



# The experience with transsphenoidal surgery and its importance to outcomes

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## Abstract

**Purpose** Surgical experience is considered paramount for excellent outcome of transsphenoidal surgery (TSS). However, objective data demonstrating the surgical success in relation to the experience of pituitary surgery units or individual experience of pituitary surgeons is sparse.

**Methods** Based on literature data, we have investigated the influence of experience with TSS for pituitary adenomas on endocrinological remission rates and on operative complications. The surgical experience was assessed by calculating the number of transsphenoidal operations per year.

**Results** For TSS of microprolactinomas, mean remission rates were 77% in centers with <2 operations per year for microprolactinomas, 82% with 2–4 operations, 84% with 4–6 operations, and 91% with >6 operations. A yearly experience with more than 10 initial operations for Cushing’s disease (CD) warrants a remission rate exceeding 70%. Remission rates in CD exceeding 86% have only been reported for single surgeon series. Extraordinarily high complication rates were found in some series with <25 yearly total operations for pituitary adenomas. Major vascular complications were less than 2% and revision rates for rhinorrhea usually <2.5% in centers performing >25 transsphenoidal operations per year.

**Conclusions** We conclude that a center with experience of >25 transsphenoidal operations for pituitary adenomas per year provides a high likelihood of safe TSS. Surgery for CD requires a particularly high level of practice to guarantee excellent remission rates. The endocrinologist has the unique opportunity to audit the surgical success by hormone measurement and to refer patients to neurosurgeons with proven excellence.

**Keywords** Transsphenoidal surgery · Surgical experience · Pituitary adenoma · Cushing’s disease · Remission rate · Complications

## Introduction

The first transsphenoidal operation for a pituitary adenoma was performed by Hermann Schloffer in 1907 [1]. The transsphenoidal approach to pituitary adenomas gained worldwide acceptance with introduction of the operating microscope by Jules Hardy in the 1960s [2] and became the preferred approach for the vast majority of pituitary adenomas. The pure endoscopic transnasal technique was pioneered by Jho [Jho] in the 1990s and has become an alternative to the microscopic technique.

The aim of transsphenoidal surgery (TSS) is to remove the adenoma as completely as possible and to achieve biochemical remission in functioning adenomas. At the same time, pituitary function should not be jeopardized and complication rates must be kept as low as possible. It is of general opinion [3] that the experience of the pituitary surgeon is important for the outcome of TSS. A much-noticed survey among neurosurgeons in the United States [4] found a significant inverse relationship between operative complications and the prior number of transsphenoidal operations. However, the complication rates were only estimated by the participating neurosurgeons. Further analysis is hampered by the fact that the prior experience of the center or the individual pituitary surgeon with TSS is not available in most published series on TSS.

Evidence from the literature suggests that a dedicated pituitary surgeon has better surgical results compared to two

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or more neurosurgeons performing TSS in a single center. Remission rates were found to be low with several pituitary surgeons [5] because of the resulting low experience of each surgeon. It has been shown that cure rates in acromegaly could be considerably improved [6, 7] by concentration of TSS in the hands of a smaller number of specialists. Similarly, complication rates of low-volume pituitary surgeons were higher compared to high-volume surgeons in the same center [8].

Several additional factors including training in a high-volume pituitary center, surgical skill and thoroughness, and availability of a multidisciplinary setting of pituitary specialists improve surgical outcome.

It is generally accepted that not only prior experience but also continuous practice with a high number of transsphenoidal operations is paramount for excellent surgical results. The level of excellence may be lost if a high caseload is not maintained [3]. However, systematic data how the frequency of transsphenoidal operations per year influences the surgical outcome are sparse. We have performed a literature search to identify publications from single centers with information on caseload of transsphenoidal operations. From this dataset, we have analyzed the rates of cure, gross total resection, and complications in relation to the caseload and current experience with TSS. The aim of the study was to provide reliable and objective data on the importance of experience to the outcome of TSS.

## Methods

### Surgical experience with TSS and remission rates in microprolactinomas

Tampourlou et al. [9] reviewed the available literature on surgical treatment of microprolactinomas published between 2000 and 2015 and assessed the remission rates. Based on this review, we identified the reported, single-center studies and selected the studies from which time span of the series was available. In the next step, the number of operations performed for microprolactinomas per year was calculated for each surgical series. Twenty-one series from 20 publications were identified [10–29]. The full text of each study was used for further analysis.

### Surgical experience with TSS and remission rates in Cushing's disease (CD)

A PubMed search was conducted to identify studies on transsphenoidal surgery (TSS) for Cushing's disease (CD) published from 1990 onward. The search terms were "Cushing\*" in combination with "transsphenoidal". All abstracts were reviewed to identify consecutive, unselected,

single-center studies in English language. Surgical series were only included if the time period when the operations were performed was exactly provided. Duplicates from the same center with overlap in study periods were removed. For each center, the number of primary transsphenoidal operations for CD per year was calculated. Two large series were included where a minority of patients had transcranial operations. Studies containing a minority of re-operations were included if the number of initial operations was not provided. Series with focus on surgery for recurrent or persistent CD were excluded. Fifty-nine publications reporting on 5,207 patients undergoing initial TSS for CD were eligible [19, 29–86]. The full text of each study was used for data analysis.

### Surgical experience with TSS and gross total resection (GTR) in non-functioning pituitary adenomas (NFPA)

A literature search (Pubmed) was performed with the search terms "non-functioning" or "nonfunctioning" in combination with "transsphenoidal" or "microscopic" or "endoscopic". Only consecutive series on TSS for NFPA from 2000 onward were included. All abstracts were reviewed to identify consecutive, unselected, single-center studies in English language. Surgical series were only included if the time span of the series was exactly provided. Duplicates from the same center with overlap in study periods were removed. For each center, the number of transsphenoidal operations for NFPA per year was calculated. Additionally, studies from the meta-analysis performed by Ammirati et al. [87] that fulfilled the selection criteria were included. In most series, the entire experience with TSS for NFPA was reported including repeat surgery. Therefore, first and also repeat operations were included in the analysis of each series. A total of 28 publications fulfilled the inclusion criteria and were eligible for data analysis [11, 14, 22, 24, 29, 45, 47, 55, 61, 67, 88–105].

### Surgical experience with TSS and complication rates in pituitary adenomas

Complication rates were assessed in total series on surgery for pituitary adenomas (including both functioning and non-functioning adenomas). In a meta-analysis, Ammirati et al. [87] reviewed the complication rates of endoscopic and microscopic pituitary adenoma surgery. Among the reported publications, we identified 14 non-selected, total series from which the time period of surgery was available [11, 14, 29, 45, 55, 90, 93, 99, 102, 106–110]. Further Pubmed search yielded 20 more recent or additional publications fulfilling the selection criteria [8, 22, 24, 41, 47, 61, 62, 67, 89, 95, 96, 103, 111–118]. Full text of each study was used for further

analysis of complications. Only precisely defined complications allowing comparison among studies were included. Only mortality directly related to the surgical procedure was assessed. Vascular complications included carotid artery or other major vessel injury, any symptomatic intratumoral, intrasellar or intracerebral hemorrhage and stroke. Bleedings from a nasal source were excluded from the analysis. For cerebrospinal fluid (CSF) leakage, only patients requiring operative repair were assessed. The rate of permanent diabetes insipidus was frequently available in the publications and was analyzed. In contrast, the rate of postoperative hypopituitarism was infrequently detailed and the applied analysis criteria were heterogeneous. Therefore, evaluation of postoperative hypopituitarism did not produce reliable data and was excluded from further analysis.

### Statistics and data evaluation

Statistical analysis was performed in SPSS (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Data are presented as mean  $\pm$  standard deviation. Homogeneity of variances was assessed by Levene's test for equality of variances. Normal distribution was assessed by Shapiro–Wilk's test. A Spearman's rank-order correlation was run to assess two variable relationships. A one-way ANOVA was carried out to determine group differences. On significant results Tukey post hoc analysis was carried out.

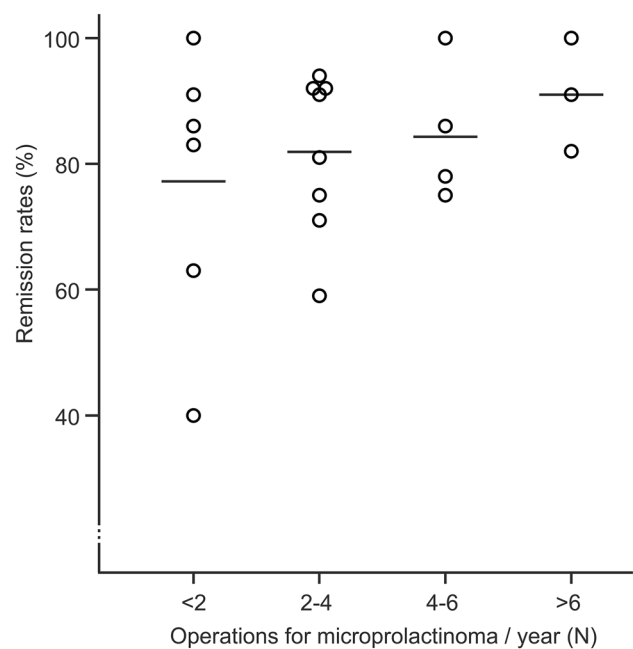
## Results

### Surgical experience with TSS and remission rates in microprolactinomas

A positive correlation was found between remission rates and operations per year for microprolactinomas. A wide spread of early remission rates between 40 and 100% was found in centers with less than 2 operations for microprolactinomas per year (Fig. 1). In contrast, high remission rates were found in all centers with more than six operations per year (range 82–100%).

Mean remission rates were 77% in centers with <2 operations for microprolactinoma per year, 82% with 2–4 operations, 84% with 4–6 operations, and 91% with >6 operations. Remission rates were normally distributed for all groups with homogeneity of variances. Due to the relatively low number of published series, the group differences did not reach statistical significance ( $p=0.64$ ).

Comparing the different experience groups, the overlap of remission rates was considerable (Fig. 1). In particular, high remission rates were not only found in centers with a high caseload, but also in some centers with a low caseload.



**Fig. 1** Early remission rates in microprolactinomas stratified by the caseload in the centers as expressed in the number of operations per year for microprolactinomas. The mean remission rate for each group is indicated by the horizontal bar

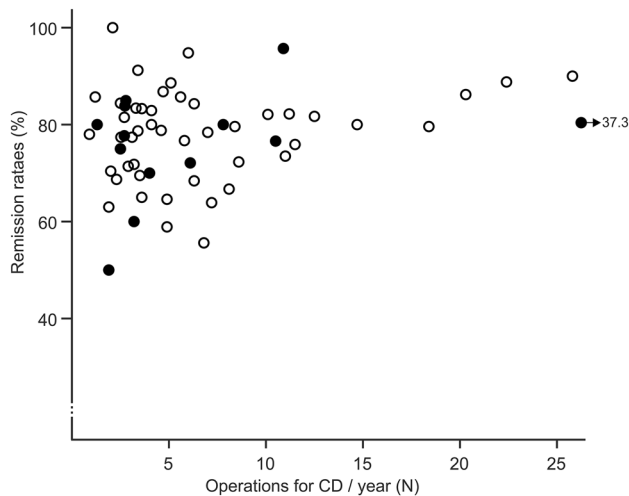
### Surgical experience with TSS and remission rates in Cushing's disease (CD)

A positive correlation was found between early remission and the number of transsphenoidal operations for CD per year. Significance level was not quite met ( $p=0.09$ ).

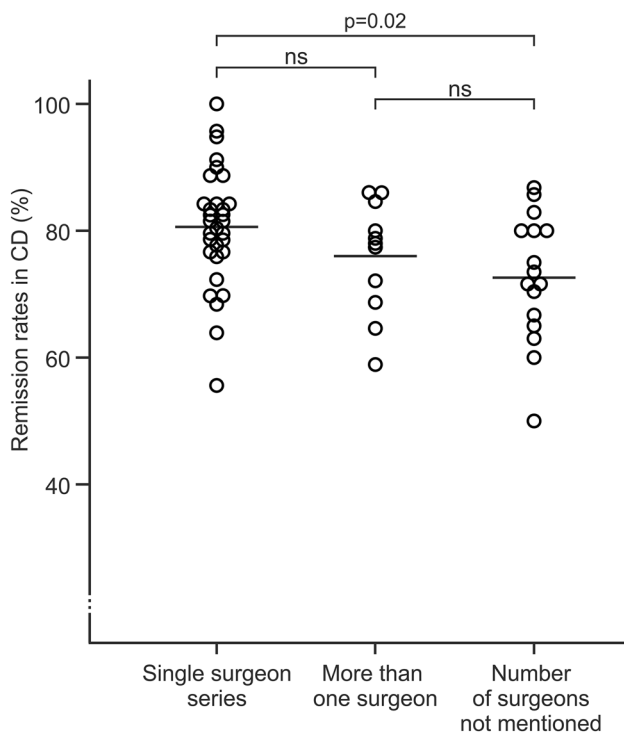
The mean remission rate of 76% in the series with less than 5 operations for CD per year was equal to the remission rate in series with 5–10 operations per year. With 83%, the remission rate was significantly higher in the centers performing more than 10 operations per year for CD.

A wide variability of early remission rates was found in centers performing less than 10 operations per year for CD (range 50–100%) (Fig. 2). In contrast, the range of remission rates observed in high volume centers with more than 10 operations per year was narrow (range 74–96%). Thirty-nine percent of the centers with less than 10 operations per year reported remission rates below 74% which is less than the lowest rate among high volume centers. On the other hand, 39% of the low volume centers had excellent initial remission rates  $\geq 80\%$  (Fig. 2). No statistically significant difference of remission rates was found if microscopic and endoscopic series were compared (Fig. 2).

The mean remission rate from single surgeon series was 81% (Fig. 3). It was 76% in series where two or more surgeons have performed the transsphenoidal operations for CD and only 73% in those series where the number of



**Fig. 2** Early remission rates after TSS for Cushing's disease (CD) in relation to the yearly number of operations for CD in the centers (closed circles: purely endoscopic series; open circles: microscopic or mixed microscopic/endoscopic series)



**Fig. 3** Early remission rates after TSS for Cushing's disease (CD) stratified by the number of surgeons performing the operations in each center. The mean remission rate for each group is indicated by the horizontal bar

surgeons has not been reported. The difference of remission rates between the single surgeon series and the series with unknown number of involved surgeons reached statistical significance ( $p = 0.02$ ) (Fig. 3). Remission rates

exceeding 86% have only been reported from single surgeon series.

### Surgical experience with TSS and gross total resection in non-functioning pituitary adenomas (NFPA)

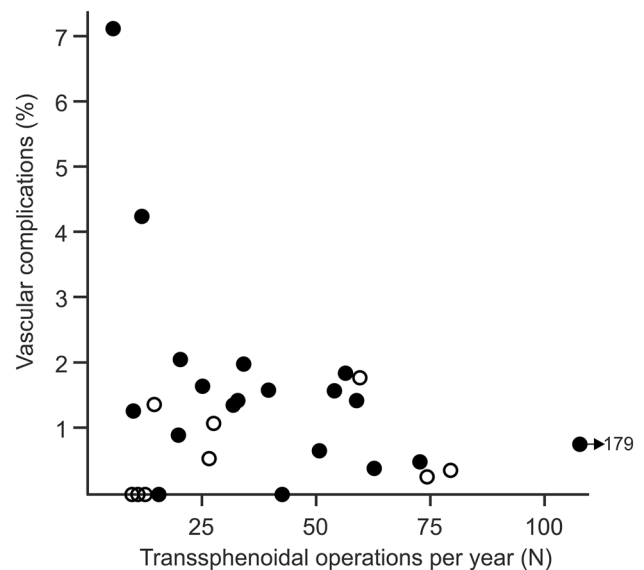
A wide scatter of operative success with gross total resection (GTR) of the adenoma is observed among low volume centers (range 43–96%). Only a slight tendency of better results in terms of GTR with an increasing yearly number of operations for NFPA was found ( $p = 0.24$ ). In all high volume centers with more than 35 patients undergoing TSS for NFPA per year, complete resection is accomplished in at least 65% of the patients. Overall, however, no clear correlation between GTR and yearly caseload in the centers was found.

### Surgical experience with TSS and complication rates in pituitary adenomas

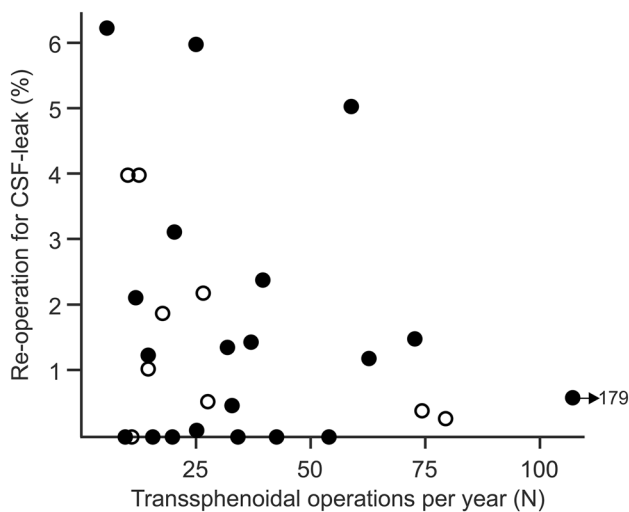
Among publications addressing operative complications, series on endoscopic transnasal surgery prevailed (Figs. 4, 5).

#### Mortality rate

As only strictly surgical mortality was assessed, the mortality rates were low. A tendency of lower surgical mortality with increasing number of adenoma operations per year was



**Fig. 4** Percentage of vascular complications in relation to the total yearly number of operations for pituitary adenomas in each center (closed circles: purely endoscopic series; open circles: microscopic or mixed microscopic/endoscopic series)



**Fig. 5** Percentage of patients requiring surgical repair of a cerebrospinal fluid leak in relation to the total yearly number of operations for pituitary adenomas in each center (closed circles: purely endoscopic series; open circles: microscopic or mixed microscopic/endoscopic series)

found ( $p=0.62$ ). The mean mortality rate was 0.4% (range 0–2.1%) in centers with less than 25 transspheoidal operations per year and also 0.4% (range 0–2.0%) in centers with 25–50 transspheoidal operations per year. The mean mortality rate of 0.3% (range 0–1.6%) was slightly lower in high volume centers with more than 50 transspheoidal operations per year. The mortality rate was >1% in 20% (2/10) of the centers with <25 transspheoidal operations per year, in 13% (1/8) of the centers with 25–50 operations, and in 11% (1/9) of the centers with >50 operations.

### Vascular complications

The mean percentage of vascular complications was 1.7% in centers with less than 25 transspheoidal operations per year and it was 1.1% in centers with more than 25 operations. Vascular complications were negatively correlated to the surgical experience as expressed in TSS for adenomas per year without reaching significance ( $p=0.23$ ) (Fig. 4). Extraordinary frequent vascular complications of 7.1 and 4.3% were observed in two low-volume centers performing only 7.6 and 11.8 adenoma operations per year, respectively. In all other publications, the rate of vascular complications was below 2.2%.

### Cerebrospinal fluid (CSF) rhinorrhea requiring operative revision

A high variability of revision rates for a postoperative CSF leak was found among series with less than 25 transspheoidal surgeries per year (Fig. 5). The highest rate was 6.3%.

Among the centers performing TSS more than 25 times per year, surgical repair for a CSF leak was necessary in less than 2.5% of the patients with only one exception. Overall, an inverse relationship was found between the operative revision rate for CSF rhinorrhea and surgical experience ( $p=0.26$ ). The mean revision rate of CSF rhinorrhea was 2.0% in operative series with less than 25 surgeries per year and it was 1.4% in series exceeding 25 surgeries.

### Postoperative diabetes insipidus

An inverse but non-significant relationship was observed between permanent postoperative diabetes insipidus and yearly center experience with TSS ( $p=0.07$ ).

## Discussion

### Surgical experience with TSS and remission rates

Among prolactinomas, we selected microprolactinomas to assess the remission rates because they represent a homogeneous group of adenomas with mostly non-invasive growth. The analyzed literature reveals that the early remission rate increases with the yearly caseload of transspheoidal operations for microprolactinomas. We assume that the number of surgeries for microprolactinomas is correlated to the overall yearly experience with TSS.

Indication and execution of TSS is particularly challenging in Cushing's disease (CD) which was the impetus to analyze the early remission rates in CD in relation to surgical experience. Our results suggest that a yearly experience with more than 10 initial transspheoidal operations for CD warrants a remission rate exceeding 70% (Fig. 2). The reference for experience with TSS is usually the total number of transspheoidal operations per year. Our literature review showed that TSS for CD on average accounts for 10% of all transspheoidal operations. This means that a yearly number of approximately 100 transspheoidal operations provides the surgical experience that guarantees a remission rate >70% in CD. Our review confirms that a particularly high level of continuous practice is required in CD in order to achieve excellent remission rates. In the systematic review by Petersenn et al. [119], only a slight trend of better remission rates with increasing surgical experience was found. However, the authors only assessed studies with at least 40 initial operations for CD.

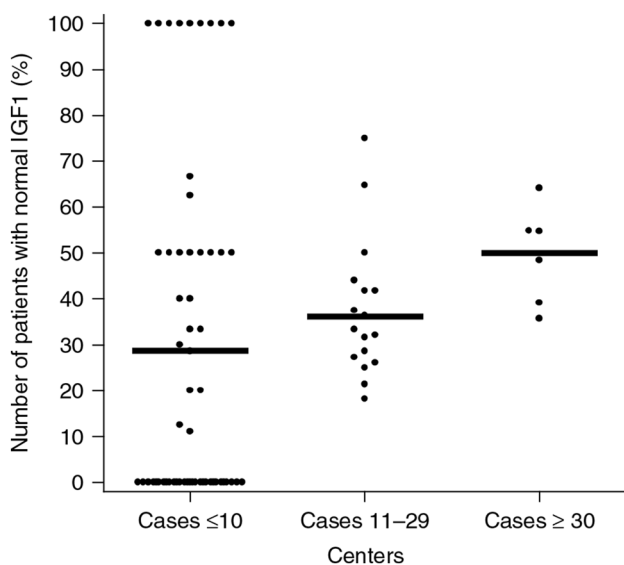
It is a well-known mindset and practice that the endocrinologist refers difficult cases with no visible adenoma in CD to the most experienced pituitary surgeons. The referral pattern results in an accumulation of particularly challenging cases in highly specialized centers. Therefore, the advantage of surgery for CD in a center with a high caseload



is probably underestimated if only remission rates are compared (Fig. 2).

The German Acromegaly Registry evaluated the long-term remission rates with normalized IGF-1 levels stratified by the centers with  $\leq 10$ , 11–29, and  $\geq 30$  documented surgical cases in the registry [120]. The results indicate a significant trend of higher cure rates in centers with more cases (Fig. 6). It was stressed that the scatter of surgical cure rates was considerable even in the large centers. Figure 6 also shows a remarkable overlap of cure rates among the three experience groups. Importantly, the data for the German Acromegaly Register are provided from endocrinological centers. Hence, we assume that the bias of publishing favorable surgical results, which particularly exists for surgical series with low case number, is excluded.

The literature analysis of cure rates for all types of functioning adenomas (i.e. prolactinomas, Cushing's disease, and acromegaly) revealed the same characteristics: A correlation exists between surgical success and the experience of the centers. A good chance of remission is guaranteed if surgery is performed in high-volume centers. However, an obvious spread of cure rates is also observed among experienced centers. A large scatter of cure rates is observed if centers with low experience are compared. While the cure rates from some low-volume centers are not acceptable, other low-volume centers achieve excellent results.



**Fig. 6** Rates of normal IGF1 in operated patients with no adjunctive radiotherapy or medical treatment at the time of the survey stratified by centers with  $\leq 10$ , 11–29,  $\geq 30$  documented surgical cases of the survey cohort. Each point represents one of the 76 centers, the median of each group is given by the horizontal bar. Amongst the centers with a 100% success rate ( $n=9$ ), there were seven centers with one and two centers with two documented cases. Reproduced with permission from Schöfl et al. [120]

## Number of surgeons performing TSS in a center and remission rates

It is anticipated that a dedicated pituitary surgery has better cure rates compared to a larger number of surgeons performing the operations in a center. With two pituitary surgeons in a center, the personal experience with TSS per year is halved compared to a single surgeon. In the setting with several surgeons, however, the surgeons could learn from each other and could also learn by assistance of a transsphenoidal operation. For CD, we have shown that the remission rates of single surgeon series are superior to the rates from centers with two or more surgeons or centers with unknown number of pituitary surgeons. In particular, outstanding remission rates were only reported from single surgeon series. In the database of the UK National Acromegaly Register, substantially improved postoperative growth hormone (GH) levels were found after 2000 [6]. The improved results were explained with a trend to concentrate pituitary surgery in the hands of a smaller number of specialists. Gittoes et al. [7] reported on a cure rate of 33% in acromegaly with eight different surgeons. From 1990 onward, the patients were referred to a single dedicated pituitary surgeon. With the modified practice, the cure rate increased to 64%. Erturk et al. [5] found a cure rate in only 33% of acromegalic patients with 7 different neurosurgeons and 0.9 mean cases for a surgeon per year. The authors stressed the importance of experience for successful surgery.

## Surgical experience with TSS and gross total resection

Gross total resection (GTR) of non-functioning pituitary adenomas (NFPA) is usually assessed by MRI performed 3–6 months postoperatively. Our analysis showed only a slight tendency of better GTR rates with increasing yearly number of transsphenoidal operations for NFPA in the centers. At first look, this result is surprising. In our opinion, however, the rating of the resection degree is subjective and comparison of published series should be performed with caution. Almutairi et al. [121] published a meta-analysis on GTR of pituitary adenomas. For NFPA, they found a possible publication bias suggesting that smaller studies showing a lower GTR rate could have been unpublished. The major determinant of incomplete resection is invasive character of a NFPA. Assessment of invasiveness is inconsistent and incomplete in the majority of reported series. Therefore, we cannot draw reliable conclusions concerning the influence of surgical experience on the success of GTR.

## Surgical experience with TSS and complication rates

Ciric et al. [4] performed a frequently cited survey among neurosurgeons in the United States. 958 respondents who reported performing transsphenoidal surgery were allocated into three groups according to the number of previous transsphenoidal operations i.e. <200, 200–500, and >500. They were asked to provide an estimate for the percentage of personally witnessed, specific complications. A significant inverse relationship was found between likelihood of complications and prior experience with TSS for all but 2 of the 14 enquiry complications. Mortality was estimated with 1.2% in the low experience group, 0.6% in moderate experience group, and 0.2% in the high experience group. The typical complication of CSF leak was estimated to occur in 4.2% of the operations in centers with low prior surgical experience, in 2.8% with moderate experience, and in 1.5% with high experience. Anterior pituitary insufficiency as a result of TSS was estimated with 20.6% by neurosurgeons with <200 prior transsphenoidal operations and with 7.2% by neurosurgeons with >500 transsphenoidal operations.

We focused on the yearly caseload of operations rather than accumulated prior transsphenoidal operations and our review analyzed published data rather than surgeons' estimates. Our literature review confirms that the complication rate is lower in experienced hands. Exceptionally high complication rates were only found in series from centers with a caseload of <25 transsphenoidal operations per year. Major vascular complications were less than 2% in all centers performing >25 transsphenoidal operations per year. The typical risk of TSS is postoperative rhinorrhea. In all but one center with a caseload >25 yearly transsphenoidal operations, the percentage of patients requiring surgical repair of a CSF leak was below 2.5%. We conclude that a center experience of greater than 25 transsphenoidal operations per year provides a good likelihood of safe TSS with a reasonable complication rate. Similarly, Petersenn et al. [119] found fewer complications with increasing surgical experience for TSS in CD. The results were significant for occurrence of diabetes insipidus, cerebrospinal fluid leakage, and meningitis. Jang et al. [95] reported on 331 consecutive patients undergoing endoscopic surgery for pituitary adenomas over a period of more than 16 years. With increasing yearly numbers of transsphenoidal operations during the study period, they found decreasing complication rates. Halvorsen et al. [8] reported 506 consecutive transsphenoidal operations at a single institution performed by 15 different surgeons. One surgeon performed 238 procedures, four surgeons performed between 26 and 102 procedures, and 10 surgeons performed <5 procedures. An odds ratio of 2.4 for occurrence of surgical complications was found if surgery was performed by low-volume surgeons. Luft et al. [122] examined mortality rates of various surgical procedures in

1498 hospitals. They found a reduction of mortality with increasing hospital's surgical volume. In our review of the literature, a trend of decreasing mortality with increasing experience was also found for transsphenoidal pituitary surgery.

## Initial learning curve in TSS

With increasing use of the endoscopic technique, several publications have analyzed the learning curve when starting with endoscopic TSS. The reported learning curves certainly reflect the familiarity with the endoscopic transnasal technique. On the other hand, the results give an idea how initial learning of TSS and improving of surgical results proceeds. The learning curve has been defined as the number of cases necessary to perform for outcomes to tend toward the long-term mean rate [123]. It has been reported from single centers, that GTR [98, 99, 124, 125], visual outcome [62], and endocrinological cure [126] were significantly improved and operation time [62, 99, 124, 127] and hospital stay [62, 124] were reduced during the initial learning period. A steady state for GTR has been described after 100 endoscopic operations for NFPA [98]. Eseonu et al. [127] found that it took 54 endoscopic operations before stable operative time was reached. Shikary et al. [128] stabilized the CSF leak rates below 5% after 100 endoscopic procedures and reached stable operative times after 120 procedures. These experiences can only reflect the early steep learning curve. Further slow improvement can be expected with increasing overall experience and continuous practice with high case numbers.

## Further factors influencing outcome in TSS

Further crucial factors which are not readily available when analyzing the results of TSS in the literature influence the surgical success. An excellent training of a resident with interest in pituitary surgery is paramount. Ideally, the resident is trained in a specialized center by a dedicated pituitary surgeon. If the preconditions for a high-level training in pituitary surgery are missing, expertise might also be acquired during a fellowship in a high-level pituitary surgery unit [3]. For example, trainees have to learn wide and sufficient exposure of the sella in order to achieve maximal resection [129]. The high importance of the surgical skill and the surgeon's diligence and meticulousness for excellent outcome must further be emphasized. It is reflected in the literature by obvious differences in surgical success among centers with similar caseload and experience.

In addition, a pituitary center with a multidisciplinary team setting including experts in endocrinology, neuroradiology, neuroophthalmology, neuropathology, radiation oncology and intensive care medicine is ideal for good

indication, optimal patient care, avoidance of complications and excellent outcome [3].

## Conclusions

In conclusion, we have reviewed the literature to analyze remission rates, rate of GTR and surgical complications in relation to surgical experience. For all sub-analyses, at least a positive trend between favorable outcome and high surgical experience was found. The literature shows that TSS in centers with a caseload > 25 per year is usually performed safely with an acceptable complication rate. In centers with a high caseload of transsphenoidal operations, an excellent chance of remission is warranted. For CD, a particularly high experience is necessary to guarantee excellent results. Outstanding results for CD were only found in single surgeon series. Among low-volume centers, the surgical outcome was highly variable. Some less experienced pituitary centers also reported excellent results. With a particularly highly skilled neurosurgeon, a lower number of operations might suffice to achieve a favourable outcome. Endocrinologists have the unique opportunity, to verify the surgical success in terms of remission and postoperative pituitary function by hormone measurement. They have the responsibility to audit the results of the neurosurgeons and to send patients to their preferred neurosurgeon who was found to achieve excellent surgical outcome.

## Compliance with ethical standards

**Conflict of interest** The authors have no conflict of interest.

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