

## REVIEW

# Starting point for benchmarking outcomes and reporting of pituitary adenoma surgery within the European Reference Network on Rare Endocrine Conditions (Endo-ERN): results from a meta-analysis and survey study

Amir H Zamanipoor Najafabadi<sup>1,2,3</sup>, Merel van der Meulen<sup>2</sup>, Ana Luisa Priego Zurita<sup>2</sup>, S Faisal Ahmed<sup>4</sup>, Wouter R van Furth<sup>1</sup>, Evangelia Charmandari<sup>5</sup>, Olaf Hiort<sup>6</sup>, Alberto M Pereira<sup>7</sup>, Mehul Dattani<sup>8</sup>, Diana Vitali<sup>9</sup>, Johan P de Graaf<sup>10</sup> and Nienke R Biermasz<sup>11</sup>

<sup>1</sup>Department of Ophthalmology, Leiden University Medical Center, Leiden, The Netherlands

<sup>2</sup>Department of Medicine, Division of Endocrinology and Centre for Endocrine Tumors, Leiden University Medical Centre, Leiden, The Netherlands

<sup>3</sup>Department of Neurosurgery, University Neurosurgical Centre Holland (UNCH), Leiden University Medical Centre, Haaglanden Medical Centre and Haga Teaching Hospitals, Leiden and The Hague, The Netherlands

<sup>4</sup>Chair of Work Package of E-Health & ICT of Endo-ERN, Developmental Endocrinology Research Group, School of Medicine, Dentistry & Nursing, University of Glasgow and Office for Rare Conditions, Royal Hospital for Children & Queen Elizabeth University Hospital, Glasgow, UK

<sup>5</sup>Pediatric Chair Main Thematic Group 6 Pituitary of Endo-ERN, Division of Endocrinology, Metabolism and Diabetes, First Department of Pediatrics, National and Kapodistrian University of Athens Medical School, 'Aghia Sophia' Children's Hospital, Athens, Greece

<sup>6</sup>Pediatric Chair and Deputy Coordinator of Endo-ERN, Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics and Adolescent Medicine, University of Lübeck, Lübeck, Germany

<sup>7</sup>Adult Chair and Coordinator of Endo-ERN, Department of Endocrinology and Metabolism, Amsterdam University Medical Center, Amsterdam, The Netherlands

<sup>8</sup>London Centre for Pediatric Endocrinology and Diabetes at Great Ormond Street Children's Hospital and University College London Hospitals, London, UK

<sup>9</sup>SOD ITALIA (Italian Organization for Septo Optic Dysplasia and other Neuroendocrine Disorders), European Patient Advocacy Group, Rome, Italy

<sup>10</sup>Dutch Pituitary Foundation, European Patient Advocacy Group, Nijkerk, The Netherlands

<sup>11</sup>Adult Chair Main Thematic Group 6 Pituitary of Endo-ERN, Department of Medicine, Division of Endocrinology and Centre for Endocrine Tumors, Leiden University Medical Centre, Leiden, The Netherlands

Correspondence should be addressed to A H Zamanipoor Najafabadi: [a.h.zamanipoor\\_najafabadi@lumc.nl](mailto:a.h.zamanipoor_najafabadi@lumc.nl)

This paper forms part of a special series collated by European Reference Network on Rare Endocrine Conditions celebrating its fifth year. The guest editors for this section are Violeta Iotova, Jérôme Berherat, and George Mastorakos.

## Abstract

**Objective:** The European Reference Network on Rare Endocrine Conditions (Endo-ERN) aims to organize high-quality healthcare throughout Europe, including care for pituitary adenoma patients. As surgery is the mainstay of treatment, we aimed to describe the current surgical practice and published surgical outcomes of pituitary adenoma within Endo-ERN.

**Design and Methods:** Systematic review and meta-analysis of studies reporting surgical outcomes of pituitary adenoma patients within Endo-ERN MTG6 pituitary reference centers between 2010 and 2019. A survey was completed by reference centers on their current surgical practice.

**Results:** A total of 18 out of 43 (42%) reference centers located in 7 of the 20 (35%) MTG6-represented countries published 48 articles. Remission rates were 50% (95% CI: 42–59) for patients with acromegaly, 68% (95% CI: 60–75) for Cushing's disease, and 53% (95% CI: 39–66%) for prolactinoma. Gross total resection was achieved in 49% (95% CI: 37–61%)

## Key Words

- ▶ Endo-ERN
- ▶ pituitary
- ▶ surgery
- ▶ registry

of patients and visual improvement in 78% (95% CI: 68–87). Mortality, hemorrhage, and carotid injury occurred in less than 1% of patients. New-onset hypopituitarism occurred in 16% (95% CI: 11–23), transient diabetes insipidus in 12% (95% CI: 6–21), permanent diabetes insipidus in 4% (95% CI: 3–6), syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in 9% (95% CI: 5–14), severe epistaxis in 2% (95% CI: 0–4), and cerebrospinal fluid leak in 4% (95% CI: 2–6). Thirty-five (81%) centers completed the survey: 54% were operated endoscopically and 57% were together with an ENT surgeon. **Conclusion:** The results of this study could be used as a first benchmark for the outcomes of pituitary adenoma surgery within Endo-ERN. However, the heterogeneity between studies in the reporting of outcomes hampers comparability and warrants outcome collection through registries.

Endocrine Connections  
(2022) 12, e220349

## Introduction

The European Reference Network on Rare Endocrine Conditions (Endo-ERN) aims to organize high-quality healthcare throughout Europe for patients with rare endocrine conditions. Through intensive collaboration between its reference centers, its aims include (i) to reduce and ultimately abolish inequalities in access to and quality of care by sharing knowledge between centers and facilitating training programs and (ii) to reinforce collaborative research needed to evaluate the care of these rare conditions (1). Eight main thematic disease groups (MTGs) define the European landscape of rare endocrine conditions. MTG6, 'Pituitary', includes three subthemes: pituitary adenoma, congenital hypopituitarism, and acquired hypopituitarism.

Pituitary adenomas comprise non-hormone-producing adenomas and adenomas producing an excess of growth hormone (acromegaly), adrenocorticotrophic hormone (Cushing's disease), prolactin (prolactinoma), thyrotropin hormone (TSH-producing adenoma), and gonadotropins (gonadotropinoma). The incidence of these rare adenomas is low, ranging from 0.03 per 100,000 person-years for TSH-producing adenoma (TSH-oma) to 1.80 per 100,000 person-years for non-functioning adenoma (2). Hence, the care for these patients is preferably organized in high-volume reference centers around multidisciplinary teams with accessibility to neurosurgical care, as current guidelines recommend transsphenoidal surgery as first-line treatment for the majority of adenoma subtypes, although many also need multimodality treatment (3, 4, 5, 6). Care for these patients is still challenging due to the lack of high-quality evidence-based multidisciplinary care guidelines, resulting in practice variation (7). Therefore, cross-border collaboration is needed in the form of expert (virtual) consultation for rare and complex cases

and in the form of registries to collect high-quality data. This might especially hold true for ultra-rare cases for which even expert centers lack extensive experience, such as pituitary tumors in children, aggressive pituitary tumors, refractory tumors, and conditions like TSH-oma or gonadotropinoma. Within a country or region, reference centers often fulfill a key network function to also ensure high-quality care in regional referring hospitals.

Historically, the outcomes of pituitary adenoma resection are published per center on a voluntary and *ad hoc* basis, with a large variety in definitions and choice of measured outcomes, which hinders comparability of these studies. Collaboration between centers is needed to provide scientifically solid studies on these rare conditions. To facilitate these kinds of collaborations, the third EU health program funded and constructed ERN-wide patient registries, the European Registries for Rare Endocrine Conditions (EuRRECa), which is the first coordinated, EU-funded clinical research effort carried out in all ERNs (7). The EuRRECa serves the Endo-ERN and facilitates data collection and subsequently comparability and pooling of data between centers (7).

The aim of this study is to describe the published surgical outcomes and current surgical practice of pituitary adenoma at Endo-ERN Pituitary Reference Centers. Furthermore, we examined the reported terminology on remission, resection grade, and surgical complications as reported in these publications. These results will enable benchmarking of surgical outcomes within Endo-ERN, which can be used as a starting point for initiatives to improve surgical care across Europe. It also facilitates the development of a minimum core outcome set for the measurement of uniform outcomes within European registries.

## Methods

### Study design and concept

This study consisted of three steps. First, we performed a systematic literature search for a systematic review and meta-analysis on the outcomes of pituitary adenoma resection within Endo-ERN. Secondly, for the identified articles, we assessed how authors defined remission, resection grade and complications, and potential (other) sources of bias. Thirdly, reference centers completed a short survey on their current pituitary surgery practice.

### Literature search and data extraction

We performed a literature search in PubMed and Embase to identify all surgical publications reported by Endo-ERN MTG6 pituitary reference centers between January 2010 and September 2019. Search terms were the names of the reference centers' representatives as known on October 2019. These names were combined with a previously used search strategy for pituitary surgery (8). Articles were eligible if they reported surgical outcomes of non-congenital pituitary patients with acromegaly, Cushing's disease, prolactinomas, and non-hormone-producing adenomas, operated in MTG6 pituitary reference centers. Although Endo-ERN is especially of value for patients with ultra-rare conditions (e.g. TSH- and gonadotropin-producing adenoma), parasellar masses, and exceptional presentations (e.g. pediatric, giant or aggressive tumors, or apoplexy), this study did not focus on these adenoma subtypes, as no reliable study-level meta-analyses can be conducted for these conditions, due to the small number of published studies describing a small number of patients. Articles reporting the outcomes of one or more MTG6 pituitary reference centers but not separately from non-MTG6 centers were excluded from the main meta-analyses. However, the publications are still presented in the systematic review part, as we acknowledge that reference centers often have a key network role in their region.

The following data points were extracted from each article, if possible, separately for different adenoma types: authors, year of publication, number of described patients, used surgical technique (endoscopic vs microscopic including endoscopy-assisted), percentage of patients in remission, percentage of patients with gross total resection, percentage of patients with visual improvement in those with preoperative visual impairment, percentage of patients with surgical complications, percentage of mortality, and patient-reported outcomes (e.g. health-related quality of life (HRQoL)). No *a priori* selection was

made for specific surgical complications, and therefore, all complications as reported by the original article were extracted. Data extraction was performed by one reviewer and controlled independently by a second reviewer.

The preferred reporting items for systematic reviews and meta-analyses statement was followed for unbiased reporting (9).

### Evaluation of used definitions of remission, resection and complications, and potential sources of bias

From the articles included in the systematic review, we extracted the definitions of remission for hormone-producing adenomas and for all adenoma types, the definitions of degree of resection and surgical complications, as reported by the authors of the original publications. Absence of these definitions in the original reports or use of unclear definitions may result in information and classification bias. For the same reason, we assessed whether studies reported if the results were described after first surgery or reoperation.

### Survey among representatives of the MTG6 pituitary reference centers

Using a survey, the identified articles from the literature search were presented to the healthcare representatives of each MTG6 pituitary reference center and articles missed with the literature search were identified. Furthermore, the survey included items regarding (i) the standard surgical technique (endoscopic or microscopic), (ii) if applicable, transition year to the endoscopic technique, (iii) the number of pituitary neurosurgeons and ENT surgeons, (iv) percentage of dedicated time of each surgeon to perform pituitary surgery, and (v) identification of non-Endo-ERN pituitary centers of excellence within the country of the reference center.

### Statistical analysis

#### Main analysis

For the main analyses, studies reporting data on adult patients treated within MTG6 centers were used. Pooled results are reported with 95% CI for the percentage of patients achieving biochemical remission, gross total adenoma resection, visual improvement in those with preoperative impairment, and surgical complications. Biochemical remission was analyzed separately for patients with GH-, ACTH-, and prolactin-producing adenomas. Gross total resection was analyzed for all patients together

and for non-functioning and hormone-producing adenomas separately. Complications were analyzed without distinction between adenoma types.

### Secondary analysis

Where possible, outcomes were also analyzed separately for studies that solely used the endoscope or microscope for pituitary surgery. Moreover, analyses were also performed excluding studies that explicitly reported to have included outcomes after repeat surgery. Furthermore, subgroup analyses were performed for studies describing complications in patients with hormone-producing adenomas and also separately for patients with acromegaly and Cushing's disease. We were unable to perform analyses for other subgroups, due to paucity of data.

### Statistical methods employed

Random-effects meta-analysis was used, following the Dersimonian and Laird method (10). A Freeman-Tuckey double arcsine transformation was performed to include studies with 0 or 100% outcomes (11). In-between study heterogeneity was described with  $I^2$ . Analyses with less than three studies were omitted.

All statistics were performed using IBM SPSS Statistics for Windows version 23.0 and Stata version 14.1 (StataCorp).

### Systematic review

The following publications were presented in a systematic fashion without meta-analyses: (i) publications from Endo-ERN representatives with patient data from non-Endo-ERN centers, (ii) studies describing patient data from both ERN centers and non-Endo-ERN European centers, without separate presentation of Endo-ERN center data, and (iii) studies in a pediatric patient population within Endo-ERN.

## Results

### Pituitary surgery practice

A total of 35 (81%) centers completed the survey about their current pituitary surgery practice. Out of these 35 centers, 19 (54%) centers only perform pituitary surgery using an endoscope, 11 (31%) centers use both endoscopic and microscopic techniques, and 5 (14%) centers only perform microscopic pituitary surgery. Six centers (32%)

transitioned to endoscopic surgery before the year 2000 and ten centers (53%) before the year 2010. A median of three pituitary surgeons (range: 1–8) work within the Endo-ERN centers. All centers have neurosurgeons working as a pituitary surgeon and 20 centers (57%) also have ENT surgeons. Dedicated time for pituitary care was less than 25% of their practice for 10 centers, 25–50% for 14 centers, 51–75% for 9 centers, and more than 75% of their practice for 2 centers.

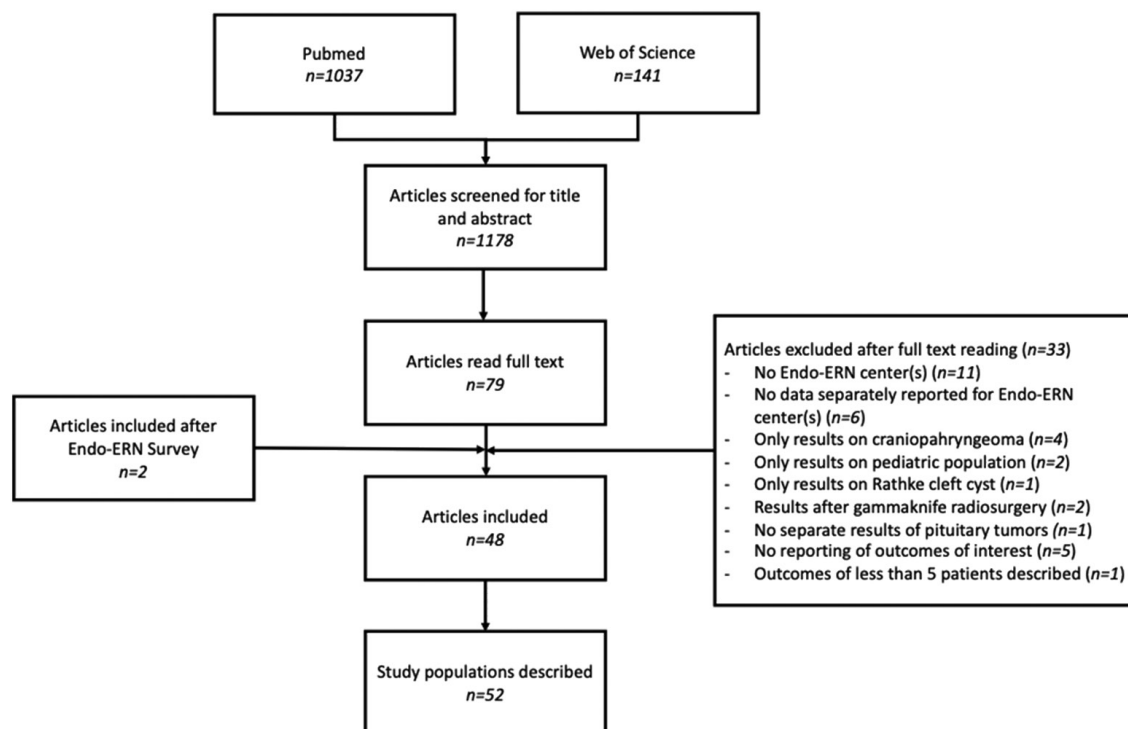
### Distribution of publications of pituitary surgery outcomes within Endo-ERN

A total of 1178 articles were screened for title and abstract, 79 of which were read full-text. An additional two articles were identified with the survey among healthcare representatives of the reference centers. A total of 48 articles were identified, describing 52 groups of patients operated in an Endo-ERN Reference Center (Fig. 1). Details of individual studies are described in Supplementary Tables 1 and 2 (see section on [supplementary materials](#) given at the end of this article). In addition, we identified five articles describing the outcomes of patients operated by a MTG6 representative in a non-Endo-ERN center, five articles that did not report outcomes separately for patients operated in an Endo-ERN center, and one study in a pediatric population. Details of these studies are described in Supplementary Tables 3 and 4.

A total of 18 of the 43 (42%) reference centers published their outcomes of pituitary surgery (Fig. 2). These reference centers were located in 8 (40%) of the 20 countries with an MTG6 pituitary reference center. Outcomes of acromegaly (1520 patients, 23 studies, as included in the main meta-analyses) were published by 13 (30%) centers located in 7 (35%) countries, Cushing's disease (1798 patients, 26 studies) by 13 (28%) reference centers located in 6 (30%) countries, prolactinoma (452 patients, 15 studies) by 10 (23%) reference centers located in 5 (25%) countries, and non-functioning adenoma (2597 patients, 18 studies) by 10 (23%) reference centers located in 5 (25%) countries.

### Remission rates, resection grade, and visual outcomes

The remission rate after surgery was 50% (95% CI: 42–59) for patients with acromegaly, 68% (95% CI: 60–75) for patients with Cushing's disease, and 53% (95% CI:



**Figure 1**  
Search strategy to identify surgical reports of Endo-ERN MTG6 reference centers.

39–66%) for patients with prolactinoma (Fig. 3). Results were similar for patients operated with the endoscopic and microscopic approach.

Overall, a gross total resection was established in 49% (95% CI: 37–61%) of patients with no difference between patients with a non-functioning (58% (95% CI: 46–70)) or hormone-producing adenoma (58% (95% CI: 40–75)) (Fig. 4). In published reports, a gross total resection was described in 66% (95% CI: 38–89) of patients operated with the microscope, compared to 49% (95% CI: 36–62) of patients operated with the endoscope.

Visual improvement in those presenting with a visual impairment was achieved in 78% (95% CI: 68–87) of patients, and normalization of vision was achieved in 41% (95% CI: 34–49). Subgroup analyses in patients operated with the endoscopic technique or hormone-producing pituitary adenomas yielded approximately similar results (Supplementary Fig. 1). Due to the lack of studies, no subgroup analyses could be performed for the microscopic technique or for patients with non-functioning pituitary adenomas.

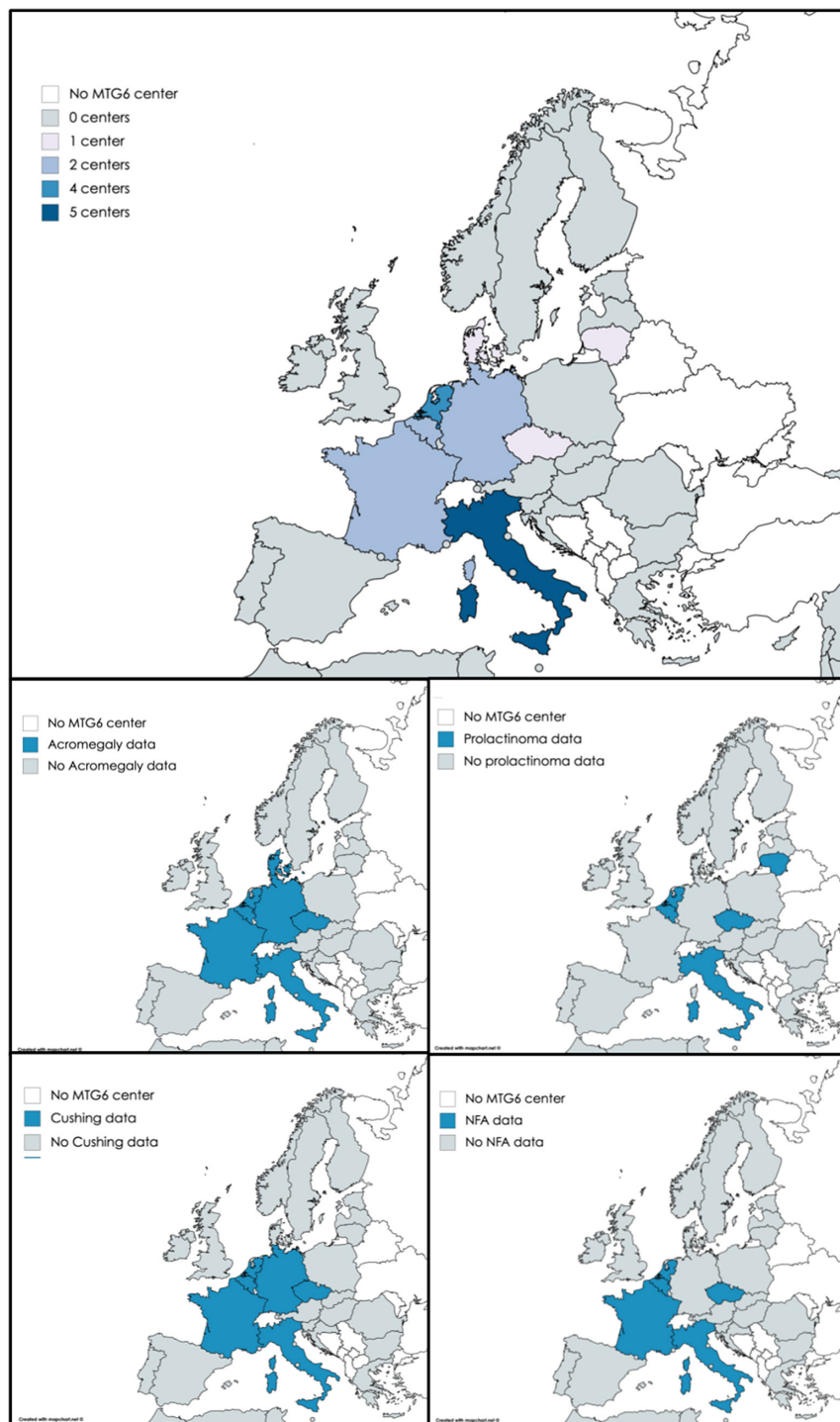
Excluding studies that explicitly reported to have included the outcomes of patients after repeat surgery resulted in outcomes comparable to first surgery regarding

remission (Fig. 3), gross total resection (Fig. 4), and visual improvement (Supplementary Fig. 1).

## Complications

Severe surgical complications such as mortality, hemorrhage, carotid injury, and hemiparesis occurred in less than 1% of patients (Fig. 5). Newly developed hypopituitarism occurred in 16% (95% CI: 11–23) of patients and panhypopituitarism in 6% (95% CI: 0–17). Transient diabetes insipidus was reported in 12% (95% CI: 6–21) and permanent diabetes insipidus in 4% (95% CI: 3–6). SIADH occurred in 6% (95% CI: 3–19). Mild epistaxis was reported in 3% (95% CI: 1–4%) and severe epistaxis in 2% (95% CI: 0–4). Cerebrospinal fluid (CSF) leak occurred in 4% (95% CI: 2–6) and meningitis in 1% (95% CI: 0–2%). Results on other complications are provided in Fig. 4.

Subgroup analyses with studies describing outcomes after the endoscopic or microscopic technique resulted in similar results (Supplementary Fig. 2 and 3). Hypopituitarism was higher in studies describing complications in patients with acromegaly (26%, 95% CI: 11–45) and Cushing's disease (33%, 95% CI: 22–46%) (Supplementary Fig. 4–6). Diabetes insipidus occurred more frequently in patients with Cushing's disease, too



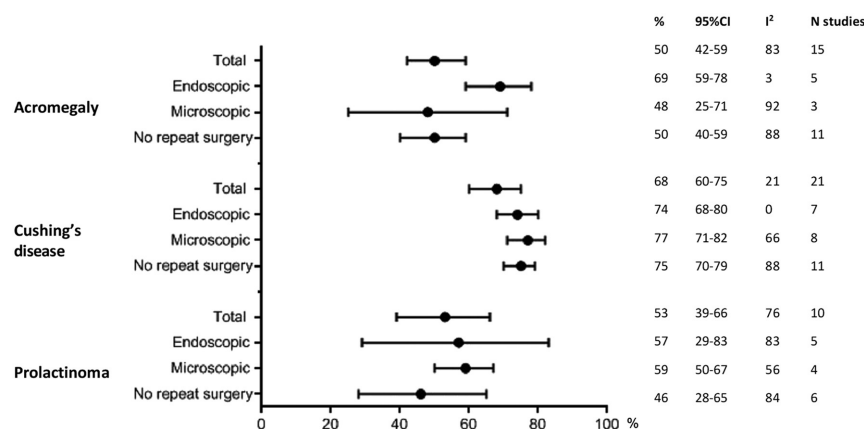
**Figure 2**  
Publications on the outcomes of pituitary surgery within Endo-ERN.

(24%, 95% CI: 9–41%). Not all complications could be analyzed in all subgroups due to paucity of data.

Excluding studies that explicitly reported to have included the outcomes of patients after repeat surgery resulted in complication rates comparable with first surgery (Supplementary Fig. 7).

### Definitions of remission, resection grade and complications, and potential sources of bias

Only 14 of the 33 (42%) studies that reported postoperative complications provided any definition or explanation of the measured complications (Supplementary Table 5).



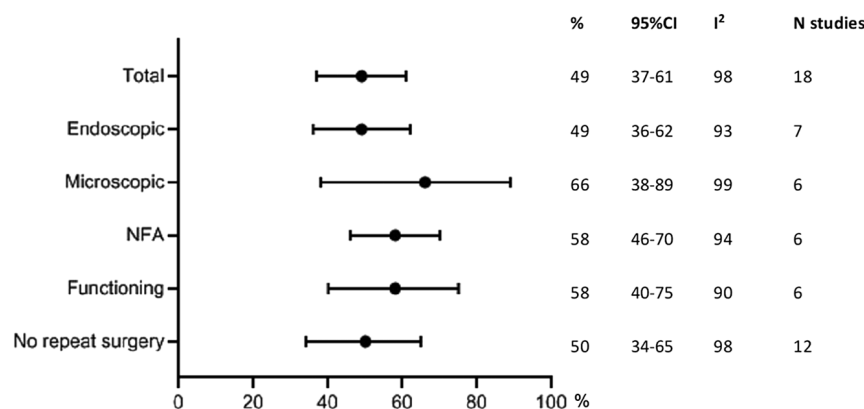
**Figure 3** Remission percentages for acromegaly, Cushing's disease, and prolactinoma.

Eight studies reported transient and permanent diabetes insipidus separately, while only three studies provided a definition for permanent diabetes insipidus. One study defined it as the need for desmopressin for a minimum of 2 months, and another study used a 3 months timeframe. Four studies reported the outcomes of mild and severe epistaxis separately, without providing a clear definition. While mortality was reported by 15 studies, only 3 studies provided a definition and timeframe. Two studies measured mortality within 2 months after surgery. It was measured as all-cause mortality in two studies and as related to surgical complications in one study. Three studies divided surgical and endocrinological complications. Surgical complications were defined by one study as complications occurring within a month and needing intervention. Complications were divided into major and minor complications by five studies. One study described major complications as complication that were permanent, fatal, or requiring surgery or readmission. CSF leaks were defined by two studies as leaks occurring postoperatively, not counting intraoperative leaks. Two studies provided a definition for meningitis, described as (i) meningism, abnormal white blood cells in the CSF and elevated protein and/or low glucose levels in the CSF, without the need for

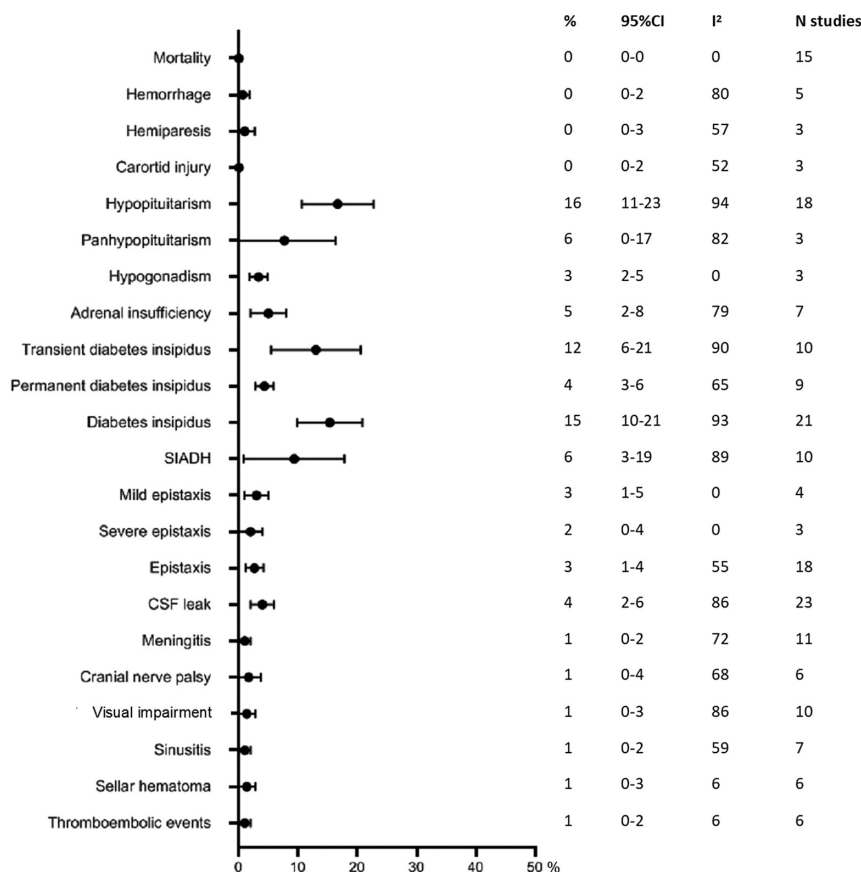
evidence of bacteria in culture and (ii) start of antibiotic treatment due to suspicion of meningitis.

Definitions for extent of resection were provided by five studies. One study classified resection grade as subtotal resection (>80%) and partial resection (<80%). Two studies classified resection grade as near total (>90%), subtotal (>70), and partial (<70%). One study used near total (>95%), subtotal (>80%), and partial (<80%). Another study used subtotal (>90%) and partial (<90%). All five studies described a total resection as 100% resection of the adenoma. Two studies based the extent of resection on the surgeon's intraoperative assessment combined with postoperative imaging. One study only relied on the intraoperative judgment of two performing surgeons. One study provided a timeframe for the postoperative assessment of resection grade: 3 months after surgery. Thirteen studies only described total and subtotal resection without a definition.

Postoperative remission was based on normalized biochemical values in 16 studies. Seven studies used a definition of remission that also required normalization of symptoms. Four studies described remission as a total adenoma resection with subsequently normalized biochemical values.



**Figure 4** Total resection percentages.



**Figure 5**  
Operative complications.

Nineteen studies did not specify whether outcomes were only from patients after first surgery or also after repeat surgery. Nine studies reported explicitly that patients after repeat surgery were included and two studies only presented the outcomes of re-operated patients. Sixteen studies only reported outcomes after first surgery.

## Discussion

Surgery is the mainstay of treatment for the majority of patients with pituitary adenoma. This study indicates that approximately 40% of the MTG6 pituitary Endo-ERN centers have reported on surgical results in the last decade through peer-reviewed publications, so 60% have not. A total of 46 publications were found with the initial literature search and 2 additional publications were collected via the MTG6 network. Published studies most frequently described the surgical outcomes of patients with acromegaly and Cushing’s disease, whereas the outcomes of patients with a prolactinoma or non-functioning pituitary adenoma were reported less frequently. Importantly, a great heterogeneity was found in the reported definitions of remission, extent

of resection and complications, warranting uniformity, and standardization to facilitate a reliable comparison of outcomes between centers.

## Promoting equal high-quality healthcare

Endo-ERN fulfills a large unmet need to collaborate and improve (access to) care for rare endocrine conditions by creating a virtual network facilitating cross-border consultation of expert panels. Throughout Europe, it aims to provide and improve standards of care for rare endocrine conditions across the lifespan. Although many reference centers for pituitary adenomas have been endorsed within Europe, delivering expert multidisciplinary care and regional consultation, complex cases, and ultra-rare conditions still benefit from cross-border consultation and the sharing of experience of other expertise centers (3). Inequalities in healthcare access are abolished by providing expert care by means of virtual multidisciplinary expert panels to the closest reference center, instead of asking patients to travel to the expert. As reference centers often fulfill a key network function within their own region, the expert care might even be brought to the local hospital. The importance of this function of Endo-ERN is supported



by our results that suggest that different centers might provide expertise for different pituitary adenoma types, at least when transparency of outcomes by publication is considered a key feature of a center of expertise.

At this starting point of Endo-ERN, published reports are predominantly provided by centers from the Netherlands and Italy, which do not represent general neurosurgical care in Europe *per se*, as we expect that only a minority of surgical outcomes within Endo-ERN have been published and some countries have not shared their outcomes in literature. For ideal benchmarking, a better coverage of Europe is warranted.

We do acknowledge that non-Endo-ERN centers contribute significantly to expert pituitary surgery in Europe, as can be seen by the large number of publications of these centers in recent meta-analyses of outcomes of pituitary surgery (12, 13, 14, 15). For example, in a recent meta-analysis on Cushing's disease, 16 publications were from Endo-ERN centers, 32 from European non-Endo-ERN centers, and 49 from centers outside Europe. In our survey, Endo-ERN centers did name 23 non-Endo-ERN centers as centers with high-volume pituitary care and pituitary expertise. Strong collaboration between Endo-ERN centers and non-Endo-ERN centers will be needed for proper dissemination of knowledge and know-how to truly provide best care throughout Europe.

In this current review, we also report that Endo-ERN reference centers collaborate and publish together with these high-volume expertise non-Endo-ERN centers, emphasizing the network function. For future analyses of the landscape and quality of surgical pituitary care, collaborations between non-Endo-ERN centers and Endo-ERN centers should be mapped to facilitate that these centers also benefit from the collaborative platforms provided by the EU. Importantly, the publications presented in our report only focus on the surgical outcomes, while for optimal care, collaboration between centers with different areas of expertise is needed. Both Endo-ERN and non-Endo-ERN centers might focus and be experts on pharmacological therapy, including chemotherapy and targeted therapy and radiotherapy including radiosurgery. Additional mapping of outcomes in multimodality treatment, for example, drugs and radiotherapy, and combination therapies in pituitary adenomas is also needed; however, these data are apparently more scarce than the surgical outcomes.

Our results also exemplify the need for further collaborative research. The number of published studies on pituitary adenoma surgery is still relatively small, especially for patients with prolactinomas and non-functioning

adenomas, and even more for specific conditions, such as aggressive tumors, pediatric tumors, and patients with ultra-rare subtypes of adenoma, such as TSH-producing adenomas and gonadotropins-producing adenomas. However, in recent years, the number of publications is increasing, although large patient numbers cannot be achieved by single centers. Through harmonized data collection within the Endo-ERN registries, surgical results of these rare conditions will be collected and highlighted in future Endo-ERN publications. Furthermore, the use of patient-reported outcome measures (PROM) was very limited in the published studies ( $n=3$  studies). Use of European registries will facilitate research on these topics and assist with cross-border comparison of outcomes, provide the possibility for pooling of outcomes, provide a platform for clinical trials, and overall strengthen the relationship between Reference Centers, which further facilitates communication between treatment teams for healthcare consultation (7). Hence, registries form a key corner for European Reference Networks and the use of registries for these purposes has been recognized and supported by the European Union (16, 17). Within Endo-ERN, the use of registries for pituitary conditions has been scored the highest priority by the representatives of Endo-ERN reference centers (7). A major advantage of registries is standardized data collection, allowing comparison of data between centers. Where possible, the use of internationally accepted criteria should be used, such as for remission in acromegaly and Cushing's disease, and otherwise, consensus should be reached on preoperative and postoperative reports to facilitate not only comparison between ERN centers but also to facilitate comparison with studies and registries from non-Endo-ERN collaborations (18, 19).

### Starting point for benchmarking surgical outcomes

Estimated pooled outcomes of published surgical studies within Endo-ERN as reported in this study are similar, with a tendency to be poorer compared to outcomes of published meta-analyses (12, 13, 14). This is an interesting observation, requiring further analyses in future studies. It may be explained by many factors, for example, the fact that reference centers tend to perform surgery on more complex cases, resulting in lower remission rates. Indeed, we report that only 35% of studies explicitly reported outcomes after first surgery, without cases of repeat surgeries. Alternatively, there might be large heterogeneity in outcomes within the network, which cannot be accounted for solely with the case-mix

variation. Conclusions can only be drawn when the network further develops with better registration, more outcome evaluations, and uniform definitions.

Furthermore, analyses were not performed separately for patients with micro- and macroadenomas, as almost none of the studies described results separately for micro- and macroadenomas. Outcomes of TSH-omas and other rare adenomas were also not analyzed due to the paucity of data, while especially for these cases, cross-border consultation and collaboration could be interesting. These results stress the need for European and international registries to collect data on specific patient groups and patient with ultra-rare pituitary adenomas, such as TSH- and gonadotropins-producing adenomas.

In accordance with older existing literature, no clear differences between the outcomes of the microscopic and endoscopic approach were found (14, 18). However, results from large case series have shown that the use of the endoscopic approach might be preferred for larger pituitary adenomas with suprasellar extension, as it provides a panoramic view of the sellar region and adjacent structures, also enabling extended approaches (19). A surgical learning curve needs to be taken into account for the endoscopic approach, which has already been finalized for the microscopic approach. Hence, better surgical outcomes might be expected in the future evaluation of the endoscopic technique. Indeed, more recent comparisons between both techniques show a preference for the endoscopic technique regarding outcomes such as gross total resection and biochemical remission (22, 23). Moreover, considerable heterogeneity exists between studies in baseline characteristics such as age, gender, and comorbidities. These results further underline the need to compare and pool data on an individual patient level, instead of study level, to consider case-mix variables affecting the outcomes of interest.

We furthermore report that most studies lack a clear definition for extent of resection and complications. Moreover, not all complications are reported, such as sino-nasal problems. Hence, these results warrant standardized and uniform definitions for data collection in international registries and also structured and systematic reporting of surgical publications of pituitary adenomas.

### Limitations

A possible limitation of this study is that we could only use available – published – outcomes of MTG6 pituitary Endo-ERN reference centers, so there are missing data. In case of a publication bias, the evaluated outcomes might be even

less favorable when considering unpublished outcomes. However, the reported outcomes of the individual studies as presented in Supplementary Tables 1 and 2 show a great heterogeneity, suggesting publication of less favorable results too. Moreover, a benefit of using published data is that data for these publications are often carefully collected and checked before publication. Another limitation could be that published reports might have been missed, as we used the names of healthcare representatives of each reference center for the search strategy. Publications might have been published by other healthcare providers from a reference center without co-authorship of the representative. Moreover, representatives might have changed from center within the period of interest of the literature search (2010–2019). However, to overcome these limitations, the results of the literature search were presented to the representatives of each center and any missed publications were consequently added to the analyses. This also represents the unmet need to easily identify these studies and center-specific outcomes for patients and healthcare professionals, which deserves attention in future developments within Endo-ERN. As this study was performed before Brexit, results from centers from the UK were included in the analysis. Future Endo-ERN reports will be without these centers. Heterogeneity of the reported outcomes hampered the analysis of long-term remission and recurrence, while these outcomes are clinically relevant and hence should be the topic of future research. Although our analysis focused on surgical outcomes, and articles describing the outcomes of combined treatment modalities were excluded, we were dependent regarding this point on the description of the authors in the original papers. Lastly, studies might have been published outside our study time window, before 2010, which are now not included in this report, as techniques have improved over the years and we aimed to present an overview of outcomes and research efforts of recent years.

### Future directions

While the results of this study could be used as a first benchmark for the outcomes of pituitary adenoma surgery within Endo-ERN, the great heterogeneity between studies in the definitions, measurement and reporting of outcomes hampers comparability. Currently, EuRREca is collecting data for pituitary conditions through an e-reporting program (e-REC) and a core registry. Uniform data collection is a prerequisite, requiring clear and uniform definitions of collected data elements to ensure

comparability of data (16). Therefore, the board of MTG6 pituitary is planning to develop a consensus statement on the reporting of surgical results. Information on the definitions of outcomes as provided by our study will provide a starting point for this consensus statement. These efforts will strengthen the collaboration between the MTG6 Pituitary Endo-ERN centers in their efforts to improve the care for rare endocrine conditions from the benchmark described in this manuscript. While this report focused only on surgical outcomes, multidisciplinary treatment is key for rare endocrine conditions, and future studies will also focus on other treatment modalities and on specific patient groups.

#### Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EC-22-0349>.

#### Declaration of interest

The authors report no conflict of interest that could be perceived as prejudicing the impartiality of this review.

#### Funding

This publication has been supported by Endo-ERN, which is co-funded by the European Union's third Health Programme (CHAFEA Framework Partnership Agreement No 739527).

#### Acknowledgements

The authors would like to thank all centres and physicians that responded to our survey. Members of the 'MTG6 Pituitary of Endo-ERN' group authorship: D Steenvoorden, I Bowring, MM van der Klauw, RA Vergeer, M Losa, P Mortini, W Drake, J Grieve, M Didi, C Mallucci, MG Shaikh, S Hassan, JOL Jorgensen, M Albarazi, S Zaharieva, A.Hadzhivanov, M Tóth, L Sípós, D Unuane, J D'Haens, U Feldt-Rasmussen, L Poulsgaard, T Brue, H Dufour, J Bertherat, S Gaillard, N Karavitaki, S Ahmed, N Unger, I Kreitschmann-Andermahr, S Gaztambide, I Pomposo, H-W Gan, N Dorward, E Fliers, J Hoogmoed, C Scaroni, L Denaro, A Nordenström, M Olsson, B Zilaitiene, A Tamašauskas, L Persani, G Lasio, D Maiter, C Raftopoulos, V Volke, T Rätsep, P Matarazzo, P Peretta, T Deutschbein, J Perez, S Zucchini, D Mazzatenta, S Grottolì, F Zenga, F Devuyt, O De Witte, F Gatto, D Rossi, K Schilbach, W Rachinger, A Beckers, D Martin, M Al-Mrayat, N Mathad, SJMM Neggers, AHG Dallenga, J Lebl, M Tichy, MM Reincke, AC van de Ven, E van Lindert, P Kotnik, R Bošnjak, B Biagetti, E Cordero, A Colao, P Cappabianca.

## References

- Vries F De, Bruin M, Cersosimo A, Beuzekom CN Van, Ahmed SF, Peeters RP, Biermasz NR, Hiort O & Pereira AM. An overview of clinical activities in Endo-ERN: the need for alignment of future network criteria. *European Journal of Endocrinology* 2020 **183** 141–148. (<https://doi.org/10.1530/EJE-20-0197>)
- Tjornstrand A, Gunnarsson K, Evert M, Holmberg E, Ragnarsson O, Rosen T & Filipsson Nystrom H. The incidence rate of pituitary adenomas in western Sweden for the period 2001–2011. *European Journal of Endocrinology* 2014 **171** 519–526. (<https://doi.org/10.1530/EJE-14-0144>)
- Casanueva FF, Barkan AL, Buchfelder M, Klubanski A, Laws ER, Loeffler JS, Melmed S, Mortini P, Wass J, Giustina A, et al. Criteria for the definition of Pituitary Tumor Centers of Excellence (PTCOE): a Pituitary Society Statement. *Pituitary* 2017 **20** 489–498. (<https://doi.org/10.1007/s11102-017-0838-2>)
- Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, Wass JA & Endocrine Society. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** 273–288. (<https://doi.org/10.1210/jc.2010-1692>)
- Katznelson L, Laws ER, Melmed S, Molitch ME, Murad MH, Utz A, Wass JAH & Endocrine Society. Acromegaly: an endocrine society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 2014 **99** 3933–3951. (<https://doi.org/10.1210/jc.2014-2700>)
- Nieman LK, Biller BMK, Findling JW, Murad MH, Newell-Price J, Savage MO & Tabarin A. Treatment of Cushing's syndrome: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 2015 **100** 2807–2831. (<https://doi.org/10.1210/jc.2015-1818>)
- Ali SR, Bryce J, Cools M, Korbonits M, Beun JG, Taruscio D, Danne T, Dattani M, Dekkers OM, Linglart A, et al. The current landscape of European registries for rare endocrine conditions. *European Journal of Endocrinology* 2019 **180** 89–98. (<https://doi.org/10.1530/EJE-18-0861>)
- Lobatto DJ, Vries F de, Zamanipoor Najafabadi AH, Pereira AM, Peul WC, Vliet Vlieland TPM, Biermasz NR & Furth WR van. Preoperative risk factors for postoperative complications in endoscopic pituitary surgery: a systematic review. *Pituitary* 2018 **21** 84–97. (<https://doi.org/10.1007/s11102-017-0839-1>)
- Moher D, Liberati A, Tetzlaff J, Altman DG & The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. *PLOS Medicine* 2009 **6** 873–880. (<https://doi.org/10.1371/journal.pmed.1000097>)
- DerSimonian R & Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986 **7** 177–188. ([https://doi.org/10.1016/0197-2456\(86\)90046-2](https://doi.org/10.1016/0197-2456(86)90046-2))
- Nyaga VN, Arbyn M & Aerts M. Metaprop: A Stata command to perform meta-analysis of binomial data. *Archives of Public Health* 2014 **72** 39. (<https://doi.org/10.1186/2049-3258-72-39>)
- Zamanipoor Najafabadi AH, Zandbergen IM, De F, Broersen LHA, Akker-Van Marle ME Van Den, Pereira AM, Peul WC, Dekkers OM, Furth WR Van & Biermasz NR. Surgery as a viable alternative first-line treatment for prolactinoma patients. A systematic review and meta-analysis. *Journal of Clinical Endocrinology and Metabolism* 2020 **105** 32–41. (<https://doi.org/10.1210/clinem/dgz144>)
- Broersen LHA, Biermasz NR, Furth WR van, Vries F de, Versteegen MJT, Dekkers OM & Pereira AM. Endoscopic vs. microscopic transsphenoidal surgery for Cushing's disease: a systematic review and meta-analysis. *Pituitary* 2018 **21** 524–534. (<https://doi.org/10.1007/s11102-018-0893-3>)
- Goudakos JK, Markou KD & Georgalas C. Endoscopic versus microscopic trans-sphenoidal pituitary surgery: a systematic review and meta-analysis. *Clinical Otolaryngology* 2011 **36** 212–220. (<https://doi.org/10.1111/j.1749-4486.2011.02331.x>)
- Dabrh AMA, Mohammed K, Asi N, Farah WH, Wang Z, Farah MH, Prokop LJ, Katznelson L & Murad MH. Surgical interventions and medical treatments in treatment-naïve patients with acromegaly: systematic review and meta-analysis. *Journal of Clinical Endocrinology and Metabolism* 2014 **99** 4003–4014. (<https://doi.org/10.1210/jc.2014-2900>)
- Kodra Y, Weinbach J, Posada-De-La-Paz M, Coi A, Lemonnier SL, Enckevort D van, Roos M, Jacobsen A, Cornet R, Ahmed SF, et al. Recommendations for improving the quality of rare disease registries. *International Journal of Environmental Research and Public Health* 2018 **15**. (<https://doi.org/10.3390/ijerph15081644>)

- 17 Azzopardi-Muscat N & Brand H. Will European Reference Networks herald a new era of care for patients with rare and complex diseases? *European Journal of Public Health* 2015 **25** 362–363. (<https://doi.org/10.1093/eurpub/cku144>)
- 18 Melmed S, Bronstein MD, Chanson P, Klibanski A, Casanueva FF, Wass JAH, Strasburger CJ, Luger A, Clemmons DR & Giustina A. A Consensus Statement on acromegaly therapeutic outcomes. *Nature Reviews. Endocrinology* 2018 **14** 552–561. (<https://doi.org/10.1038/s41574-018-0058-5>)
- 19 Fleseriu M, Auchus R, Bancos I, Ben-Shlomo A, Bertherat J, Biermasz NR, Boguszewski CL, Bronstein MD, Buchfelder M, Carmichael JD, *et al.* Consensus on diagnosis and management of Cushing's disease: a guideline update. *Lancet. Diabetes and Endocrinology* 2021 **9** 847–875. ([https://doi.org/10.1016/S2213-8587\(21\)00235-7](https://doi.org/10.1016/S2213-8587(21)00235-7))
- 20 Ammirati M, Wei L & Ciric I. Short-term outcome of endoscopic versus microscopic pituitary adenoma surgery: A systematic review and meta-analysis. *Journal of Neurology, Neurosurgery, and Psychiatry* 2013 **84** 843–849. (<https://doi.org/10.1136/jnnp-2012-303194>)
- 21 Oostra A, Furth W van & Georgalas C. Extended endoscopic endonasal skull base surgery: From the sella to the anterior and posterior cranial fossa. *ANZ Journal of Surgery* 2012 **82** 122–130. (<https://doi.org/10.1111/j.1445-2197.2011.05971.x>)
- 22 Almutairi RD, Muskens IS, Cote DJ, Dijkman MD, Kavourdis VK, Crocker E, Ghazawi K, Broekman MLD, Smith TR, Mekary RA, *et al.* Gross total resection of pituitary adenomas after endoscopic vs. microscopic transsphenoidal surgery: a meta-analysis. *Acta Neurochirurgica (Wien)* 2018 **160** 1005–1021. (<https://doi.org/10.1007/s00701-017-3438-z>)
- 23 Song S, Wang L, Qi Q, Wang H & Feng L. Endoscopic vs. microscopic transsphenoidal surgery outcomes in 514 nonfunctioning pituitary adenoma cases. *Neurosurgical Review* 2022 **45** 2375–2383. (<https://doi.org/10.1007/s10143-022-01732-4>)

Received in final form 10 October 2022

Accepted 3 November 2022

Accepted Manuscript published online 3 November 2022