1	11.3	0.0	33.3
34.7	15.0	27.7	19.1	**37.5**	**12.5**	23.5	11.8	**41.3**	**12.0**	25.0	50.0
26.7	13.3	23.4	19.1	26.1	13.0	18.8	12.5	32.0	8.0	0.0	50.0
38.3	**14.4**	**36.2**	**19.1**	29.2	8.3	29.4	11.8	**44.0**	**12.0**	50.0	50.0
39.4	**15.8**	**36.2**	**21.3**	29.2	8.3	46.7	6.7	**44.0**	**14.7**	25.0	50.0
32.3	**18.6**	23.4	23.4	39.1	4.3	26.7	13.3	**37.0**	**20.5**	33.3	33.3
14.0	13.4	21.3	14.9	8.0	12.0	6.7	6.7	13.5	13.5	0.0	33.3
13.8	12.5	11.4	15.9	13.0	8.7	6.3	6.3	17.6	12.2	0.0	33.3
23.2	14.0	25.5	17.0	20.8	8.3	18.8	12.5	24.3	13.5	0.0	33.3
24.7	16.0	**33.3**	**17.8**	20.8	8.3	18.8	12.5	23.0	17.6	0.0	33.3
29.1	12.7	**32.6**	**19.6**	29.2	4.2	28.6	7.1	28.2	11.3	0.0	33.3
28.7	17.7	**27.7**	**25.5**	24.0	12.0	25.0	18.8	31.5	13.7	33.3	33.3
16.4	12.1	17.4	17.4	16.0	12.0	5.9	11.8	18.9	8.1	0.0	33.3



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Healthcare utilization and costs among patients with non-functioning pituitary adenomas

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ABSTRACT

Purpose

Non-functioning pituitary adenomas (NFPA) have a substantial impact on patients' health status, yet research on the extent of healthcare utilization and costs among these patients is scarce. The objective was to determine healthcare usage, associated costs, and their determinants among patients treated for an NFPA.

Methods

In a cross-sectional study, 167 patients treated for an NFPA completed four validated questionnaires. Annual healthcare utilization and associated costs were assessed through the medical consumption questionnaire (MTA iMCQ). In addition, the Leiden Bother and Needs Questionnaire for pituitary patients (LBNQ-Pituitary), Short Form-36 (SF-36), and EuroQol (EQ-5D) were administered. Furthermore, age, sex, endocrine status, treatment, and duration of follow-up were extracted from the medical records. Associations were analyzed using logistic/linear regression.

Results

Annual healthcare utilization included: consultation of an endocrinologist (95% of patients), neurosurgeon (14%), and/or ophthalmologist (58%). Fourteen percent of patients had ≥1 hospitalization(s) and 11% ≥1 emergency room visit(s). Mean overall annual healthcare costs were € 3040 (SD 6498), highest expenditures included medication (31%), inpatient care (28%), and specialist care (17%). Factors associated with higher healthcare utilization and costs were greater self-perceived disease bother and need for support, worse mental and physical health status, younger age, and living alone.

Conclusion

Healthcare usage and costs among patients treated for an NFPA are substantial and were associated with self-perceived health status, disease bother, and healthcare needs rather than endocrine status, treatment, or duration of follow-up. These findings suggest that targeted interventions addressing disease bother and unmet needs in the chronic phase are needed.

INTRODUCTION

Patients with pituitary adenomas report impairments in health-related-quality of life (HRQoL) and a high disease burden [1–4]. In many cases, patients require lifelong (medical) treatment and monitoring by a multidisciplinary care team. Therefore, it is conceivable that total treatment costs are high, particularly in patients with endocrine deficits. Knowledge of the long-term healthcare utilization as well as the accompanying costs in patients with pituitary adenomas, however, is scarce.

NFPAs are highly prevalent among all pituitary adenomas [5] and can be considered as a separate entity, presenting with specific symptoms related to mass effects instead of hormonal excess. Studies describing healthcare utilization and/or costs of patients with pituitary adenomas, however, have focused primarily on functioning adenomas (i.e., Cushing's disease, acromegaly, prolactinoma) [6–12]. The only study presenting data on healthcare use among patients with an NFPA lacked physician-specific information (e.g., specialties visited, number of visits), as well as factors associated with increased healthcare utilization or costs. The study did confirm higher healthcare utilization and costs compared to a reference population of people without a pituitary disease [11].

The current study aims to determine healthcare usage, associated costs and their determinants among patients treated for an NFPA. It was hypothesized that in patients with an NFPA hypopituitarism, postoperative radiotherapy, and/or shorter duration of follow-up were associated with higher healthcare utilization and costs. We anticipated an association between a higher disease burden and needs for support and higher healthcare utilization and costs. It is expected that the identification of these disease- or care-related determinants for healthcare utilization and costs will be helpful for the further understanding and improvement of healthcare utilization/cost drivers, as well as improve value for the patient by making care more efficient, and improve outcomes.

PATIENTS AND METHODS

Study design

We performed a cross-sectional study in the Leiden cohort consisting of patients treated for an NFPA. The Leiden University Medical Center (LUMC) is a tertiary referral center in the Netherlands for the treatment of pituitary adenomas. The study was approved by the ethical committee of the Leiden University Medical Center prior to the study (p12.067). This study was part of a larger project, also assessing work-related disability [13].

Patients

All patients with an NFPA, aged ≥18 years, and currently under active follow-up, were identified from the hospital registries and invited by their treating physician by means of a letter to participate. Exclusion criteria were follow-up of <6 months, insufficient Dutch language skills, incapacity to fill out the questionnaires, and living abroad. Recruitment took place between September 2016 and March 2017. In case of no response, participants were re-approached once through a letter. Written consent was obtained from each participant after full explanation of the purpose and nature of the study.

Assessments

The assessment consisted of a set of four validated questionnaires concerning healthcare usage and costs (Medical Consumption Questionnaire (iMTA MCQ)), perceived bother of disease and needs for support (Leiden Bother and Needs Questionnaire for pituitary patients (LBNQ-P)), HRQoL (Short Form-36 (SF-36), utility (EuroQol (EQ-5D)) and could be completed either digitally or on paper. In addition, sociodemographic and clinical data were collected from self-reports and medical records.

Sociodemographic characteristics

The following disease-specific and sociodemographic characteristics were collected from the medical records: age, sex, date of diagnosis, and treatment. Self-reported characteristics were: marital status, educational level, employment status, and endocrine status. Level of education was categorized into low, intermediate or high, based on the guidelines of Statistics Netherlands (CBS) [14], which corresponds with UNESCO's International Standard Classification of Education: Fields of Training and Education 2013 [15]. Employment status was categorized into three categories: (1) paid job, (2) no paid job, (3) retired. Treatment was divided into three categories: (1) wait-and-scan, (2) surgically treated patients, and (3) postoperative radiotherapy. Endocrine status was categorized as hypopituitarism (≥1 endocrine deficit(s)) or no deficits, according to hormone replacement therapy based on self-reported medication usage.

Healthcare utilization

The iMTA MCQ assesses whether patients had an appointment with various healthcare professionals (HCPs) during the past 12 months and the frequency of appointments. For this study, those HCPs considered relevant for patients with a pituitary adenoma were included (e.g., endocrinologist, neurosurgeon, ophthalmologist, ENT-doctor, neurologist, radiation oncologist, cardiologist, internist). Patients were allowed to add additional HCPs through an open question (other). Furthermore, the questionnaire assesses home care (i.e., nursing care, (government-subsidized) household help, including frequency and duration), emergency care (i.e., ambulance rides, emergency room (ER)

visits, including frequency), hospital admissions (including frequency and duration) and medication usage (including frequency and dosage). A binary specialist care utilization score was computed: specialist care utilization was defined as high or low according to the median total number of visits to medical specialists during the previous 12 months (high use: ≥4 visits).

Perceived bother and needs for support

The LBNQ-Pituitary is a disease-specific questionnaire, which was developed based on focus group interviews with patients [16]. For this study, the LBNQ-Pituitary consisted of 26 items divided into five subscales: mood problems, negative illness perceptions, issues in sexual functioning, physical and cognitive complaints, and issues in social functioning, from which index scores can be calculated (range 0–100). A detailed description of how the items are scored has been previously published. Higher scores indicate greater bother by the consequences of the disease and higher needs for support [16].

Health-Related-Quality of Life and utility

The SF-36 is a 36-item HRQoL questionnaire, which covers eight domains: physical function, physical role, bodily pain, general health, vitality, social function, emotional role, and mental health. These subscales range from 0 to 100, from which the physical and mental component score can be calculated. Higher scores indicate better HRQoL [17].

The EQ-5D (5-level) is a utility questionnaire consisting of five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, from which utility (range 0 to 1) can be calculated (EQ-5D index). The EQ-5D also includes a visual analog scale (VAS), which records self-reported health status (range 0–100). Higher scores indicate a better perceived health status [18].

Costs

Cost prices were obtained according to the Dutch manual for costing research [19], and prices were based on reference prices for 2016. Relevant reference prices are presented in Supplementary Table 4. Conversion of costs can be made based on the purchasing power parity provided by the Organization for Economic Co-operation and Development (OECD), which was 0.816 per dollar in 2016 [https://data.oecd.org/conversion/purchasing-power-parities-ppp.htm, accessed on 2 November 2018].

Statistics

Data entry was performed through an online survey platform. All statistical analyses were performed with IBM SPSS 23.0 software (IBM SPSS Inc., New York, USA). Continuous variables are presented as means and standard deviations (SD) or medians with

interquartile ranges (IQR), analyzed through unpaired t-test or Mann–Whitney U, where applicable. Categorical variables were calculated as frequencies with percentages and comparisons were performed through Chi-square analyses and Fisher's exact test, where applicable. Logistic regression analysis was used to determine the relationship between specialist care utilization (high/low) as a dependent factor and possible contributing factors (i.e., disease-specific characteristics, sociodemographic characteristics, HRQoL, cost-utility, disease bother, needs for support). Associations are expressed as odds ratios (ORs) with the 95% confidence intervals (CIs) and p-values. Linear regression was used to determine the relationship between overall healthcare costs and all possible factors, which were in accordance with those of the logistic regression analysis. Associations are expressed as regression coefficients (B) with corresponding 95% confidence intervals and p-values. To control for confounding, variables associated with both the determinant and the outcome and not in the causal pathway of the relationship of interest were used as covariates in the multivariate analyses [20]. All associations were corrected for age and gender, depending on the determinant also for treatment type. ANCOVA was performed for the analysis of the disease bother and needs for support, correcting for age and gender (Supplementary Table 5).

For all analyses, results were considered statistically significant if the p-value was smaller than 0.05 (two-sided). Missing data on the questionnaires were handled by complete case analysis due to the low amount of missings (<5%).

RESULTS

Study population and patient characteristics

A total of 317 patients with an NFPA were identified from the hospital registry. After exclusion of ineligible patients, letters were sent to 265 patients, ultimately enrolling 167 (63%) patients for this study (Fig. 1). In total, 93 (56%) patients were male, the mean age was 66.8 (SD 12.1) years and the median time since diagnosis was 9 years (IQR 4.8–18.4). Most patients (n = 105, 63%) had undergone surgical treatment, followed by postoperative radiotherapy (40, 24%), and only wait-and-scan approach (22, 13%). The majority of patients (121, 73%) had one or more endocrine deficits. Adrenal insufficiency was present in 77 patients (46%), which was highest among patients who had undergone postoperative radiotherapy (28, 68%), followed by surgical treatment (43, 41%) and wait-and-scan (6, 27%) (Table 1).

Healthcare utilization

Primary care

The general practitioner was consulted in the previous year by 86 patients (52%). Fifty-eight patients (35%) had seen at least one other primary care health professional, most commonly the physiotherapist (44, 27%). There was no association between primary care utilization and patients with or without endocrine deficits, or duration of follow-up. Patients who had received postoperative radiotherapy had higher total physiotherapist and dietician visits (Tables 2 and 3).

Specialist care

Nearly all patients (165, 99%) had visited a medical specialist in the previous year, with a median of 2 (IQR 1–3) specialists per year and a median of 3 visits (IQR 2–5) per year. The most commonly visited specialists were the endocrinologist (158 patients, 95%), the ophthalmologist (97, 58%), and the neurosurgeon (23, 14%) (Tables 2 and 3).

Hospital admissions and emergency care

During the previous year, 23 patients (14%) had been admitted to a hospital at least once (mean hospital stay: 6.8; range 1–99 days). Furthermore, ten patients (6%) had at least one ambulance ride (mean 1.2; range 1–3 rides) and 19 patients (11%) had visited the ER at least once during the previous year (mean 1.3; range 1–5 visits). There were no significant differences in the amount of ambulance rides, ER visits, nor in the number or duration of hospitalizations between patients with or without endocrine deficits, based on applied treatments or duration of follow-up (Tables 2 and 3).

Determinants for healthcare utilization

After correcting for relevant confounders, older patients (OR 0.973, 95% CI 0.948;1.000), patients with longer time since diagnosis (OR 0.966, 95% CI 0.933;1.000), as well as patients with a better mental and physical health status (SF-36) (OR 0.929, 95% CI 0.896;0.962), and higher utility (EQ-5D) (OR 0.913, 95% CI 0.870; 0.960) were significantly less likely to have high specialist care utilization. Contrarily, patients with higher overall perceived disease bother (OR 1.048, 95% CI 1.020;1.076) and needs for support (LBNQ-Pituitary) (OR 1.033, 95% CI 1.012;1.055) were significantly more likely to have high specialist care utilization. More specific, there was a significant need for support for issues regarding physical and cognitive complaints, mood, negative illness perceptions and social functioning, but not for sexual functioning. There were no differences in specialist care utilization between patients with postoperative radiotherapy compared to other treatment regimens, as well as for those with and without hypopituitarism (Table 4).

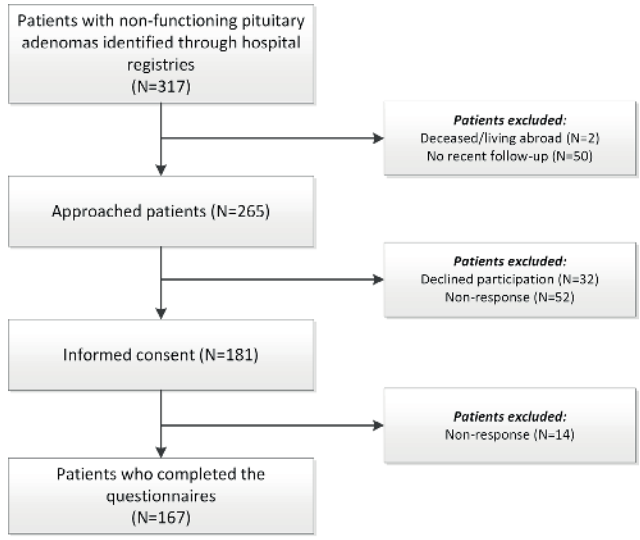

Figure 1. Flow chart of in-/exclusion of patients with an NFPA

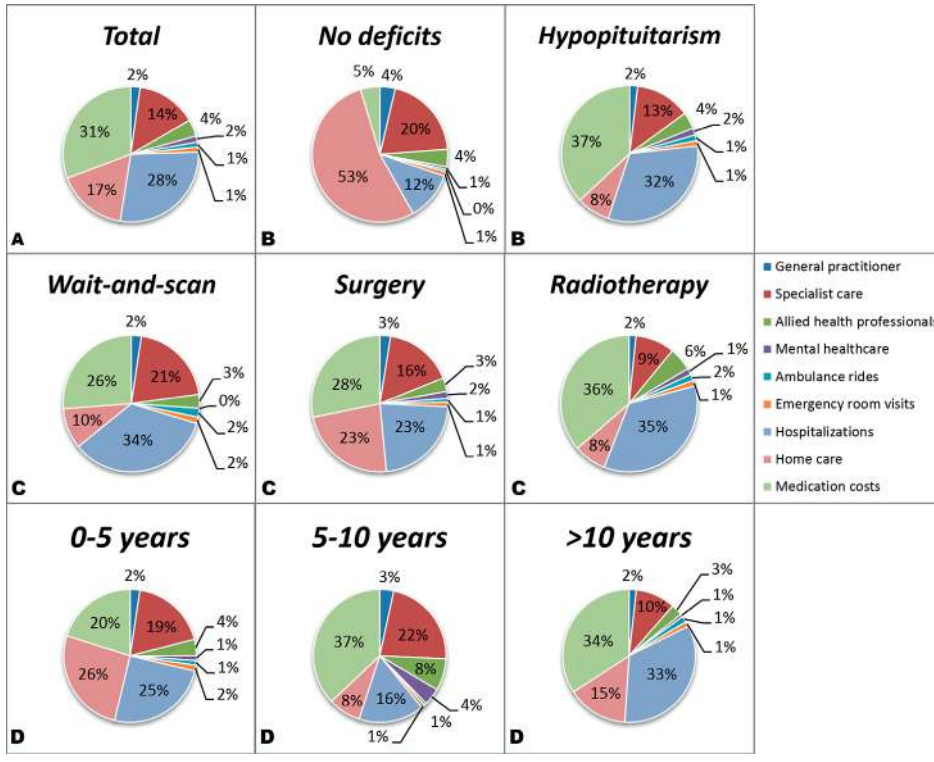

Figure 2. Overall costs among all patients with an NFPA (A), categorized per endocrine status (B), treatment algorithm (C) and duration of follow-up (D)

Table 1. Characteristics of 167 patients diagnosed with and treated for an NFPA categorized by endocrine deficits

	Total (N=167)	No deficits (N=46)	Hypopituitarism (N=121)	p-value
Demographic characteristics				
Sex, N (%)				
Female	74 (44.3)	28 (60.9)	46 (38.0)	**.008**
Age in years, mean (SD)	66.8 (12.1)	66.9 (11.2)	66.8 (12.5)	.963
Marital status, N (%)				
Relationship/married	128 (76.6)	36 (77.8)	92 (76.0)	.840
Education, N (%)				
Low	71 (42.5)	21 (45.7)	50 (41.3)	
Intermediate	41 (24.6)	10 (21.7)	31 (25.6)	
High	55 (32.9)	15 (32.6)	40 (33.1)	.838
Employment status, N (%)				
Paid job	58 (34.9)	20 (44.4)	38 (31.4)	
No paid job	25 (15.1)	4 (8.9)	21 (17.4)	
Retired	84 (50.3)	22 (46.7)	62 (51.2)	.229
Disease characteristics				
Time since diagnosis in years, median (IQR)	9.0 (4.8-18.4)	6.8 (4.5-13.5)	10.3 (5.1-19.4)	.054
Treatment, N (%)				
Wait-and-scan	22 (13.2)	13 (28.3)	9 (7.4)	
Surgery	104 (62.3)	28 (60.9)	76 (62.8)	
Postoperative radiotherapy	41 (24.6)	5 (10.9)	36 (29.8)	**<.001**
Current Health Status				
EQ-5D score, mean (SD)[a]	0.910 (0.089)	0.914 (0.075)	0.909 (0.094)	.771
EQ-5D VAS, mean (SD)[a]	73.6 (20.5)	74.8 (21.8)	73.2 (20.1)	.660
SF-36 PCS, mean (SD)[a]	44.5 (10.6)	44.6 (10.0)	44.4 (10.8)	.899
SF-36 MCS, mean (SD)[a]	50.7 (10.3)	51.0 (10.7)	50.6 (10.2)	.788
LBNQ-Pituitary index score, mean (SD)[b]	13.4 (15.9)	11.5 (15.6)	14.0 (16.0)	.397

Due to rounding, not all percentages of the categorical variables add up to 100%

NFPA non-functioning pituitary adenoma, N number, SD standard deviation, IQR interquartile range, VAS visual analog scale, EQ-5D EuroQoL, SF-36 short form-36, LBNQ-Pituitary Leiden bother and needs questionnaire-pituitary, MCS mental component scale, PCS physical component scale

[a]Higher scores indicate better HRQoL

[b]Lower scores indicate lower disease burden

Bold values indicates $p < 0.05$

Costs

The mean annual costs for patients with an NFPA were € 3040 (SD 6498) (Table 3). The three largest expenditures were (pituitary-specific) medication (31% of overall costs) inpatient care (28%), and specialist care (17%) (Fig. 2). The overall costs did not significantly differ between patients with and without hypopituitarism, even though

there were significantly higher costs for medication among those with hypopituitarism, postoperative radiotherapy, and longer duration of follow-up ($p < 0.05$) (Table 3).

Determinants for increased costs

Concerning healthcare costs, patients who were living alone had significantly higher healthcare costs (B 2960, 95% CI 510;5415) compared to those in a relationship. Patients with worse mental (B −107, 95% CI −206;−9) or worse physical health status (SF-36) (B −178, 95% CI −273;−82), lower utility (EQ-5D) (B −267, 95% CI −374;−161), greater disease bother (B 123, 95% CI 58;188), and a higher need for support (LBNQ-Pituitary) (B 130, 95% CI 79;180) also had significantly higher costs, which was the case for all domains. Hypopituitarism, postoperative radiotherapy and duration of follow-up were not associated with higher costs (Table 4).

Table 2. Average healthcare usage over the past 12 months in 167 patients with NFPA categorized by endocrine deficits

Healthcare service	Total (*N* = 167)		No endocrine deficits (*N* = 46)		Hypopituitarism (*N* = 121)		*p*-value
	Number of patients, %	Visits among those visiting, mean	Number of patients, %	Visits among those visiting, mean	Number of patients, %	Visits among those visiting, mean	
General practitioner	51.5	4.1	50.0	4.8	52.1	3.9	0.101
NFPA related medical specialists							
Endocrinologist	94.6	2.1	89.1	1.8	96.7	2.2	0.685
Neurosurgeon	13.9	1.7	19.6	1.1	11.7	2.1	0.084
Ophthalmologist	58.4	2.1	65.2	2.4	55.8	2.0	0.311
ENT-doctor	9.0	1.8	15.2	1.1	6.7	2.4	0.179
Neurologist	9.6	2.2	8.7	2.0	10.0	2.3	0.885
Radiation oncologist	1.8	1.3	2.2	1.0	1.7	1.5	0.642
Cardiologist	10.2	1.8	10.9	1.2	9.9	2.0	0.907
Internist	11.4	2.2	10.9	2.0	11.7	2.2	0.151
Others	24.6	2.2	32.6	2.1	21.5	2.3	0.798
Total number of different specialists							
0	1.2	–	2.2	–	0.8	–	
1	24.6	1.9	23.9	1.5	24.8	2.0	
2	37.1	3.6	26.1	3.3	41.3	3.7	
3	20.4	5.3	26.1	4.8	18.3	5.5	
4 or more	16.2	11.9	21.7	10.4	14.2	12.8	0.300
Occupational care							
Occupational	6.6	3.8	6.5	1.0	6.7	4.9	0.054
physician							
Mental healthcare							
Psychologist/	8.4	8.2	4.3	5.0	10.0	8.8	0.764
psychiatrist							
Allied health professionals							
Physiotherapist	26.5	12.2	26.1	9.3	26.7	13.2	0.271
Speech therapist	0.6	10.0	–	–	0.8	10.0	1.00
Dietician	6.6	2.3	6.5	2.7	6.7	2.1	0.431
Occupational therapist	0	–	0	–	0	–	–
Total number of different allied health professionals							
0	64.7	–	69.6	–	63.3	–	
1	29.9	9.2	23.9	6.1	32.5	10.1	
2	4.2	17.4	4.3	14.0	4.2	18.8	
3	0.6	28.0	2.2	28.0	0	–	
4	0	–	0	–	0	–	0.244

Table 2. Average healthcare usage over the past 12 months in 167 patients with NFPA categorized by endocrine deficits (continued)

Healthcare service	Total (*N* = 167)		No endocrine deficits (*N* = 46)		Hypopituitarism (*N* = 121)		*p*-value
	Number of patients, %	Visits among those visiting, mean	Number of patients, %	Visits among those visiting, mean	Number of patients, %	Visits among those visiting, mean	
Emergency care							
Ambulance rides, *N*	6.0	1.2	2.2	1.0	7.4	1.2	1.00
(%), mean							
Emergency room visit	11.4	1.3	8.7	1.0	12.4	1.3	0.622
(s), *N* (%), mean							
Hospital admission(s)	13.8	6.8	13.0	4.0	14.0	16.2	0.222
N (%), duration							
Home care							
Community nurse, *N*	1.2	122.5	–	–	1.7	122.5	–
(%), hours							
Informal care, *N* (%),	3.0	87.2	4.3	118.0	2.5	66.7	0.287
hours							
Household help, *N*	3.6	132.3	6.5	185.3	2.5	79.3	0.306
(%), hours							

NFPA non-functioning pituitary adenoma, *N* number, *SD* standard deviation
P-value based on number and frequency of visits, (bold) $p < 0.05$

DISCUSSION

The present study demonstrated that the overall healthcare utilization and costs in patients with an NFPA are substantial. Furthermore, this study shows that the endocrinologist and ophthalmologist are both actively involved in the care of over 50% of patients with an NFPA. In contrast to our hypothesis, overall healthcare utilization and overall costs did not differ between patients with or without endocrine deficits, or between the various treatments. Also, longer duration of follow-up was associated with lower healthcare utilization instead of higher utilization. These findings are intriguing, especially since it was anticipated that the burden of multiple hormone replacement therapy would have a significant impact on overall healthcare utilization.

Differences between patients appeared to be more related to subjective measurements such as HRQoL, disease bother and needs for support than objective outcomes or treatment variation. For instance, there was a strong association between lower HRQoL, higher self-perceived disease bother (on all domains of the LBNQ-Pituitary) and needs

Table 3. Medical and medication costs in euros (€) over the past 12 months in 167 patients with an NFPA categorized by endocrine deficits

Medical costs	Total (*N* = 167)				No endocrine deficits (*N* = 46)				Hypopituitarism (*N* = 121)				Overall *p*-value
	Number of patients		Costs among those visiting		Number of patients		Costs among those visiting		Number of patients		Costs among those visiting		
	N	%	mean	SD	*N*	%	mean	SD	*N*	%	mean	SD	
General practitioner	86	51.5	135.67	131.28	23	50.0	159.00	156.99	63	52.1	126.97	120.68	0.498
Specialist care	165	98.8	444.52	511.96	45	97.8	438.82	428.71	120	99.2	446.66	541.52	0.878
Allied health professionals[a]	58	34.9	348.21	378.54	14	30.4	289.93	245.31	44	36.7	366.75	412.67	0.339
Mental healthcare[b]	14	8.4	525.71	449.88	2	4.3	320.00	271.53	12	10.0	560.00	472.77	0.211
Ambulance rides	10	6.0	618.00	325.71	1	2.2	515.00	–	9	7.4	629.44	343.33	0.215
Emergency room visits	19	11.4	327.16	169.22	4	8.7	259.00	0.00	15	12.4	345.33	187.45	0.323
Hospitalization	23	13.8	6188.00	10737.13	6	13.0	1904.00	2624.48	17	14.0	7700.00	12126.60	0.282
Home care[c]	7	4.2	12094.57	5731.49	3	6.5	17462.67	2058.55	4	3.3	8068.50	3527.91	0.060
Total medical costs	167	100	2103.43	6420.38	46	100	2028.41	4610.01	121	100	2131.95	7003.58	0.926

Medication costs	Number of patients		Costs among those using medication		Number of patients		Costs among those using medication		Number of patients		Costs among those using medication		Overall *p*-value
	N	%	Mean	SD	*N*	%	Mean	SD	*N*	%	Mean	SD	
Androgel	56	33.5	445.88	258.61	0				56	46.3	445.88	258.61	<0.001
Desmopressine	11	6.6	99.12	66.92	0	–	–	–	11	9.0	99.12	66.92	0.079
Thyrax	90	53.9	34.29	12.94	0	–	–	–	90	74.4	34.29	12.94	<0.001
Genotropin	30	18.0	2917.47	1505.46	0	–	–	–	30	24.8	2917.47	1505.46	0.001
Cabergoline	3	1.8	1887.71	2227.07	1	2.2	4423.92	–	2	1.7	619.60	520.66	0.158
Quinagolide	2	1.2	1056.00	1405.73	1	2.2	62.00	–	1	0.8	2050.00	–	0.572
Hydrocortison	77	46.1	411.82	218.94	0	–	–	–	77	63.6	411.82	218.94	<0.001
Anticonceptives	4	2.4	43.41	31.03	2	4.3	27.90	–	2	1.7	58.93	43.88	0.861
Total drug costs	125	74.9	1250.63	1610.18	4	8.7	1135.43	2192.39	121	100	1254.44	1599.53	<0.001
Overall costs	167	100	3039.53	6498.22	46	100	2127.15	4632.22	121	100	3386.39	7065.90	0.265

Reference prices are presented in Supplementary Table 4

NFPA non-functioning pituitary adenoma, *N* number, *IQR* interquartile range aPhysiotherapists, Speech therapists, Dieticians, Occupational therapists bPsychiatrists, psychologists cCommunity nurse, informal care, household help Bold values indicates $p < 0.05$

Table 4. Logistic/linear regression analysis per determinant for medical specialist utilization and costs among patients with an NFPA

Determinant	High specialist utilization (adjusted for demographics)			Healthcare costs (adjusted for demographics)		
	OR	95% CI	p-value	B	95% CI	p-value
Sociodemographic						
Sex (ref: male gender)[a]	1.504	0.804;2.814	0.202	1606	−404;3617	0.117
Age[b]	0.973	0.948;1.000	0.047	51	−32;133	0.226
Marital status (ref: relationship/married)[a,b]						
Single/divorced/widow	2.195	0.982;4.905	0.055	2963	510;5415	0.018
Education (ref: high)[a,b]						
Intermediate	1.559	0.728;3.337	0.253	1666	−980;4311	0.216
Low	1.778	0.768;4.116	0.179	687	−1712;3087	0.572
Employment status (ref: paid job)[a,b]						
No paid job	0.580	0.206;1.635	0.303	−941	−4235;2354	0.574
Retired	0.608	0.221;1.674	0.336	−1061	−4293;2171	0.518
Disease specific						
Time since diagnosis[a,b]	0.966	0.933;1.000	0.047	91	−9;191	0.074
Treatment (ref: wait-and-scan)[a,b]						
Surgery	0.656	0.483;3.179	0.656	484	−2520;3488	0.751
Postoperative radiotherapy	0.644	0.442;3.743	0.644	1895	−1520;5310	0.275
Endocrine status (ref: no deficits)[a,b,c]						
Hypopituitarism	0.734	0.414;1.861	0.734	1456	−945;3857	0.233
HRQoL, utility, disease bother and needs for support SF-36[a,b]						
Mental component scale	0.942	0.909;0.976	0.001	−107	−206;−9	0.033
Physical component scale	0.929	0.896;0.962	<0.001	−178	−273;−82	<0.001
EQ-5D[a,b]						
EQ index (rescaled to 0–100)	0.913	0.870;0.960	<0.001	−267	−374;−161	<0.001
EQ VAS (scale 0–100)	0.968	0.951;0.986	0.001	−98	−146;−51	<0.001
Disease bother (LBNQ-Pituitary)[a,b]						
Physical and cognitive complaints	1.037	1.016;1.059	<0.001	77	25;130	0.004
Mood	1.036	1.015;1.057	0.001	60	7;114	0.028
Negative illness perceptions	1.044	1.018;1.070	0.001	61	−5;127	0.070
Sexual functioning	1.021	1.003;1.038	0.018	111	64;159	<0.001
Social functioning	1.030	1.004;1.056	0.021	146	86;207	<0.001
Total index score	1.048	1.020;1.076	0.001	123	58;188	<0.001
Needs for support (LBNQ-Pituitary)[a,b]						
Physical and cognitive complaints	1.031	1.013;1.049	0.001	88	44;131	<0.001
Mood	1.026	1.010;1.043	0.001	80	38;122	<0.001
Negative illness perceptions	1.019	1.004;1.035	0.013	51	8;95	0.021
Sexual functioning	1.013	0.998;1.029	0.096	131	90;172	<0.001
Social functioning	1.023	1.001;1.044	0.036	155	104;206	<0.001
Total index score	1.033	1.012;1.055	0.002	130	79;180	<0001

SF-36, EQ-5D: higher scores indicate better HRQoL or utility/LBNQ-Pituitary: lower scores indicate lower disease bother or needs for support

Ref reference category, (bold) $p < 0.05$, *OR* odds ratio, *CI* confidence interval, *HRQoL* Health-Related Quality of Life, *SF-36* Short Form-36, *EQ-5D* EuroQoL, *LBNQ-Pituitary* Leiden Bother and Needs Questionnaire

a,b,cAdjusted for age (1), gender (2), treatment (3)

for support (on all domains, except for sexual functioning) and increased healthcare utilization and costs. This makes patient-reported outcome measures (PROMS) a promising tool to gain better insight into the patient's condition and when to consider interventions to reduce healthcare utilization and costs and to optimize care trajectories. Further investigation towards optimal strategies supporting this hypothesis is necessary, perhaps through self-management interventions [21, 22].

Our study can be best compared to the study by Swearingen et al. [11], which is the only other currently available study reporting on healthcare utilization among 3792 patients with an NFPA. Comparable results were found for hospitalizations and office visits, however they found a higher number of ER visits (24% vs. 11%). This study, however, presented aggregated data from insurance claims databases, limiting comprehensive insight into which healthcare providers are consulted, lacked information on treatment and endocrine status and did not look at determinants for healthcare utilization and costs.

Other studies among patients with a functioning pituitary adenoma have mostly shown higher rates of hospitalizations (range 9–38.4% vs. 14%), comparable rates of proportion of patients visiting specialists (range 94–99% vs. 99%), and also higher ER visits (23–34% vs. 11%) [6–12]. The major differences in disease characteristics, however, limit comparability.

Concerning the costs of patients treated for an NFPA, the mean total costs found in our study were approximately fourfold lower compared to those reported by Swearingen et al. [11] ($ 13,708 vs. € 3039), which can be explained, at least in part, by the higher healthcare costs in the USA [23], but also show the variation between costs for patients with different types of pituitary adenomas. The most notable difference is the mean costs for medication, which is nearly ten times as high among the study by Swearingen et al. ($ 11,181 vs. € 1250). With regard to functioning adenomas, the mean total costs among patients with Cushing's disease ranged between $ 26,269 and $ 34,992; for acromegaly between € 9200 and $ 32,807 [6–12]. Both are considerably higher compared to the costs found in our study.

Pertaining to determinants, to the best of our knowledge, no other study has described determinants for healthcare utilization or costs of care for patients with an NFPA. One other study among patients with acromegaly previously reported that younger age, female gender, and hypopituitarism were associated with higher healthcare costs, and that the presence of an increasing amount of comorbidities was associated with an

increased risk for hospitalizations and ER visits [7]. These results could not be confirmed in our study.

A strength of our study was the high response rate (63%). The use of self-reported information on healthcare services was another strength of our study. This has recently been reported as the most suitable method for the measurement of healthcare utilization [24], thereby supporting the results presented here. This, however, was also a limitation of our study; since questionnaires were based on self-reports, it is possible that patients had difficulty distinguishing between various medical terms, i.e., differentiating between radiologists and radiation oncologists. Another important limitation is that even though we acknowledge that comorbidities are an important factor for a patient's HRQoL [7, 25], we were unable to analyze the impact of comorbidities in our study. Furthermore, the decision to invite only those patients who had visited the outpatient clinic in the prior 2 years (based on the tertiary referral function of our center) may have introduced a selection bias. We anticipated that this would influence results in both a negative and a positive way, since not only patients with better health status are referred back to the center they were referred by, but also patients with worse health status who are unable to travel to our center. The single center setting in which this study took place is another limitation that restricts generalizability of this study. However, by providing mean visits per patient, comparisons between healthcare systems can be made. Finally, we only included pituitary-specific medication in the analysis of the medication costs, which underestimates total medication costs.

The high active involvement by the endocrinologist and ophthalmologist in the care of patients with an NFPA in combination with the association between subjective determinants for healthcare utilization and costs are potential targets for future interventions. A next step could be to define trajectories of care and match these with the health status and healthcare needs of specific subgroups of patients in order to generate patient-tailored care. This might ultimately improve HRQoL and could lead to cost reductions in the long haul, however, prospective studies are necessary to confirm this hypothesis.

CONCLUSION

Healthcare utilization and costs among patients with an NFPA are substantial. Intriguingly, the extent of healthcare utilization and costs is independent of endocrine status and treatment algorithm, and costs are independent of duration of follow-up. Instead, worse HRQoL and more bother by the negative consequences of the disease and needs

for support were associated with higher healthcare utilization and costs and can potentially be used as a tool to differentiate healthcare usage and cost drivers.

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Supplementary table 1a. Characteristics of 167 patients diagnosed with and treated for NFPA categorized by treatment

	Total (N=167)	Wait-and-scan (N=22)	Surgery (N=104)	Postoperative Radiotherapy (N=41)	p-value
Demographic characteristics					
Sex, N (%)					
Female	74 (44.3)	8 (36.4)	44 (42.3)	22 (53.7)	.336
Age in years, mean (SD)	66.8 (12.1)	68.7 (12.6)	67.6 (12.5)	63.9 (10.5)	.197
Marital status, N (%)					
Relationship/married	128 (76.6)	17 (77.3)	83 (79.8)	28 (68.3)	.336
Education, N (%)					
Low	71 (42.5)	6 (27.3)	45 (43.3)	20 (48.8)	
Intermediate	41 (24.6)	6 (27.3)	25 (24.0)	10 (24.4)	
High	55 (32.9)	10 (45.5)	34 (32.7)	11 (26.8)	.527
Employment status, N (%)					
Paid job	58 (34.9)	10 (45.5)	38 (36.9)	10 (24.4)	
No paid job	25 (15.1)	0 (0.0)	12 (11.7)	13 (31.7)	
Retired	84 (50.3)	12 (54.5)	54 (51.9)	18 (43.9)	**.008**
Disease characteristics					
Time since diagnosis in years, median (IQR)	9.0 (4.8-18.4)	10.1 (6.7-16.0)	6.8 (4.1-13.3)	18.4 (11.1-24.9)	**<.001**
Endocrine status, N (%)					
Hypopituitarism	121 (72.5)	9 (40.9)	76 (73.1)	36 (87.8)	**<.001**
Current Health Status					
EQ-5D score, mean (SD)*	0.910 (0.089)	0.917 (0.068)	0.911 (0.085)	0.906 (0.110)	.894
EQ-5D VAS, mean (SD)*	73.6 (20.5)	72.7 (14.4)	75.1 (21.1)	70.5 (21.6)	.479
SF-36 PCS, mean (SD)*	44.5 (10.6)	45.8 (9.4)	45.1 (10.9)	42.1 (10.1)	.242
SF-36 MCS, mean (SD)*	50.7 (10.3)	51.0 (10.4)	50.5 (10.7)	50.9 (9.5)	.965
LBNQ-Pituitary index score, mean (SD)†	13.4 (15.9)	11.3 (15.4)	11.9 (15.7)	18.1 (15.9)	.092

NFPA (non-functioning pituitary adenoma), N (number), SD (standard deviation), IQR (interquartile range), VAS (visual analogue scale), EQ-5D (EuroQoL), SF-36 (short form-36), LBNQ-Pituitary (Leiden bother and needs questionnaire-pituitary), MCS (mental component scale), PCS (physical component scale), (bold) $p < 0.05$

* Higher scores indicate better HRQoL

† Lower scores indicate lower disease burden

Due to rounding, not all percentages of the categorical variables add up to 100%

Supplementary table 1b. Characteristics of 167 patients diagnosed with and treated for NFPA categorized by duration of follow-up

	Total (N=167)	0-5 years (N=43)	5-10 years (N=45)	>10 years (N=79)	p-value
Demographic characteristics					
Sex, N (%)					
Female	74 (44.3)	17 (39.5)	20 (44.4)	37 (46.8)	.740
Age in years, mean (SD)	66.8 (12.1)	63.9 (13.2)	64.0 (11.7)	70.1 (11.0)	**.004**
Marital status, N (%)					
Relationship/married	128 (76.6)	34 (79.1)	38 (84.4)	56 (70.9)	.209
Education, N (%)					
Low	71 (42.5)	14 (32.6)	24 (53.3)	33 (41.8)	
Intermediate	41 (24.6)	14 (32.6)	9 (20.0)	18 (22.8)	
High	55 (32.9)	15 (34.9)	12 (26.7)	28 (35.4)	.332
Employment status, N (%)					
Paid job	58 (34.9)	25 (58.1)	14 (31.1)	19 (24.4)	
No paid job	25 (15.1)	2 (4.7)	10 (22.2)	13 (16.7)	
Retired	84 (50.3)	16 (37.2)	21 (46.7)	47 (59.5)	.002
Disease characteristics					
Time since diagnosis in years, median (IQR)	9.0 (4.8-18.4)	3.1 (2.5-4.3)	6.9 (6.2-8.0)	18.7 (13.5-24.9)	**<.001**
Treatment, N (%)					
Wait-and-scan	22 (13.2)	4 (9.3)	6 (13.3)	12 (15.2)	
Surgery	104 (62.3)	38 (88.4)	31 (68.9)	35 (44.3)	
Postoperative radiotherapy	41 (24.6)	1 (2.3)	8 (17.8)	32 (40.5)	**<.001**
Endocrine status, N (%)					
Hypopituitarism	121 (72.5)	30 (69.8)	28 (62.2)	63 (79.7)	.099
Current Health Status					
EQ-5D score, mean (SD)*	0.910 (0.089)	0.926 (0.067)	0.913 (0.079)	0.900 (0.103)	.316
EQ-5D VAS, mean (SD)*	73.6 (20.5)	74.9 (21.8)	75.3 (17.8)	72.0 (21.4)	.634
SF-36 PCS, mean (SD)*	44.5 (10.6)	46.1 (10.0)	44.3 (11.6)	43.6 (10.3)	.468
SF-36 MCS, mean (SD)*	50.7 (10.3)	50.2 (11.3)	48.1 (11.8)	52.4 (8.4)	.073
LBNQ-Pituitary index score, mean (SD)†	13.4 (15.9)	11.8 (16.7)	17.9 (18.2)	11.4 (13.3)	.076

NFPA (non-functioning pituitary adenoma), N (number), SD (standard deviation), IQR (interquartile range), VAS (visual analogue scale), EQ-5D (EuroQoL), SF-36 (short form-36), LBNQ-Pituitary (Leiden bother and needs questionnaire-pituitary), MCS (mental component scale), PCS (physical component scale), (bold) $p < 0.05$

* Higher scores indicate better HRQoL

† Lower scores indicate lower disease burden

Due to rounding, not all percentages of the categorical variables add up to 100%

Supplementary table 2a. Average healthcare usage over the past 12 months in 167 patients with an NFPA categorized by treatment

	Total (N=167)		Wait-and-scan (N=22)		Surgery (N=104)		Postoperative radiotherapy (N=41)		
Healthcare service	Number of patients, %	Visits among those visiting, mean	Number of patients, %	Visits among those visiting, mean	Number of patients, %	Visits among those visiting, mean	Number of patients, %	Visits among those visiting, mean	p-value
General practitioner	51.5	4.1	40.9	4.0	51.0	4.0	46.3	4.4	.950
NFPA related medical specialists									
Endocrinologist	94.6	2.1	86.4	1.9	94.2	2.2	100.0	1.8	.560
Neurosurgeon	13.9	1.7	0	-	20.2	1.7	4.9	2.0	.039
Ophthalmologist	58.4	2.1	72.7	1.7	57.7	2.2	48.8	2.4	.904
ENT-doctor	9.0	1.8	9.1	1.5	9.6	1.8	7.3	2.0	.964
Neurologist	9.6	2.2	0	-	8.7	2.2	17.1	2.1	.193
Radiation oncologist	1.8	1.3	0	-	1.0	2.0	4.9	1.0	.146
Cardiologist	10.2	1.8	18.2	2.5	9.6	1.6	7.3	1.3	.166
Internist	11.4	2.2	9.1	1.0	13.5	2.5	4.9	1.0	.195
Others	24.6	2.2	36.4	3.5	20.2	2.1	29.3	1.4	.064
Total number of different specialists									
0	1.2	-	4.5	-	1.0	-	0	-	
1	24.6	1.9	13.6	1.7	27.2	1.8	24.4	2.1	
2	37.1	3.6	36.4	3.1	35.0	3.9	43.9	3.3	
3	20.4	5.3	22.7	5.2	20.4	5.1	19.5	5.9	
4 or more	16.2	11.9	22.7	11.2	16.3	12.9	12.2	9.2	.689
Occupational care									
Occupational physician	6.6	3.8	9.1	2.0	4.8	4.8	9.8	3.5	.867
Mental healthcare									
Psychologist/psychiatrist	8.4	8.2	0	-	7.7	9.4	14.6	6.7	.468
Allied health professionals									
Physiotherapist	26.5	12.2	27.3	7.5	22.1	10.7	36.6	16.3	**.044**
Speech therapist	0.6	10.0	0	-	0	-	2.4	10.0	.219
Dietician	6.6	2.3	0	-	3.8	2.0	17.1	2.4	**.006**
Occupational therapist	0	-	0	-	0	-	0	-	-
Total number of different allied health professionals									
0	64.7	-	68.2	-	70.9	-	48.8	-	
1	29.9	9.2	27.3	6.3	27.2	8.7	39.0	11.3	
2	4.2	17.4	4.5	11.0	1.9	17.0	9.8	19.3	

Supplementary table 2a. Average healthcare usage over the past 12 months in 167 patients with an NFPA categorized by treatment (continued)

	Total (N=167)		Wait-and-scan (N=22)		Surgery (N=104)		Postoperative radiotherapy (N=41)		
Healthcare service	Number of patients, %	Visits among those visiting, mean	Number of patients, %	Visits among those visiting, mean	Number of patients, %	Visits among those visiting, mean	Number of patients, %	Visits among those visiting, mean	p-value
3	0.6	28.0	0	-	0	-	2.4	28.0	
4	0	-	0	-	0	-	0	-	.089
Emergency care									
Ambulance rides, N(%), mean	6.0	1.2	9.1	1.0	4.8	1.0	7.3	1.7	.350
Emergency room visit(s), N(%), mean	11.4	1.3	13.6	1.0	9.6	1.2	14.6	1.5	.531
Hospital admission(s) N(%), duration	13.8	6.8	22.7	7.2	13.5	5.1	9.8	12.5	.205
Home care									
Community nurse, N(%), hours	1.2	122.5	0	-	1.0	20.0	2.4	225.0	-
Informal care, N(%), hours	3.0	87.2	4.5	96.0	2.9	85.3	2.4	84.0	.990
Household help, N(%), hours	3.6	132.3	0	-	4.9	146.8	2.4	60.0	.234

NFPA (non-functioning pituitary adenoma), N (number), SD (standard deviation)
p-value based on number and frequency of visits, (bold) $p < 0.05$

Supplementary table 2b. Average healthcare usage over the past 12 months in 167 patients with an NFPA categorized by treatment

	Total (N=167)		0-5 years (N=43)		5-10 years (N=45)		>10 years (N=79)		
Healthcare service	Number of patients, %	Visits among those visiting, mean	Number of patients, %	Visits among those visiting, mean	Number of patients, %	Visits among those visiting, mean	Number of patients, %	Visits among those visiting, mean	p-value
General practitioner	51.5	4.1	55.8	4.3	40.0	5.1	49.4	3.6	.411
NFPA related medical specialists									
Endocrinologist	94.6	2.1	90.7	2.9	97.8	2.1	94.9	1.6	**.018**
Neurosurgeon	13.9	1.7	23.3	1.4	22.2	2.0	3.8	1.7	**.008**
Ophthalmologist	58.4	2.1	62.8	2.6	64.4	2.0	50.6	2.0	.127
ENT-doctor	9.0	1.8	7.0	3.3	6.7	1.0	11.4	1.6	.558
Neurologist	9.6	2.2	14.0	2.8	8.9	2.0	7.6	1.7	.184
Radiation oncologist	1.8	2.7	4.7	1.5	2.2	1.0	0	-	.315
Cardiologist	10.2	1.8	9.3	2.5	8.9	1.0	11.4	1.8	.623
Internist	11.4	2.2	11.6	3.6	11.1	1.4	10.1	1.8	.357
Others	24.6	2.2	27.9	2.8	20.0	2.2	25.3	1.8	.167
Total number of different specialists									
0	1.2	-	2.3	-	0	-	1.3	-	
1	24.6	1.9	20.9	2.8	15.6	1.6	31.6	1.6	
2	37.1	3.6	32.6	3.2	42.2	4.2	36.7	3.5	
3	20.4	5.3	25.6	6.9	22.2	4.5	16.5	4.5	
4 or more	16.2	11.9	18.6	18.1	20.0	9.4	12.7	9.2	.506
Occupational care									
Occupational physician	6.6	3.8	11.6	4.6	11.1	3.4	1.3	2.0	.083
Mental healthcare									
Psychologist/psychiatrist	8.4	8.2	4.7	13.0	20.0	6.6	3.8	10.0	.257
Allied health professionals									
Physiotherapist	26.5	12.2	32.6	10.6	20.0	19.9	26.6	9.9	.673
Speech therapist	0.6	10.0	0	-	2.2	10.0	0	-	.262
Dietician	6.6	2.3	0	-	4.4	2.5	11.4	2.2	.081
Occupational therapist	0	-	0	-	0	-	0	-	-
Total number of different allied health professionals									
0	64.7	-	60.5	-	68.9	-	64.6	-	
1	29.9	9.2	34.9	9.9	26.7	13.5	29.1	6.6	
2	4.2	17.4	4.7	12.0	2.2	21.0	5.1	19.3	
3	0.6	28.0	0	-	2.2	28.0	0	-	

Supplementary table 2b. Average healthcare usage over the past 12 months in 167 patients with an NFPA categorized by treatment (continued)

	Total (N=167)		0-5 years (N=43)		5-10 years (N=45)		>10 years (N=79)		
Healthcare service	Number of patients, %	Visits among those visiting, mean	Number of patients, %	Visits among those visiting, mean	Number of patients, %	Visits among those visiting, mean	Number of patients, %	Visits among those visiting, mean	p-value
4	0	-	0	-	0	-	0	-	.671
Emergency care									
Ambulance rides, N(%), mean	6.0	1.2	7.0	1.0	2.2	1.0	7.6	1.3	.767
Emergency room visit(s), N(%), mean	11.4	1.3	14.0	1.3	6.7	1.0	12.7	1.3	.764
Hospital admission(s) N(%), duration	13.8	6.8	14.0	4.5	8.9	5.5	16.5	8.3	.858
Home care									
Community nurse, N(%), hours	1.2	122.5	0	-	2.2	20.0	1.3	225.0	-
Informal care, N(%), hours	3.0	87.2	4.7	118.0	2.2	20.0	2.5	90.0	.315
Household help, N(%), hours	3.6	132.3	4.7	174.0	2.2	78.0	3.8	122.7	.522

NFPA (non-functioning pituitary adenoma), N (number), SD (standard deviation)
p-value based on number and frequency of visits, (bold) $p < 0.05$

Supplementary table 3a. Medical and medication costs in euros (€) over the past 12 months in 167 patients with an NFPA categorized by treatment strategy

	Total (N=167)				Wait-and-scan (N=22)				Surgery (N=104)				Postoperative radiotherapy (N=41)				
Medical costs	Number of patients		Costs among those visiting		Number of patients		Costs among those visiting		Number of patients		Costs among those visiting		Number of patients		Costs among those visiting		Overall p-value
	N	%	mean	SD	N	%	mean	SD	N	%	mean	SD	N	%	mean	SD	
General practitioner	86	51.5	135.67	131.28	9	40.9	132.0	80.8	53	51.0	133.2	125.2	19	46.3	144.2	168.3	.829
Specialist care	165	98.8	444.52	511.96	21	95.5	485.3	393.9	103	99.0	460.3	596.2	41	100.0	377.7	293.3	.636
Allied health professionals*	58	34.9	348.21	378.54	7	31.8	231	117.4	30	28.8	304.7	330.9	21	51.2	449.4	476.6	**.014**
Mental healthcare**	14	8.4	525.71	449.88	0	0.0	-	-	8	7.7	600.0	472.7	6	14.6	426.7	439.1	.468
Ambulance rides	10	6.0	618.00	325.71	2	9.1	515.0	0	5	4.8	515.0	0	3	7.3	858.3	594.7	.442
Emergency room visits	19	11.4	327.16	169.22	3	13.6	259.0	0	10	9.6	310.8	163.8	6	14.6	388.5	216.7	.466
Hospitalization	23	13.8	6188.00	10737.13	5	22.7	3427.2	2389.5	14	13.5	4692.0	7463.1	4	9.8	14875.0	21741.5	.609
Home care***	7	4.2	12094.57	5731.49	1	4.5	4800.0	-	5	4.8	13356.4	5808.6	1	2.4	13080	-	.690
Total medical costs	167	100	2103.43	6420.38	22	100.0	1670.0	2670.1	104	100.0	1986.2	4842.8	41	100.0	2633.3	10320.3	.815

Supplementary table 3a. Medical and medication costs in euros (€) over the past 12 months in 167 patients with an NFPA categorized by treatment strategy (continued)

	Total (N=167)				Wait-and-scan (N=22)				Surgery (N=104)				Postoperative radiotherapy (N=41)				
Medication costs	Number of patients		Costs among those using medication		Number of patients		Costs among those using medication		Number of patients		Costs among those using medication		Number of patients		Costs among those using medication		Overall p-value
	N	%	mean	SD	N	%	mean	SD	N	%	mean	SD	N	%	mean	SD	
Androgel	56	33.5	445.88	258.61	6	27.3	297.0	148.9	35	33.7	427.3	243.8	15	36.6	548.8	297.8	.201
Desmopressine	11	6.6	99.12	66.92	1	4.5	53.5	-	6	5.8	81.8	70.2	4	9.8	136.5	59.7	.229
Thyrax	90	53.9	34.29	12.94	5	22.7	35.9	10.5	55	52.9	32.6	12.5	30	73.2	37.1	13.9	**.001**
Genotropin	30	18.0	2917.47	1505.46	2	9.1	1407.7	1016.8	14	13.5	3233.0	1679.7	14	34.1	2817.6	1298.6	**.025**
Cabergoline	3	1.8	1887.71	2227.07	1	4.5	4423.9	-	1	1.0	251.4	-	1	2.4	987.8	-	.052
Quinagolide	2	1.2	1056.00	1405.73	2	9.1	1056.0	1405.7	0	0.0	-	-	0	0.0	-	-	**.029**
Hydrocortison	77	46.1	411.82	218.94	6	27.3	270.6	145.9	43	41.3	435.4	268.1	28	68.3	405.9	117.4	**.007**
Anticonceptives	4	2.4	43.41	31.03	2	9.1	27.9	0	1	1.0	90.0	-	1	2.4	27.9	-	.629
Total drug costs	125	74.9	1250.63	1610.18	13	59.1	1003.5	1439.7	76	73.1	1073.2	1554.3	36	87.8	1714.4	1727.9	**.016**
Overall costs	167	100	3039.53	6498.22	22	100.0	2263.0	3119.9	104	100.0	2770.5	4932.2	41	100.0	4138.6	10282.6	.437

NFPA (non-functioning pituitary adenoma), N (number), IQR (interquartile range), (bold) $p < 0.05$

* Physiotherapists, Speech therapists, Dieticians, Occupational therapists

** Psychiatrists, psychologists

***Community nurse, informal care, household help

Reference prices are presented in supplementary table 4

Supplementary table 3b. Medical and medication costs in euros (€) over the past 12 months in 167 patients with an NFPA categorized by follow-up

	Total (N=167)				0-5 years (N=43)				5-10 years (N=45)				>10 years (N=79)				
Medical costs	Number of patients		Costs among those visiting		Number of patients		Costs among those using medication		Number of patients		Costs among those using edication		Number of patients		Costs among those using medication		Overall p-value
	N	%	mean	SD	N	%	mean	SD	N	%	mean	SD	N	%	mean	SD	
General practitioner	86	51.5	135.67	131.28	24	55.8	141.6	133.2	18	40.0	186.8	44.0	39	49.4	117.6	95.7	.829
Specialist care	165	98.8	444.52	511.96	42	97.7	630.5	849.0	45	100.0	444.9	338.4	78	98.7	344.2	282.7	.636
Allied health professionals*	58	34.9	348.21	378.54	17	39.5	333.9	213.8	14	31.1	497.4	513.3	27	34.2	279.9	370.6	**.014**
Mental healthcare**	14	8.4	525.71	449.88	2	4.7	832.0	633.6	9	20.0	419.6	389.4	3	3.8	640.0	586.6	.468
Ambulance rides	10	6.0	618.00	325.71	3	7.0	515.0	0	1	2.2	515.0	-	6	7.6	686.7	420.5	.442
Emergency room visits	19	11.4	327.16	169.22	6	14.0	345.3	211.5	3	6.7	259.0	0	10	12.7	336.7	174.8	.466
Hospitalization	23	13.8	6188.00	10737.13	6	14.0	5950.0	11121.5	4	8.9	3570.0	2734.4	13	16.5	7103.4	12439.1	.609
Home care***	7	4.2	12094.57	5731.49	2	4.7	18602.0	828.7	1	2.2	7094.0	-	4	5.1	10091.0	4853.1	.690
Total medical costs	167	100	2103.43	6420.38	43	100.0	2645.1	6641.6	45	100.0	1254.0	1893.4	79	100.0	2292.5	7831.9	.815

Supplementary table 3b. Medical and medication costs in euros (€) over the past 12 months in 167 patients with an NFPA categorized by follow-up (continued)

	Total (N=167)				0-5 years (N=43)				5-10 years (N=45)				>10 years (N=79)				
Medication costs	Number of patients		Costs among those using medication		Number of patients		Costs among those using medication		Number of patients		Costs among those using medication		Number of patients		Costs among those using medication		Overall p-value
	N	%	mean	SD	N	%	mean	SD	N	%	mean	SD	N	%	mean	SD	
Androgel	56	33.5	445.88	258.61	14	32.6	429.4	199.2	14	31.1	490.0	331.5	28	35.4	432.0	250.7	.201
Desmopressine	11	6.6	99.12	66.92	2	4.7	148.4	67.1	4	8.9	101.0	67.0	5	6.3	78.0	70.2	.229
Thyrax	90	53.9	34.29	12.94	22	51.2	29.7	13.7	20	44.4	34.7	11.1	48	60.8	36.3	13.0	**.001**
Genotropin	30	18.0	2917.47	1505.46	4	9.3	2905.0	898.9	8	17.8	2293.6	889.9	18	22.8	3197.5	1769.6	**.025**
Cabergoline	3	1.8	1887.71	2227.07	1	2.3	4423.9	-	1	2.2	251.4	-	1	1.3	987.8	-	.052
Quinagolide	2	1.2	1056.00	1405.73	1	2.3	62.0	-	1	2.2	2050.0	-	0	0.0	-	-	**.029**
Hydrocortison	77	46.1	411.82	218.94	13	30.2	429.4	394.3	15	33.3	443.5	246.2	49	62.0	397.5	136.9	**.007**
Anticonceptives	4	2.4	43.41	31.03	0	0.0	-	-	2	4.4	27.9	0	2	2.5	58.9	43.9	.629
Total drug costs	125	74.9	1250.63	1610.18	31	72.1	922.2	1248.4	29	64.4	1147.1	1458.4	65	82.3	1453.5	1806.5	**.016**
Overall costs	167	100	3039.53	6498.22	43	100.0	3310.0	6578.8	45	100.0	1993.2	2162.7	79	100.0	3488.3	7940.3	.437

NFPA (non-functioning pituitary adenoma), N (number), IQR (interquartile range), (bold) $p < 0.05$

* Physiotherapists, Speech therapists, Dieticians, Occupational therapists

** Psychiatrists, psychologists

***Community nurse, informal care, household help

Reference prices are presented in supplementary table 4

Supplementary table 4. Unit costs in euros (€)

Direct medical costs	*Value (€)*	*Reference*	*Source*	*Remark*
General practitioner	33	2016	Guideline*	Per visit
Specialist care	91	2016	Guideline*	Per visit
Paramedical care**	33	2016	Guideline*	Per visit
Mental healthcare***	64-98	2016	Guideline*	Per visit
Ambulance rides	515	2016	Guideline*	Per visit
Emergency room visits	259	2016	Guideline*	Per visit
Inpatient care	476	2016	Guideline*	Per visit
Community nurse	73	2016	Guideline*	Per visit
Informal care	50	2016	Guideline*	Per visit
Household help	20	2016	Guideline*	Per visit
Drug costs				
Androgel	0.31-10.49	2018	Medicijnkosten.nl	Dependent on individual dosage, price per unit, plus 6€ for a prescription
Desmopressine	0.13-1.00	2018	Medicijnkosten.nl	Dependent on individual dosage, price per unit, plus 6€ for a prescription
Thyrax	0.02-0.32	2018	Medicijnkosten.nl	Dependent on individual dosage, price per unit, plus 6€ for a prescription
Genotropin	3.34-10.13	2018	Medicijnkosten.nl	Dependent on individual dosage, price per unit, plus 6€ for a prescription
Cabergoline	4.72	2018	Medicijnkosten.nl	Dependent on individual dosage, price per unit, plus 6€ for a prescription
Quinagolide	0.80	2018	Medicijnkosten.nl	Dependent on individual dosage, price per unit, plus 6€ for a prescription
Hydrocortison	0.02-2.50	2018	Medicijnkosten.nl	Dependent on individual dosage, price per unit, plus 6€ for a prescription
Anticonceptives	0.06-2.20	2018	Medicijnkosten.nl	Dependent on individual dosage, price per unit, plus 6€ for a prescription

* Dutch guidelines for healthcare cost calculation

** Physiotherapists, Speech therapists, Dieticians, Occupational therapists

*** Psychiatrists, psychologists

Supplementary table 5a. Disease bother and needs for support among 167 patients with a non-functioning adenoma categorized by endocrine deficits corrected for age and gender

	Total (N=167)		No deficits (N=46)*		Hypopituitarism (N=121)*		P-value*
Disease bother	mean	SD	mean	SD	mean	SD	
Physical & cognitive complaints	16.9	20.0	12.5	19.2	19.0	19.6	.058
Mood	14.1	19.1	11.9	19.0	15.0	18.5	.372
Negative illness perceptions	11.5	15.7	11.7	15.6	11.4	15.3	.914
Sexual functioning	14.8	21.1	9.4	20.5	16.7	20.6	**.048**
Social functioning	7.9	16.1	5.4	15.7	9.1	16.4	.192
Total index score	13.4	15.9	10.7	15.2	14.5	15.1	.181
Needs for support							
Physical & cognitive complaints	17.8	23.1	10.7	22.1	21.1	21.8	**.007**
Mood	16.4	23.7	11.3	23.2	18.6	22.9	.078
Negative illness perceptions	17.5	23.5	16.3	23.2	18.0	23.0	.682
Sexual functioning	14.5	23.0	8.2	22.0	17.0	22.7	**.028**
Social functioning	8.7	18.5	4.2	17.9	10.8	18.6	**.041**
Total index score	15.4	19.6	10.2	18.6	17.7	19.4	**.030**

NFPA (non-functioning pituivtary adenoma), N (number), SD (standard deviation), (bold) p<0.05
Lower scores indicate lower disease bother and lower needs
* corrected for age and gender

Supplementary table 5b. Disease bother and needs for support among 167 patients with a non-functioning adenoma categorized by endocrine deficits corrected for age and gender

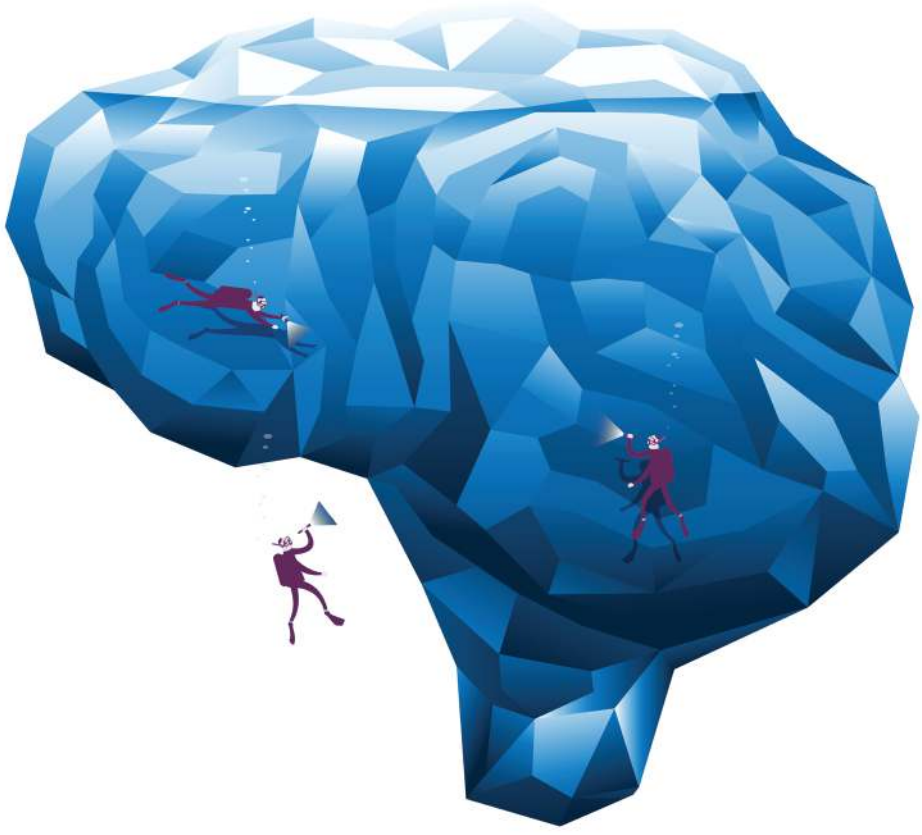
	Wait-and-scan (N=22)*		Surgery (N=104)*		Radiotherapy (N=41)*		P-value*
Disease bother	mean	SD	mean	SD	mean	SD	
Physical & cognitive complaints	12.2	18.8	16.2	19.0	22.1	18.6	.099
Mood	13.3	18.8	13.0	19.0	17.2	19.0	.482
Negative illness perceptions	9.5	15.1	9.8	15.1	16.6	15.2	**.047**
Sexual functioning	17.1	20.2	12.8	19.8	18.2	20.0	.314
Social functioning	6.3	15.9	7.7	16.1	10.1	15.8	.602
Total index score	11.9	15.2	12.2	14.8	17.5	15.0	.165
Needs for support							
Physical & cognitive complaints	11.7	22.0	17.3	22.1	23.5	21.8	.110
Mood	12.9	23.0	15.7	23.1	20.4	23.4	.411
Negative illness perceptions	11.6	22.5	15.5	22.3	25.7	22.1	**.024**
Sexual functioning	16.3	22.0	12.0	21.9	20.2	21.9	.127
Social functioning	5.7	17.8	7.4	18.2	14.7	17.7	.061
Total index score	11.7	18.8	14.0	18.8	21.8	18.7	.053

NFPA (non-functioning pituitary adenoma), N (number), SD (standard deviation), (bold) p<0.05
Lower scores indicate lower disease bother and lower needs
* corrected for age and gender

Supplementary table 5c. Disease bother and needs for support among 167 patients with a non-functioning adenoma categorized by follow-up corrected for age and gender

	0-5 years (N=43)*		5-10 years (N=45)*		>10 years (N=79)*		P-value*
Disease bother	mean	SD	mean	SD	mean	SD	
Physical & cognitive complaints	12.6	18.8	23.6	18.8	15.9	19.2	**.015**
Mood	11.9	18.8	18.5	18.8	12.7	19.1	.175
Negative illness perceptions	9.7	15.6	14.6	15.4	10.5	15.6	.250
Sexual functioning	15.2	20.5	13.9	20.1	15.0	20.4	.947
Social functioning	6.0	15.7	11.4	15.4	7.3	15.6	.229
Total index score	11.0	15.6	17.4	15.4	12.4	15.3	.105
Needs for support							
Physical & cognitive complaints	14.5	22.0	24.2	22.1	16.6	21.9	.081
Mood	16.6	23.3	19.8	23.5	14.5	23.5	.489
Negative illness perceptions	14.8	23.3	21.3	22.8	16.8	22.8	.380
Sexual functioning	13.9	22.4	15.4	22.1	14.4	22.2	.949
Social functioning	6.9	18.4	11.1	18.1	8.8	18.3	.551
Total index score	13.7	19.4	19.4	18.8	14.5	18.8	.295

NFPA (non-functioning pituitary adenoma), N (number), SD (standard deviation), (bold) p<0.05
Lower scores indicate lower disease bother and lower needs
* corrected for age and gender



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General discussion

This thesis comprehensively describes the outcomes of treatment of patients with a pituitary tumor, using the framework of Value Based Health Care (VBHC) [1].

TREATMENT CHOICE BASED ON OUTCOMES: PREOPERATIVE ASSESSMENT OF RISK FACTORS FOR POSTOPERATIVE COMPLICATIONS

According to the VBHC model, treatments offered to patients must be based on outcomes [1]. In clinical practice, healthcare providers have to continuously evaluate risks and benefits of certain treatments in relation to the goal of treatment. When deciding on the best treatment option for an individual patient, the stakeholders i.e. the patient, his/her family and the physician, must consider the anticipated outcomes of various treatment options and weigh these against the risks of a certain treatment. For patients with pituitary tumors, a rare condition which considerably affects various aspects of a patient's health status, a substantial number of studies have reported outcomes of surgery, risk factors for complications, but an overview was lacking. Such an overview facilitates preoperative counseling of patients and identifies patients with high and low risks for complications. Initially, we performed a systematic literature review (**Chapter 2**) in which we identified two consistent risk factors for postoperative complications, namely **older age and intraventricular extension**. Main limitations of the literature currently available are the lack of large, prospective studies reporting results of their outcomes and a lack of uniform definitions. In situations where evidence is uncertain, medical decisions are complex and cannot yet be based on measured outcomes, but are based on best practice of the center. This is the case in many pituitary conditions and is exemplified by the cases presented in **Chapters 3 and 4**.

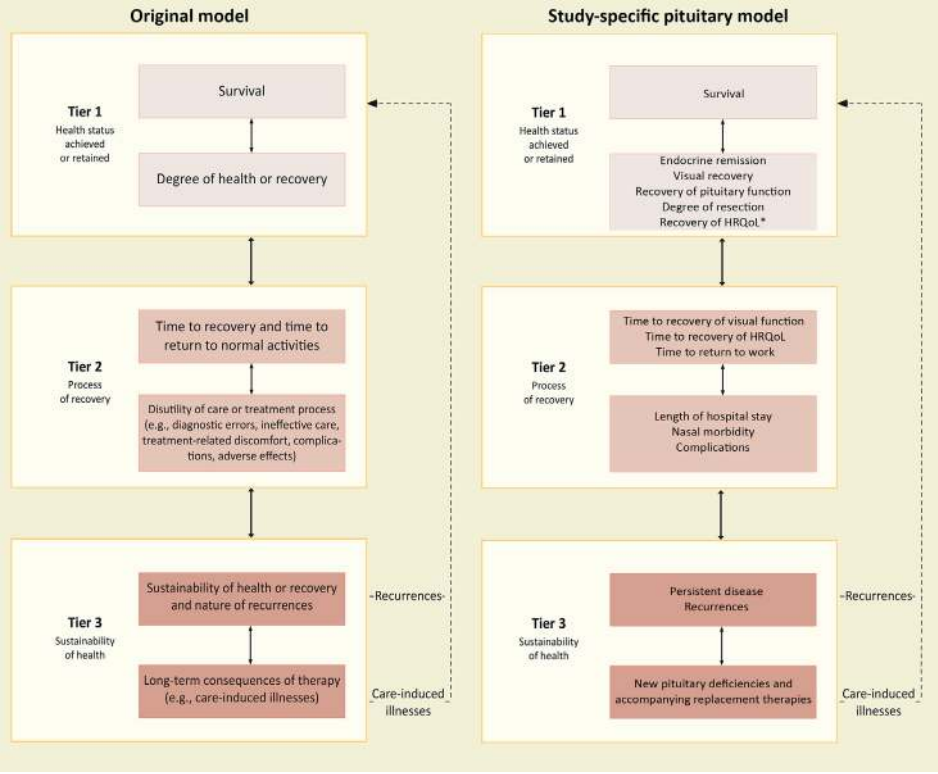
Consensus by the community on practical, uniform definitions for outcomes, including complications, is a first step towards obtaining the necessary data to support decision-making. We adapted prospective registration of outcomes and complications at our center. Following this, prospective registration of outcomes on a larger scale across large multicenter cohorts of patients is required to reliably identify predictive factors. A current ongoing multicenter initiative in the Netherlands is the neurosurgical quality registry, the QRNS (Quality Registry Neuro Surgery). This registry requires physicians to register outcomes of several neurosurgical conditions, one of them being pituitary tumors. Currently, the QRNS is in the process of data-validation, which is a necessary step preceding evaluation and reporting of outcomes, but also to enable evaluation of potential risk factors across a large multicenter cohort. Ultimately, it is important that such registries report their outcomes, including outcomes over the full-cycle of care,

specifically including patient-reported outcomes (PROs), which will enable tailoring treatments towards unmet needs of patients.

FOCUS ON PATIENT-RELEVANT OUTCOMES INSTEAD OF BIOCHEMICAL PARAMETERS: PERIOPERATIVE PATIENT-PERCEIVED OUTCOMES

A major feature of the VBHC model is the emphasis placed on the measurement of such PROs. Until recently, in patients with pituitary tumors, the use of patient-reported outcome measures (PROMs) to evaluate the outcomes of medical treatment was limited and knowledge of perioperative PROMs was restricted to a handful of studies reporting on generic PROMs, showing, in general, that health-related quality of life (HRQoL) improves after treatment [2–9]. There were also a limited number of studies that showed outcomes of a specific physical domain, such as nasal morbidity or visual functioning [5–11]. Most studies, however, included a limited number of patients, or failed to show outcomes over the full cycle of care. Although these initial studies are very important in the context of patient-centered care, a broader range of outcomes is necessary to reflect on what matters most to patients. In **Chapter 5**, we have integrated such a comprehensive set of outcomes (figure 1), which was based on a combination of issues considered relevant by pituitary tumor patients [12], the availability and face validity of PROMs used among patients with pituitary tumors and the opinion of a group of pituitary experts. Results reported in **Chapter 5** show that we are well capable of measuring outcomes through a comprehensive set over the full cycle of care for patients with pituitary tumors and that we are also capable of differentiating outcomes between tumor types. Although this study can serve as a benchmark for future studies, the community should also agree on a uniform core outcome set that measures what is most important to patients, but also includes a small number of questions to limit the patient burden. Ideally, decisions made during the process of designing such a set are evidence-based, which would require further evaluation of PROMs in the perioperative setting. Another step, although not as necessary at first, is the prospective assessment of long-term follow-up of PROMs. Currently, PROMs are mainly used to evaluate outcomes. However, when fully integrated into clinical practice, it is likely that treatment decisions can be altered based on these outcomes. It has been acknowledged that pituitary diseases are highly suitable for outcome-based decision making, in particular PROM-based decision making, for several reasons:

1) Hormone effects are highly individual and classical blood measurements do not fully reflect homeostasis nor well-being, while PROMs enable finetuning of endocrine balances for the individual patients.



* HRQoL, disease burden, utility

Figure 1. Example of the three-tier model of VBHC applied to pituitary tumor patients
Modified from Porter NEJM 2006, published Lobatto et al. EJE 2019.

2) Pituitary tumors are benign and slow growing tumors, leaving room for extensive evaluation of PROMS and consequent shared decision making. Specifically, in cases where multiple treatment options are possible and justifiable.
3) Subjective symptoms play a major role in the regulation of endocrine suppressive treatment and endocrine replacement therapies. Therefore, caregivers of pituitary patients are accustomed to provide chronic, life-long care with a holistic approach.

THE PATIENT AS A STAKEHOLDER: PATIENT EMPOWERMENT

Besides measuring outcomes, which is mostly performed through electronic applications, there is another benefit of electronic communication with patients with pituitary tumors, namely, active participation in surveillance after discharge in the home setting. In **Chapter 6**, we have shown that by actively incorporating patients as participants in their own care trajectory, a select group of patients is able to go home sooner and

safely after surgery. More importantly, however, it enables patient empowerment and gives healthcare providers the possibility to intervene in the postoperative setting, even after discharge. Although results show that we were able to discharge a select group of patients sooner and safely after surgery, it remains important to keep re-evaluating outcomes. Preferably, this is performed through a plan-do-study-act cycle (PDSA), which is a more pragmatic method to iteratively evaluate quality improvement interventions [13, 14] and is necessary to further improve such interventions. Although results presented in **Chapter 6** did not show an overall decrease in hospital costs, we believe that this is mainly caused by the complex financial structure of the Dutch healthcare system in combination with a low threshold for readmissions during the initial implementation phase of the care trajectory. Implementation of the fast-track care trajectory at our center has led to improved multidisciplinary treatment, improved risk stratification and an increase in the number of annually performed operations.

LONG-TERM DISEASE BURDEN AND SOCIETAL PARTICIPATION

Previous research performed at our center extensively looked at the disease burden of patients with pituitary tumors after long-term follow-up of multimodality treatment. This project was undertaken in line with the multidimensional model of Wilson and Cleary, also applied in **Chapter 7**, and includes biopsychosocial factors and patient perception [15]. It was found that difficulties in performing work was the second largest issue reported by patients [12]. The extent of this issue, however was largely unknown in the literature. The research presented in **Chapter 8** shows that work-related disability is high and that there is a need for increased attention towards work-related disabilities, possibly early in the care trajectory. Since patients are often of working age, the benefit of maintaining a paid job is particularly relevant. Further evaluation of potential interventions is required, as well as prospective measurement of work-related disabilities. By measuring sooner in the care trajectory, healthcare providers might be able to prevent or decrease long-term work disability. Although these early interventions might prevent disability, there is often a delay prior to diagnosing patients with this condition and the effect of an early intervention might therefore be limited. Another important factor to consider when treating these patients is the 2-year interval to return to work after initial sick leave in the Netherlands, which is particularly relevant for patients with pituitary tumors, due to these delays in diagnosing a pituitary tumor. After diagnosis, treatment up to normalization of endocrine status may take months to years, caused by long-lasting endocrine effects, which emphasizes the need for minimization of care related delays, e.g. diagnostic delays, extensive surgical waiting lists, indolent attitude of endocrinologists to up titrate medical treatment for tumors or endocrine replace-

ment. We consider it highly indicated that in the early phase of treatment, interventions are aligned with the work status, e.g. optimal endocrine / medical intervention, but also attention to actively refer patients to rehabilitation care and psychosocial support. In **Chapter 8**, we have shown that such alterations should focus on limiting the mental and social demands of work, including difficulties in concentrating. Although these considerations are relevant for the Dutch situation, it is unclear how these results can be extrapolated to other countries, since social security benefits vary per country. The Dutch situation can be best compared to Scandinavia and Germany, which do not have the same, but comparable social security benefits [16]. However, it is likely that many of the work-related disabilities are universal and that awareness of the limitations of patients with a pituitary tumor and potential work adjustments might lead to a decrease of work disability.

EXTENT OF HEALTHCARE USAGE

In line with increased work disability, patients with pituitary tumors also make substantial use of healthcare, even in the chronic phase of their disease (**Chapter 9**). Although previous studies have focused on functioning tumors, knowledge of healthcare use among patients with non-functioning tumors was scarce. With the increasing costs of healthcare worldwide, knowledge regarding healthcare costs is essential and will enable physicians to define care trajectories. One of the key findings of our study (**Chapter 9**) was that the extent of healthcare utilization and costs was independent of endocrine status, e.g. pituitary hormone deficiencies and treatment algorithm, and that length of follow up was independent of endocrine status. Furthermore, we found that healthcare utilization and costs were better reflected by patient-reported outcomes, such as HRQoL, disease bother and needs for support, again showing an important role for the use of PROMs in clinical care. The impact of endocrine disorders on an individual patient level are highly variable and the relationship between HRQoL and healthcare use may therefore indicate that those with more limitations have an increased need for support. Alternatively, it is interesting to speculate that a multidimensional approach, which aims at improving HRQoL, might reduce healthcare costs in the chronic setting of the disease. A next step would be to perform a prospective cost analysis alongside reporting of outcomes over the full cycle of care. This will provide more accurate data and will enable further comparisons between centers by using the value quotient (value is outcomes divided by costs), as proposed by Porter [1].

MULTIDISCIPLINARY CARE TOWARDS BUILDING AN INTEGRATED PRACTICE UNIT (IPU): PRACTICAL IMPLICATIONS

In recent years, the implementation of care according to the principles of VBHC has led to several changes in the clinical care delivered. As shown in the introduction of this thesis, we have adapted our care trajectory and have added a pituitary-specific case manager to our team. Furthermore, we have implemented a postoperative discharge protocol, which enables us to discharge selected patients sooner after surgery, and actually lengthens the period of surveillance. We have also implemented the use of patient-reported outcome measures in clinical practice (figure 2), which has already led to several targeted interventions based on these outcomes.

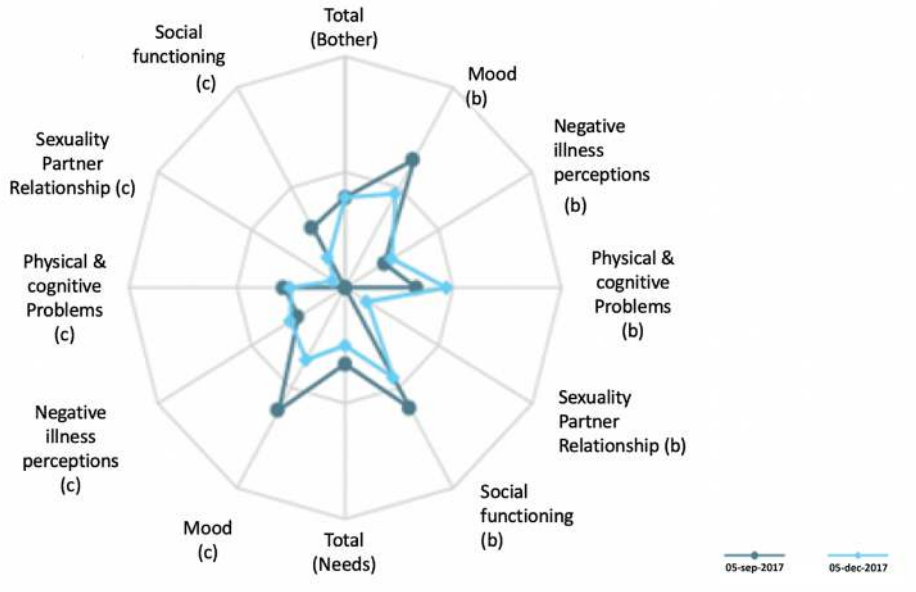


Figure 2. Example of outcomes before and after a clinician-initiated intervention

Alongside these endeavours, we have developed an automated registration form in our electronic patient files, which not only limits the burden of registration, but can also be used for evaluation of care, both at an institutional level through our automatically updated patient dashboard (figure 3) and at a national level through the quality registries (QRNS). This was done in collaboration with the ICT and a team of other healthcare professionals of the national program to reduce duplicative registration "Registration at the source" (registratie aan de bron).

Figure 3. Example of a patient-dashboard for the daily evaluation of outcomes

CRITICISM AND LIMITATIONS OF VBHC

Although there are many benefits of applying VBHC to the care of patients, there are also limitations to the current way VBHC has been interpreted. One of these limitations is that although VBHC aims to organize care around patients' medical conditions, one may wonder whether a definition of a single medical condition can be applied to all medical conditions. This can be well illustrated by the example of pituitary tumors. Even though most pituitary tumors are treated roughly the same way, the clinical implications of the different tumor types show great variability. The question arises whether rare disease groups, such as pituitary tumors, are able to fit under a single overarching umbrella, and whether the model of VBHC is easily generalizable. On the one hand, it seems to be the case, since we are able to detect an increasing number of sparsely varying rare diseases; on the other hand, even among the most frequently used implementation strategy, that of ICHOM (International Consortium for Health Outcomes Measurement), there are large variations between the various outcome sets. This may suggest that it is necessary to develop, partly overarching, but mainly disease-specific outcome sets for each medical condition.

Throughout this dissertation, multiple important barriers have been discussed and need to be addressed prior to implementation of VBHC in a rare disease. In my opinion, the applicability of VBHC depends largely on the work that has been done in a specific field. Even in highly prevalent diseases, the implementation of VBHC requires a major effort, though it can lead to great value for the patient when we are able to improve outcomes over the full cycle of care. In rare diseases, the knowledge of outcomes is often more limited and requires an even greater effort from the field. For patients with pituitary tumors, in my opinion, there is currently insufficient knowledge to be able to fully utilize the interesting potential VBHC encompasses. However, the implementation of VBHC in pituitary care has the potential to change the way we treat our patients on a daily basis and will enable us to better understand what matters most to patients. One of the first barriers is the lack of uniform definitions and the limited number of available perioperative outcomes available. Although we have utilized a broad set of PROMS throughout the course of this thesis, I believe expansion of these outcomes is necessary to properly assess the disease burden of patients to be aware of what matters most to patients at certain time points during treatment and to be able to steer treatment on an individual, but also a population level. In the future, it is likely possible to narrow down the number of questions considerably, however the current broad view will enable coverage of outcomes over the full cycle of care and enable evidence-based and data driven evaluations. To reach this stage, international collaborations are necessary

to further improve the care for patients with pituitary tumors. The ENDO-ERN serves as an interesting platform to facilitate such initiatives.

CONCLUSIONS

While VBHC has gained popularity over the past decade, the research presented in this thesis points out that for patients with pituitary tumors, as an example of patients with a rare disease, there are still several remaining challenges. Practical definitions, prospective clinical and patient-reported outcomes on a large scale are necessary to enable further implementation of VBHC in clinical practice. The feasibility of measuring such outcomes has been confirmed throughout this thesis and the patient-reported outcomes appear to play a key role in the measurement of outcomes.

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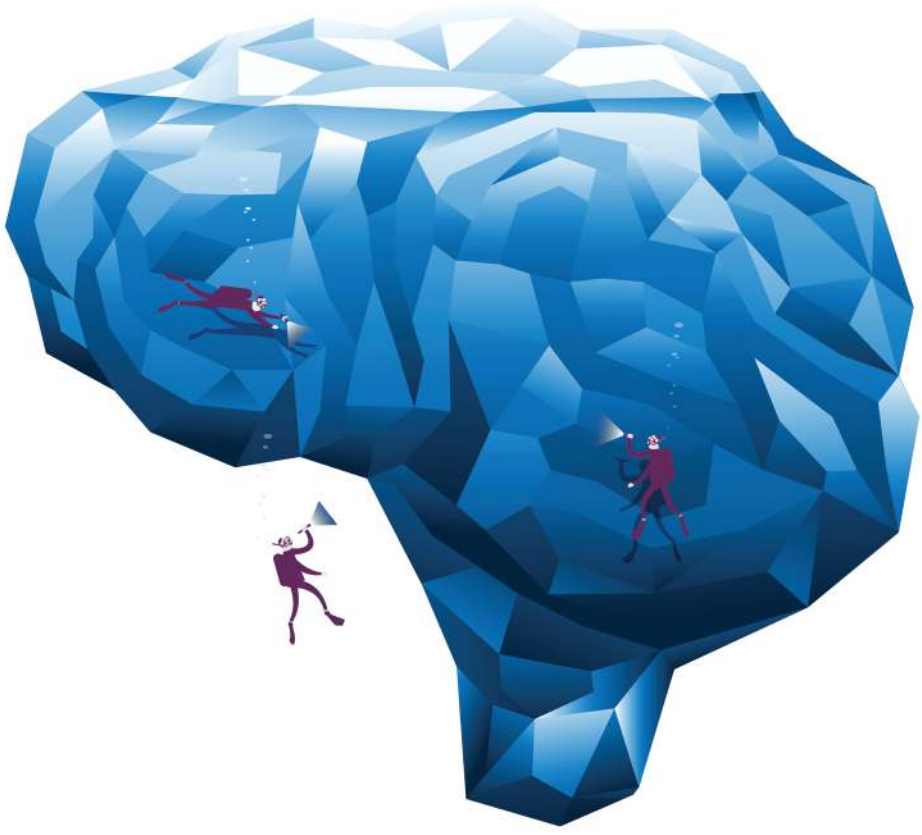

11

Summary

The main goal of Value Based Health Care (VBHC) is to create value for the patient, with value expressed as the ratio between patient-relevant outcomes and costs. Basic elements of the framework are: working along defined multidisciplinary care trajectories over the full cycle of care and structurally measuring outcomes and costs (1). Over the past decade, many health care organizations have actively adopted VBHC as a new framework for the provision of care. However, there are still many unanswered questions regarding the transformation towards value based care. For patients with rare diseases, in particular patients with pituitary tumors, some of these hurdles need to be addressed in order to optimally introduce value based care.

In **Chapter 1,** the epidemiology and treatment of pituitary tumors was presented and the VBHC framework was introduced. In particular, current gaps in the literature regarding outcomes of the treatment of pituitary tumors were described. Related to these knowledge gaps, the following aims of this thesis were formulated:

- What risk factors should we be aware of when treating patients with pituitary tumors?
- What are comprehensive acute and subacute perioperative outcomes of surgically treated patients with pituitary tumors, either or not in the context of a defined short-stay care trajectory?
- To what extent can patients with pituitary tumors maintain or regain societal participation, with emphasis on paid employment?
- What is the current healthcare utilization of patients with pituitary tumors in the chronic phase of their condition?

The studies described in **Chapters 2, 3 and 4** focused on the process of selecting the optimal treatment for individual patients with a pituitary tumor and addressed which risk factors we should be aware of when treating these patients (aim I).

Chapter 2 provided the results of a systematic literature review on preoperative risk factors for postoperative complications in endoscopic pituitary surgery. In total, 23 studies (20 retrospective, 3 prospective) were included, all describing one or more risk factors for postoperative complications. Among the included studies, we found two factors consistently associated with an increased risk of complications, namely older age (for complications in general) and intraventricular extension (for cerebrospinal fluid (CSF) leaks). Another main finding of this literature review was the observed lack of uniform definitions of complications and the relatively low overall methodological quality of the included studies, warranting the need for well-designed studies and uniform definitions of the various complications of endoscopic pituitary surgery.

In **Chapters 3 and 4**, we presented two cases of patients with highly complex pituitary tumors and described the process of discussing treatment options with a patient at the stage of initially failed surgery. We provided insight into which alternative treatment options could be offered, e.g. multimodality treatments, and into several difficulties often seen during clinical practice of such complex cases, e.g. the hesitation towards repetitive surgery from the patient's perspective. As the pros and cons of the various treatment options may not be easy to oversee for patients and difficult to explain by physicians, the use of decision aids to optimally involve patients in the decision-making process is advocated.

Studies in **Chapters 5 and 6** described the outcomes of a comprehensive set of perioperative outcomes for patients treated for a pituitary tumor through endoscopic transsphenoidal surgery and the results of the implementation of a fast-track care trajectory (aim II).

In **Chapter 5** we presented the results of a study which prospectively assessed a comprehensive set of outcome measures alongside routine perioperative care. The outcome set was structured according to the three-tier model of VBHC and tailored to the specific needs of patients undergoing surgery for a pituitary tumor. Assessments were performed over a period of 2 1/2 years among 103 patients with varying tumor types (47 patients with non-functioning adenomas (NFA), 14 acromegaly (ACRO), 15 Cushing's disease (CD), 16 prolactinomas (PRL), 6 Rathke's cleft cysts and 5 craniopharyngiomas). Assessments were measured at baseline (prior to the surgery), 2 days, 5 days, 6 weeks, and 6 months after surgery. We evaluated various clinician- (e.g. remission of hormone excess, recovery of pituitary function, visual deficits) and patient-reported outcomes (e.g. self-perceived disease bother (Leiden Bother and Needs Questionnaire-pituitary (LBNQ-Pituitary)(2)), general health-related quality of life (HRQoL) and utility (Short Form-36 (SF-36)(3,4), EuroQoL (EQ-5D)(5,6)), visual functioning (visual functioning questionnaire-25 (VFQ-25)(7)), and nasal morbidity (anterior skull base nasal inventory-12 (ASK nasal-12)(8), sinonasal outcome test-22 (SNOT-22)(9)). Among the clinician-reported outcomes, remission of hormone excess was achieved in 69% of patients, recovery of pituitary function was seen in 24% of patients, and recovery of visual function was achieved in 98% of all patients with preoperative deficits, which were all in line with previous studies reporting on outcomes of surgery.

Regarding patients' health status before surgery, we found that patients with a PRL, mostly refractory or intolerant for medication, had a comparable self-perceived disease bother at baseline compared to patients with CD (mean difference 8.3, 95% CI -21.7;5.0, p=.22). Patients with an NFA or ACRO had a comparable disease bother at baseline

(mean difference 0.6, 95% CI -3.3;5.9, p=.85), which was significantly lower compared to patients with a PRL (mean difference 27.1, 95% CI 16.1;38.1, p<.001 (PRL vs. NFA), respectively 26.5, 95% CI 14.6;38.3, p<.001 (PRL vs. ACRO)). The amount patients with an NFA or ACRO were bothered by the consequences of the disease was also significantly less compared to patients with CD (mean difference 18.8, 95% CI 9.8;27.7, p<.001 (CD vs. NFA), respectively 18.1, 95% CI 8.3;27.9, p<.001 (CD vs. ACRO)). On average patients with a PRL improved most significantly after surgery (mean improvement 19.1, 95% CI 12.1;26.2, p<.001), while patients with CD did not (mean improvement 6.8, 95% CI -4.1;17.7, p=.22). Patients with an NFA also clearly improved after surgery (mean improvement 4.2, 95% CI 0.03;8.3, p=.05), as well as patients with ACRO (mean improvement 5.8, 95% CI 0.3;11.3, p=.04). In this study we found comparable results for all patient-reported outcomes and differences between tumor types were best illustrated by the LBNQ-Pituitary, a disease specific list, developed recently in our center together with patients.

Based on the results reported above in combination with the high response rate of 96-100% at all measurement points and the small quantity of missing items per questionnaire (0.1-8.0%), this study illustrates that we are capable of measuring a comprehensive set of outcomes of endoscopic transsphenoidal surgery for a pituitary tumor. Results found in this study could serve as a benchmark for future studies describing the outcomes of surgical treatment of a pituitary tumor. However, more research, including international consensus, is needed to underpin which outcomes should ultimately be implemented in a core outcome set for pituitary tumor patients.

In **Chapter 6** we investigated whether the implementation of a fast-track care trajectory was feasible and safe and evaluated its clinical effectiveness. During a 2-year period, consecutive patients scheduled for surgical treatment of a pituitary tumor were preoperatively evaluated for eligibility for fast-track discharge by our pituitary multidisciplinary team. Patients were compared to patients not eligible for fast-track discharge (n=76) and a retrospective cohort of patients who were treated between January 2010 and November 2016 at our center, which was prior to implementation of the fast-track protocol (n=307).

The fast-track care trajectory consisted of discharge on postoperative day (POD) 2 or 3, after which patients were instructed to keep track of their fluid balance, weight and to report symptoms on a daily basis to our pituitary case manager. The case manager evaluated these reports and instructed patients on whether they could continue their current situation or had to perform additional testing. The feasibility of selecting patients eligible for the fast-track care trajectory was evaluated, alongside postoperative complications, patient-reported outcomes and costs.

In total, 155 patients with pituitary tumors were included in the prospective part of the study, of whom 79 (51%) were considered eligible for fast-track discharge. Of these, 69 patients (87%) were discharged at POD 2 or 3. Among patients not considered eligible at preoperative counseling a priori, 7 (9%) were discharged within 3 days after surgery. In comparison, only 61 patients (20%) were discharged within 3 days after surgery in the historic cohort.

The most frequent reason for readmittance after fast-track discharge was delayed hyponatremia (n=6, 43%), which was also the case among the two other groups. Regarding the patient-perception, among those discharged through the fast-track protocol, the overall perceived sense of safety was higher among those not readmitted compared to those who were. Although the readmission rates were higher among the more recent cohort compared to historic controls, we did not encounter any life-threatening complications. It is likely that the readmission rates were high due to a low threshold for readmitting patients and the close follow-up. Furthermore, we believe that with increasing experience, more patients can be stratified towards the fast-track discharge group. Also, the other patient-reported outcomes did not differ between the fast-track and non-fast-track groups, indicating that the earlier discharge did not decrease overall HRQoL. All in all, this study showed that the implementation of a short stay protocol can be performed safely and is feasible when performed alongside a well-defined care trajectory.

The final three chapters **(Chapters 7, 8, 9)** focused on the long-term implications of having a pituitary tumor, as we focused on societal participation, specifically paid employment and healthcare utilization (aims III and IV).

HRQoL improves considerably after treatment for an NFA (10). The literature on the normalization of HRQoL after treatment, however, is inconclusive. Some have described a persistently decreased HRQoL compared to reference data (11,12), while others have not (13,14). Considering the variety in observed HRQoL outcomes, the aim of the literature review of **Chapter 7** was to provide a literature overview of health outcomes in patients with an NFA, using a conceptual HRQoL model, and we used the Wilson and Cleary model (15) to illustrate this. This biopsychosocial model integrates the clinical paradigm (which focuses on biological, physiologic and clinical outcomes) and the quality of life model (which focuses on dimensions such as functioning and overall well-being). Alongside models such as the Wilson and Cleary model, but also models like the ICF-model (international classification of functioning disability and health) (16), outcomes can be categorized into various domains of a conceptual HRQoL model. When looking at outcomes for patients with an NFA through the Wilson and Cleary model, it

can be seen that the HRQoL improves considerably after treatment, however remains impaired in some patients compared to reference data. This model also illustrates domains at which patients may experience problems, e.g. cognitive functioning, coping behavior, and illness perception. Furthermore, it does not intervene with the thoughts and processes of VBHC, but can go side by side with the concepts of VBHC depending on the needs of patients.

Until now, outcome research has mainly focused on pituitary functioning and complications of treatment rather than the impact of the condition and its treatment on daily activities and societal participation. The majority of patients with a pituitary tumor are of working age, which makes maintenance of or return to paid employment a very relevant outcome. Previous research performed at our center had shown that the second most frequently reported issue reported by patients was that they experience difficulties in performing work (2). Knowledge of the extent of this problem among patients with pituitary tumors, however, was scarce. Therefore, **Chapter 8** presents the results of a cross-sectional study, including 241 patients who were treated for a pituitary tumor and of working age (18-65 years). Participants were asked to complete five validated questionnaires assessing work disability (Short Form-Health and Labor Questionnaire (SF-HLQ), Work Role Functioning Questionnaire 2.0 (WRFQ)), HRQoL and utility (SF-36, EQ-5D) and disease bother (LBNQ-Pituitary). Additional data were extracted from the medical records.

Among the participating 241 patients, the median time since diagnosis was 11 years and many patients had previously undergone multimodality treatment, most of whom had undergone surgery (n=96, 40%). Within this group of 241 patients, we found that 68 (28%) patients did not have a paid job. Factors associated with not having a paid job, included the tumor type (ACRO and CD), as well as the presence of pituitary deficiencies ((pan)hypopituitarism). At the treatment level, we found that a history of undergoing radiotherapy was associated with not having a paid job. From the sociodemographic perspective, not being in a durable relationship and a lower level of education were associated with not having a paid job. Finally, we found that patients with lower HRQoL and an increased disease bother were also more often without a paid job. Among the 173 (72%) who had been able to maintain their paid jobs, 70 (40%) reported health-related absenteeism in the previous year. Issues specifically reported by patients to bother them were within the mental and social domains. Based on the results found in this study, we recommend incorporating work disability during clinical guidance of patients.

In **Chapter 9,** healthcare utilization and costs were described among 167 patients with non-functioning pituitary adenomas participating in the same cross-sectional study

as described in **Chapter 8**. Patients were asked to fill out a set of four validated questionnaires, assessing annual healthcare utilization, costs (the medical consumption questionnaire (MTA iMCQ)), disease bother (LBNQ-Pituitary), HRQoL and utility (SF-36, EQ-5D). Additional data were extracted from the medical records.

We found that annual healthcare utilization was substantial among the 167 patients (mean annual healthcare costs of € 3040 (SD 6498)), even long after treatment (median follow-up of 9 years). In contrast to what was anticipated beforehand, the extent of healthcare utilization was independent of endocrine status (OR 0.73, 95% CI 0.41;1.86, p=0.73) and treatment algorithm (OR 0.66, 95% CI 0.48;3.18, p=0.66 (surgery vs. wait-and-scan), OR 0.64 95% CI 0.44;3.74, p=0.64 (radiotherapy vs. wait-and-scan)). Longer follow-up (OR 0.97, 95% CI 0.93;1.00, p=0.047) was even associated with lower healthcare utilization. Instead, worse HRQoL (OR 0.94, 95% CI 0.91;0.98, p=0.001 (mental component scale)) and an increased bother caused by the negative consequences of the disease (OR 1.05, 95% CI 1.02;1.08, p=0.001), as well as the needs for support (OR 1.03, 95% CI 1.01;1.06, p=0.002) were associated with higher healthcare utilization. Regarding costs, we had also anticipated costs to be associated with endocrine status, treatment algorithm and follow-up, which was not the case. Instead, however worse HRQoL (B 107, 95% CI 9-206, p=0.03), increased disease bother (123, 95% CI 58;188, p<0.001), and the need for support (B 130, 95% CI 79;180, p<0.001) were again associated with higher costs. These findings suggest that targeted interventions addressing disease bother and unmet needs in the chronic phase are needed.

In conclusion, the research in this thesis highlights several challenges we came across while transitioning towards VBHC-based care. In order to proceed to a truly value based system, we are dependent on the quality of reporting, specifically uniform definitions and prospective reporting of outcomes. We have shown that it is feasible to organize patient-centered care in a fast-track care trajectory for patients with a pituitary tumor and report outcomes through a comprehensive set of perioperative outcomes. Regarding the long-term outcomes, it was shown that the impact of the disease is high, both on overall health status as well as on participation. This could possibly be improved in the future; however, further research is necessary to identify the optimal targets and means for potential long-term interventions.

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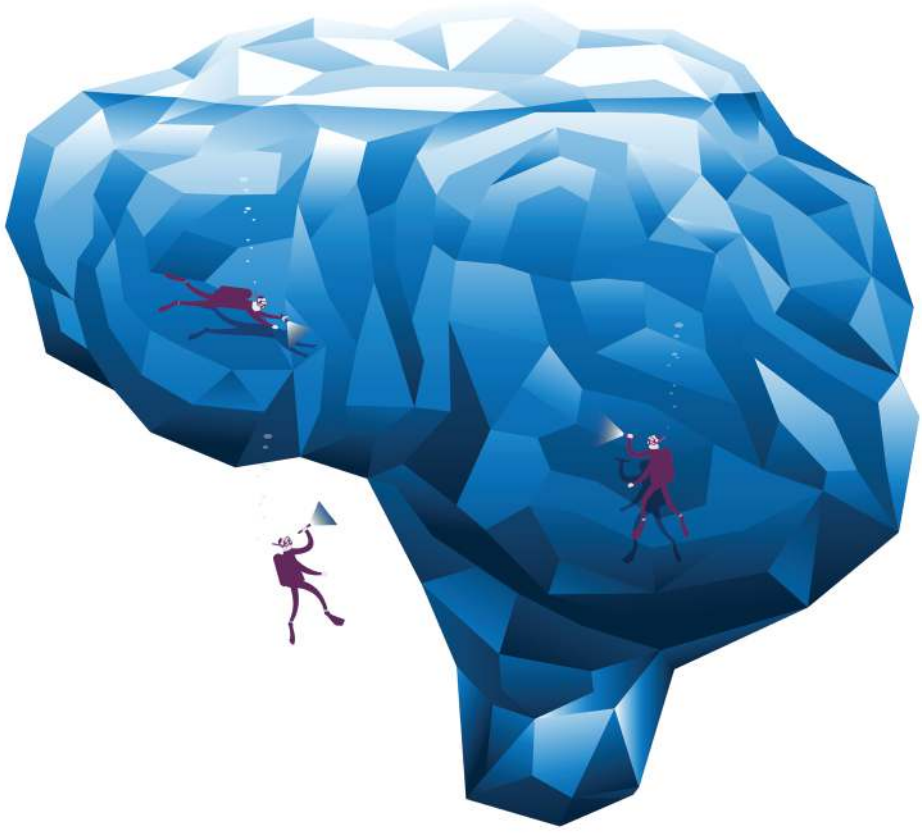

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Dutch Summary
(Nederlandse samenvatting)

Het hoofddoel van Value Based Health Care (VBHC), ook wel waardegedreven zorg genoemd, is om waarde te creëren voor de patiënt. Hierbij is waarde de uitkomst van de ratio tussen uitkomsten die relevant zijn voor de patiënt en de kosten. Basiselementen van het raamwerk van VBHC zijn: het werken volgens gedefinieerde multidisciplinaire zorgpaden over de gehele zorgcyclus en het gestructureerd meten van uitkomsten en kosten (1). Het afgelopen decennium hebben veel zorginstellingen actief de werkwijze van VBHC geadopteerd en gebruikt als raamwerk voor hoe zij zorg leveren. Er zijn echter nog veel onbeantwoorde vraagstukken omtrent de transformatie naar zorg die geleverd wordt volgens het VBHC-model. Voor patiënten met zeldzame ziektes, specifiek patiënten met hypofysetumoren, zullen deze vraagstukken beantwoord moeten worden om VBHC optimaal te kunnen introduceren in de zorg.

In **hoofdstuk 1,** werd de epidemiologie en de behandeling van hypofysetumoren besproken, daarnaast werd het raamwerk van VBHC geïntroduceerd. De huidige kennishiaten in de literatuur met betrekking tot de uitkomsten van de behandeling van hypofysetumoren werden verder ook besproken. Gerelateerd aan deze kennishiaten, werden de volgende doelen van dit proefschrift geformuleerd:

- Van welke risicofactoren dienen we bewust te zijn wanneer we patiënten met hypofysetumoren behandelen?
- Wat zijn de uitgebreide acute en subacute perioperatieve uitkomsten van chirurgisch behandelde patiënten met hypofysetumoren, al dan niet in de context van een gedefinieerd zorgpad met een korte opname?
- In hoeverre kunnen patiënten met hypofysetumoren hun maatschappelijke participatie behouden of terugkrijgen, specifiek gelet op het hebben van een betaalde baan?
- Wat is het actuele zorggebruik van patiënten met hypofysetumoren in de chronische fase van hun aandoening?

De studies beschreven in **hoofdstukken 2,3 en 4** richten zich op de manier waarop een optimale behandeling voor de individuele patiënt met een hypofysetumor wordt gekozen, welke risicofactoren van belang zijn en waar we van bewust dienen te zijn wanneer we patiënten met hypofysetumoren behandelen (doel I).

In **hoofdstuk 2** werden de resultaten besproken van een systematische review over preoperatieve factoren voor postoperatieve complicaties in endoscopische hypofyse chirurgie. In totaal werden 23 studies (20 retrospectief, 3 prospectief) geïncludeerd, welke allen één of meerdere risicofactoren voor postoperatieve complicaties beschreven. Onder de geïncludeerde studies vonden we twee factoren die consequent geassocieerd waren met een verhoogd complicatierisico, namelijk het hebben van een ho-

gere leeftijd (voor complicaties in het algemeen) en intraventriculaire uitbreiding (voor liquorlekkage). Een andere belangrijke bevinding van deze literatuurstudie was het geobserveerde gebrek aan eenduidige definities en de relatief lage methodologische kwaliteit van de geïncludeerde studies. Dit toont de noodzaak voor goed ontworpen studies en uniformiteit van definities van de verschillende complicaties die binnen de endoscopische hypofysechirurgie kunnen optreden.

In **hoofdstuk 3 en 4** werden twee casus gepresenteerd over patiënten met hoog-complexe hypofysetumoren. Het proces rondom het bespreken van verdere behandelopties voor een patiënt met in eerste instantie een onsuccesvolle chirurgische behandeling van een hypofysetumor werd behandeld. We hebben inzicht gegeven in welke alternatieve behandelopties aangeboden kunnen worden, zoals bijvoorbeeld een combinatie van verschillende behandelmodaliteiten. Verder toonden we welke problemen vaak gezien worden gedurende de behandeling van dergelijke complexe casuïstiek, zoals bijvoorbeeld de terughoudendheid van een patiënt om opnieuw een operatie te ondergaan. Omdat de argumenten voor en tegen de verschillende behandelopties moeilijk te overzien zijn voor patiënten en daarnaast ook moeilijk uit te leggen zijn door artsen, pleiten we voor het gebruik van beslishulpen om patiënten optimaal te betrekken bij het besluitvormingsproces.

In **hoofdstukken 5 en 6** werden de uitkomsten besproken van een uitgebreide set van perioperatieve uitkomsten van patiënten die endoscopisch transsfenoïdaal geopereerd zijn aan een hypofysetumor. Daarnaast werden de resultaten van de implementatie van een kort opname zorgpad besproken (doel II).

In **hoofdstuk 5** staan de resultaten van een studie waarin prospectief gekeken is naar een uitgebreide set van uitkomsten welke gemeten werden aan de hand van routine perioperatieve zorg. De uitkomsten set was gestructureerd volgens het drielaags model van VBHC en aangepast om aan de specifieke behoeften te voldoen van patiënten die een hypofysetumor operatie ondergingen.

Gedurende een periode van tweeëneenhalf jaar werden 103 patiënten met verschillende tumor types (47 patiënten met niet-functionerende adenomen (NFA), 14 met acromegalie (ACRO), 15 met de ziekte van Cushing (CD), 16 met een prolactinoom (PRL), 6 met een Rathke's cleft cyste en 5 met een craniofaryngioom) geanalyseerd. Analyses werden verricht voor de operatie en 2 dagen, 5 dagen, 6 weken en 6 maanden na de operatie. We maten hierbij verschillende dokter- (bijvoorbeeld remissie van hormoon overproductie, herstel van hypofysefunctie, visuele defecten) en patiënt-gerapporteerde uitkomsten (bijvoorbeeld zelf-ervaren ziektelast (Leiden Bother and Needs Questionnaire-pituitary

(LBNQ-Pituitary)(2)), algemeen gezondheid gerelateerde kwaliteit van leven (HRQoL) en utiliteit (Short Form-36 (SF-36)(3,4), EuroQoL (EQ-5D)(5,6)), visueel functioneren (visual functioning questionnaire-25 (VFQ-25)(7)), nasale morbiditeit (anterior skull base nasal inventory-12 (ASK nasal-12)(8), sinonasal outcome test-22 (SNOT-22)(9))). Resultaten van de dokter-gerapporteerde uitkomsten toonde dat 69% van de patiënten met een verhoogde hormoonproductie in remissie waren, dat hypofysefunctie zich herstelde in 24% van de patiënten en er herstel optrad bij 98% van de patiënten met preoperatieve uitval van visueel functioneren. Deze resultaten kwamen overeen met eerder gerapporteerde chirurgische uitkomsten.

Wanneer we keken naar de gezondheidsstatus van patiënten zagen we dat de zelfervaren ziektelast van patiënten met een PRL (overwegend patiënten met refractaire ziekte of intolerantie voor medicatie) voor de operatie vergelijkbaar was met die van patiënten met CD (gemiddeld verschil 8.3, 95% CI -21.7;5.0, p=.22).

Patiënten met een NFA of met ACRO hadden een vergelijkbare ziektelast op baseline (gemiddeld verschil 0.6, 95% CI -3.3;5.9, p=.85), wat significant lager was vergeleken met patiënten met een PRL (gemiddeld verschil 27.1, 95% CI 16.1;38.1, p<.001 (PRL vs. NFA), respectievelijk 26.5, 95% CI 14.6;38.3, p<.001 (PRL vs. ACRO)). De mate waarin patiënten last hadden van de gevolgen van hun aandoening was ook significant lager onder patienten met een NFA of met ACRO vergeleken met patiënten met CD (gemiddeld verschil 18.8, 95% CI 9.8;27.7, p<.001 (CD vs. NFA), respectievelijk 18.1, 95% CI 8.3;27.9, p<.001 (CD vs. ACRO)).

Gemiddeld genomen verbeterden patiënten met een PRL het meest na een operatie (gemiddelde verbetering 19.1, 95% CI 12.1;26.2, p<.001), terwijl patiënten met CD niet verbeterden (gemiddelde verbetering 6.8, 95% CI -4.1;17.7, p=.22). Patiënten met een NFA verbeterden ook na een operatie (gemiddelde verbetering 4.2, 95% CI 0.03;8.3, p=.05), evenals patiënten met ACRO (gemiddelde verbetering 5.8, 95% CI 0.3;11.3, p=.04).

In deze studie vonden we vergelijkbare resultaten voor alle patiënt-gerapporteerde uitkomsten en verschillen tussen tumor types werden het best geïllustreerd door de LBNQ-pituitary, een ziekte-specifieke vragenlijst, welke ontwikkeld is in het LUMC in samenwerking met patiënten.

Op basis van de bovenstaande resultaten en in combinatie met het hoge responspercentage van 96-100% bij alle meetmomenten en de kleine hoeveelheid missende items per vragenlijst (0,1-8,0%), kunnen we concluderen dat we in deze studie aangetoond hebben dat het mogelijk is om een uitgebreide set van uitkomsten van endoscopische trans-

sfenoïdale operaties voor patiënten met een hypofysetumor te meten. De resultaten uit deze studie kunnen als benchmark fungeren voor toekomstige studies die uitkomsten beschrijven van de chirurgische behandeling van hypofysetumoren. Er is echter meer onderzoek nodig, inclusief internationale consensus, om te bepalen welke uitkomsten definitief geïmplementeerd dienen te worden in een set met kernuitkomsten voor patienten met een hypofysetumor.

In **hoofdstuk 6** onderzochten we of de implementatie van een verkort zorgtraject uitvoerbaar en veilig was en evalueerden we de klinische effectiviteit hiervan. Gedurende een periode van 2 jaar werd door ons multidisciplinaire team preoperatief gekeken of patiënten, die op de wachtlijst stonden voor de chirurgische behandeling van een hypofysetumor, in aanmerking kwamen voor een verkorting van hun opname. Patiënten werden vergeleken met patiënten die niet in aanmerking kwamen voor de korte opname (n=76) en een retrospectief cohort van patiënten die geopereerd zijn voorafgaand aan de implementatie van het korte opname protocol en behandeld zijn tussen januari 2010 en november 2016 in ons centrum (n=307). Het korte opname traject bestond uit ontslag op postoperatief dag (POD) 2 of 3, waarna patiënten werden geïnstrueerd om dagelijks hun vochtbalans, gewicht en klachten/symptomen bij te houden en deze terug te koppelen aan onze hypofyse casemanager. De casemanager evalueerde deze rapportages en koppelde vervolgens aan patiënten terug of ze additionele testen moesten ondergaan of dat patiënten de rapportages konden vervolgen. De haalbaarheid van het selecteren van patiënten die in aanmerking kwamen voor de korte opname werd geëvalueerd, evenals postoperatieve complicaties, patiënt-gerapporteerde uitkomsten en kosten. In totaal werden 155 patiënten met een hypofysetumor geïncludeerd in het prospectieve deel van deze studie, waarvan bij 79 (51%) werd ingeschat dat ze in aanmerking zouden komen voor de korte opname. Hiervan konden er 69 (87%) patiënten ontslagen worden op POD 2 of 3. Van de patiënten waarbij van tevoren een inschatting werd gemaakt dat ze niet in aanmerking zouden komen voor de korte opname, konden er 7 (9%) binnen 3 dagen na de operatie ontslagen worden. Als patiënten na hun verkorte opname heropgenomen moesten worden, dan was de primaire oorzaak een late hyponatriëmie (n=6, 43%). Dit was ook de meest voorkomende reden van heropname bij de andere twee groepen. Ten aanzien van de perceptie van patiënten, hadden patiënten die ontslagen waren volgens het korte opname protocol en in de periode na ontslag niet heropgenomen waren een hoger gevoel van veiligheid vergeleken met patiënten die wel heropgenomen waren.

Ondanks dat er meer heropnames waren dan in het historische cohort, zijn er geen levensbedreigende complicaties opgetreden na het invoeren van het korte opname protocol. Mogelijk kan het hogere aantal verklaard worden door de lage drempel die we hadden om patiënten opnieuw op te nemen en de nauwlettende follow-up. Verder

denken wij dat naarmate we meer ervaring krijgen met het vernieuwde zorgpad, er meer patiënten gestratificeerd kunnen worden in de korte opname groep. Verder was er ook geen verschil in de overige patiënt-gerapporteerde uitkomsten tussen de korte opname groep en de reguliere opname groep, illustratief dat er geen verslechtering optrad in kwaliteit van leven. Concluderend toont deze studie aan dat het korte opname protocol veilig en haalbaar is wanneer deze uitgevoerd wordt aan de hand van een goed gedefinieerd zorgpad.

De laatste hoofdstukken (**hoofdstukken 7, 8, 9**) richten zich op de implicaties van het hebben van een hypofysetumor op de lange termijn. Hierbij richtten we ons op maatschappelijke participatie, specifiek op het hebben van een betaalde baan en op het zorggebruik (doel III en IV).

Gezondheid gerelateerde kwaliteit van leven (HRQoL) verbetert aanzienlijk na de behandeling van een NFA (10). De literatuur omtrent het normaliseren van HRQoL na de behandeling is echter niet eenduidig. Waar sommigen een persisterend verminderde HRQoL beschrijven ten opzichte van referentie data (11,12), doen anderen dat niet (13,14). Gezien de verscheidenheid aan geobserveerde HRQoL uitkomsten, was het doel van de review, beschreven in **hoofdstuk 7,** om een literatuuroverzicht te tonen van de gezondheidsuitkomsten van patiënten met een NFA aan de hand van een conceptueel HRQoL model. We hebben om dit te illustreren het Wilson en Cleary model (15) gebruikt. Dit biopsychosociale model integreert het klinische paradigma (waarbij de focus ligt op biologische, psychologische en klinische uitkomsten) met het kwaliteit van leven model (welke focust op dimensies als functioneren en algemeen welzijn). Naast modellen zoals het Wilson en Cleary model, maar ook het ICF model (international classification of functioning disability and health) (16), kunnen uitkomsten gecategoriseerd worden in verschillende domeinen van een conceptueel HRQoL model. Wanneer er aan de hand van het Wilson en Cleary model gekeken wordt naar de uitkomsten van patiënten met een NFA, zien we dat HRQoL aanzienlijk verbeterd na de behandeling, maar dat sommige patiënten toch aangedaan blijven vergeleken met referentie data. Het model illustreert ook domeinen waar patiënten problemen bij kunnen ervaren, zoals cognitief functioneren, coping en ziekteperceptie. Het Wilson en Cleary model interfereert niet met de gedachten en processen van VBHC, maar kan hand in hand gaan met de concepten van VBHC afhankelijk van de behoeften van patiënten.

Tot nu toe richtte onderzoek naar uitkomsten zich voornamelijk op het functioneren van de hypofyse en complicaties van de behandeling en niet zozeer welke gevolgen de aandoening (en de behandeling) heeft op het dagelijks functioneren en maatschappelijke participatie. Omdat het merendeel van de patiënten met een hypofysetumor zich in

de werkende leeftijd bevinden, is het behouden van of de terugkeer naar een betaalde baan een zeer relevante uitkomst. Voorgaand onderzoek uitgevoerd in ons centrum heeft aangetoond dat moeite met het uitvoeren van werkzaamheden vaak voorkomt en dat het zelfs op nummer 2 stond van meest frequent gerapporteerde problemen, zoals ervaren door patiënten met een hypofysetumor (2). Er was echter onvoldoende in beeld wat de omvang van het probleem was. In **hoofdstuk 8** worden de resultaten getoond van een cross-sectionele studie, waarin 241 patiënten werden geïncludeerd die behandeld zijn voor een hypofysetumor en die zich in de werkzame leeftijdscategorie bevonden (18-65 jaar). Deelnemers werden verzocht om vijf gevalideerde vragenlijsten in te vullen, welke keken naar arbeidsparticipatie (Short Form-Health and Labor Questionnaire (SF-HLQ), Work Role Functioning Questionnaire 2.0 (WRFQ)), HRQoL en utiliteit (SF-36, EQ-5D) en ziektelast (LBNQ-Pituitary). De overige informatie werd uit de medische dossiers gehaald. Onder de 241 deelnemende patiënten, was de mediane duur sinds de diagnose 11 jaar en veel patiënten hadden verschillende behandelingen ondergaan. Hiervan waren de meeste geopereerd (n=96, 40%). Van de 241 patiënten hadden er 68 (28%) geen betaalde baan. Factoren die geassocieerd waren met het niet hebben van een betaalde baan waren tumor type (ACRO en CD), evenals de aanwezigheid van uitval van hypofysefunctie ((pan)hypopituïtarisme). We vonden daarnaast dat patiënten die radiotherapie hadden gehad minder vaak een betaalde baan hadden ten opzichte van patiënten die dat niet hadden gehad. Sociodemographisch gezien, was het niet hebben van een duurzame relatie en een lager opleidingsniveau geassocieerd met het niet hebben van een betaalde baan. Ten slotte vonden we dat patiënten met een lagere HRQoL en een verhoogde ziektelast ook vaker geen betaalde baan hadden. Onder de 173 (72%) patiënten die hun betaalde baan wisten te behouden, rapporteerden 70 (40%) patiënten gezondheid gerelateerd absenteïsme in het afgelopen jaar. Patiënten hadden met name moeite met zaken in de mentale en sociale domeinen. Gebaseerd op de resultaten van deze studie, adviseren we om arbeidsparticipatie te integreren en implementeren bij de klinische begeleiding van patiënten.

In **hoofdstuk 9** beschreven we het zorggebruik en de kosten onder 167 patiënten met een NFA, uit dezelfde cross-sectionele studie welke beschreven is in **hoofdstuk 8.** Patiënten werden gevraagd om een viertal gevalideerde vragenlijsten in te vullen. Deze lijsten keken naar jaarlijks zorggebruik, kosten (the medical consumption questionnaire (MTA iMCQ)), ziektelast (LBNQ-Pituitary), HRQoL en utiliteit (SF-36, EQ-5D). De overige informatie werd uit de medische dossiers gehaald.

Het jaarlijkse zorggebruik onder de 167 patiënten was aanzienlijk (gemiddelde jaarlijkse zorgkosten van € 3040 (SD 6498)), zelfs lang na de behandeling (mediane follow-up van 9 jaar). In tegenstelling tot wat we van tevoren hadden geanticipeerd, was de mate van

zorggebruik onafhankelijk van de endocriene status (OR 0.73, 95% CI 0.41;1.86, p=0.73) of behandelstrategie (OR 0.66, 95% CI 0.48;3.18, p=0.66 (operatie ten opzichte van wait-and-scan), OR 0.64 95% CI 0.44;3.74, p=0.64 (radiotherapie ten opzichte van wait-and-scan)). Een langere follow-up (OR 0.97, 95% CI 0.93;1.00, p=0.047) was zelfs geassocieerd met een lager zorggebruik. Slechtere HRQoL (OR 0.94, 95% CI 0.91;0.98, p=0.001 (mental component scale)), meer last van de negatieve gevolgen van de aandoening (OR 1.05, 95% CI 1.02;1.08, p=0.001) en een grotere behoefte aan ondersteuning (OR 1.03, 95% CI 1.01;1.06, p=0.002) waren allen geassocieerd met verhoogd zorggebruik. We hadden van tevoren geanticipeerd dat kosten ook geassocieerd waren met endocriene status, behandelstrategie en follow-up. Dit was echter niet het geval. Daarentegen, was slechtere HRQoL (B 107, 95% CI 9-206, p=0.03), toegenomen last van de aandoening (B 123, 95% CI 58;188, p<0.001) en behoefte aan ondersteuning (B 130, 95% CI 79;180, p<0.001) wel geassocieerd met hogere kosten. Deze resultaten suggereren dat gerichte interventies gericht op ziektelast en onvervulde behoeften in de chronische fase van de ziekte noodzakelijk zijn.

Concluderend, belicht het onderzoek dat hier gepresenteerd is verschillende uitdagingen die we tegenkwamen gedurende de transitie naar VBHC-gebaseerde zorg. Om verder te kunnen gaan richting een op waarde gebaseerd systeem, zijn we afhankelijk van de kwaliteit van rapportering, specifiek uniforme definities en prospectieve verslaglegging van uitkomsten.

We hebben aangetoond dat het haalbaar is om patiëntgerichte zorg te leveren via een verkort opname traject voor patiënten met een hypofysetumor en om uitkomsten te beschrijven met een uitgebreide set van perioperatieve uitkomsten. Met betrekking tot de lange termijn uitkomsten toonden we aan dat de gevolgen van de ziekte groot zijn, zowel ten aanzien van algemene gezondheidsstatus, alsmede de maatschappelijke participatie. Het is mogelijk dat dit in de toekomst verbeterd kan worden, maar het is noodzakelijk om meer onderzoek te verrichten om optimale doelen en middelen te identificeren voor lange termijn interventies.

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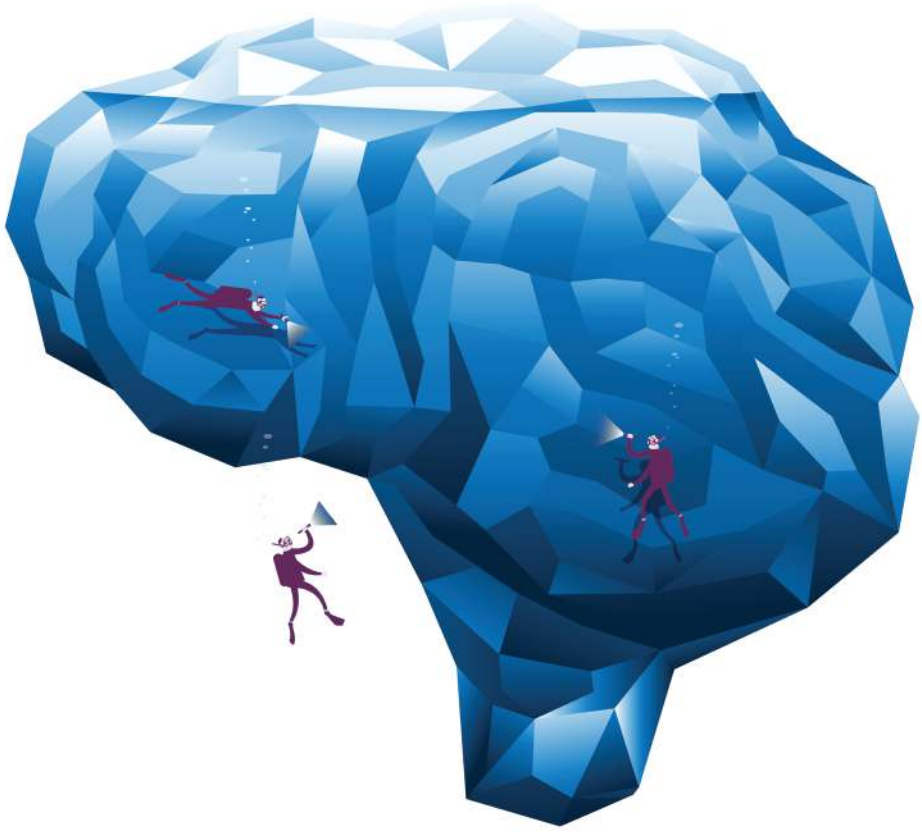

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Pap, ook jij bedankt voor alles wat je voor mij doet en hebt gedaan over de jaren, de onvoorwaardelijke steun en liefde van mam en jou betekent veel voor me en heeft me gemaakt tot wie ik ben. Ik had me geen betere ouders kunnen wensen. Han, Josi en ik hopen nog veel mooie momenten samen te beleven.

Lieve Han, wat ben ik blij dat jij in mijn leven bent gekomen. Jouw steun en liefde maakt me nog steeds iedere dag blij. Ik ben ontzettend trots op jou, het leven wat we samen hebben opgebouwd en kijk uit naar onze toekomst samen. Ik hou van je.

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CURRICULUM VITAE

Daniel Jacob Lobatto was born in Leiden on the 11th of November, 1987. After graduating from high school (Willem de Zwijger College, Bussum) in 2006, Daniel decided he wanted to go to medical school in Leiden. Unfortunately, he did not get through the lottery system and decided that if he could not become a doctor, law school would be second-best. Although he enjoyed his first year as a law student, he still really wanted to become a doctor and decided to give medical school another shot. This time, he placed his bets on Rotterdam, due to the increased odds of getting in for people who played sports at a national level (Baseball). This second time was the charm and got him into medical school. From 2008 onwards, Daniel combined his studies with the work at BISLIFE. He continued working there as a chief retrieval technician for heart valves and corneas until his graduation in 2013. With American roots, Daniel always wanted to live in the United States for a period of time and therefore Daniel had arranged a 6-month research internship at the Hospital for Special Surgery (HSS) in New York under the wing of orthopaedic surgeon prof. David Dines. Prior to his trip to New York, Daniel started a small research project with Godard de Ruiter, Neurosurgeon at the Medical Center Haaglanden (MCH), The Hague. During this time, his interest in the field of Neurosurgery started. Although he really enjoyed his time at HSS, Daniels interest in the field of Neurosurgery grew significantly. This led to his first medical position as Neurosurgical resident not in training (ANIOS) in 2013 at the Medical Center Haaglanden, The Hague. In 2015 Daniel transferred to the Leiden University Medical Center and started a formal PhD program in 2016 on Value Based Health Care in Pituitary Care, which led to this thesis. In the meantime, Daniel obtained a master's degree in 2018 in Epidemiology at EpidM in Amsterdam and started his Neurosurgical residency in July 2019, which he aims to complete in July 2025.