

# Impact of Technique on Cushing Disease Outcome Using Strict Remission Criteria

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**ABSTRACT: Background:** Cushing disease (CD) constitutes a challenging condition for the pituitary surgeon. Given the variety of factors affecting outcomes in CD, it is uncertain whether the newer endoscopic technique improves the results of surgery. **Methods:** A review was conducted of CD cases at our institution between 2000 and 2010. Analysis was done to: determine if surgical technique had an effect on outcome, identify the predictors of outcome and provide details of failed cases. Remission was defined as normal postoperative 24-hour urinary free cortisol (24-h UFC), suppression of morning serum cortisol to <50 nmol/L after 1mg of dexamethasone or being dependent on steroid replacement. **Results:** Forty-two patients met our inclusion criteria. Average follow-up period was 33 months. There were 15 macroadenomas and 27 microadenomas. Seventeen patients had an endoscopic transsphenoidal surgery and twenty-five patients had a microscopic transsphenoidal procedure. Long-term overall remission was achieved in 26 (62%) patients. There was no significant difference in remission rates between the two techniques (p value 0.757). Patient's subjective symptomatic improvement and drop of morning serum cortisol in the postoperative period to less than 100 nmol/L correlated with long-term remission (p value 0.0031 and 0.0101, respectively) while repeat surgery was the only predictor of the lack of postoperative remission (p value 0.0008). **Conclusions:** Revision surgery predicted poor remission rate for CD. Within the power of our study size, there was no difference in outcome between the endoscopic and microscopic approaches. Surgical outcomes should be reviewed in association with remission criteria used in a study.

**RÉSUMÉ: Évaluation de l'impact de la technique utilisée, au moyen de critères de rémission rigoureux, sur le résultat de la chirurgie dans le traitement de la maladie de Cushing.** **Contexte :** La maladie de Cushing (MC) présente des défis pour le chirurgien qui la traite. Compte tenu de la variété des facteurs qui influencent le résultat du traitement dans la MC, nous ne savons pas si la nouvelle technique endoscopique améliore le résultat de la chirurgie. **Méthode :** Nous avons revu les dossiers des patients atteints de la MC traités dans notre institution entre 2000 et 2010. Nous avons examiné si la technique chirurgicale influençait le résultat et identifié les facteurs de prédiction du résultat et nous fournissons également des détails sur les échecs. La rémission était définie comme étant un taux postopératoire normal de cortisol libre urinaire de 24 heures (24-h CLU), une suppression du cortisol sérique matinal à < 50nmol / L après administration de 1mg de dexaméthasone ou une dépendance à un remplacement stéroïdien. **Résultats :** Quarante-deux patients rencontraient nos critères d'inclusion. La durée moyenne du suivi était de 33 mois, 15 patients étaient porteurs de macroadénomes et 27 patients de microadénomes. Dix-sept patients ont eu une chirurgie transsphénoïdale endoscopique et 25 patients on eu une chirurgie transsphénoïdale microscopique. Une rémission à long terme a été observée chez 26 patients (62%). Il n'y avait pas de différence significative dans les taux de rémission entre les deux techniques (p = 0,757). L'amélioration symptomatique subjective des patients et l'abaissement du cortisol sérique matinal au cours de la période postopératoire à moins de 100 nmol / L était corrélée à une rémission à long terme (p = 0,0031 et 0,0101 respectivement), et une réintervention était le seul facteur de prédiction de l'absence de rémission après la chirurgie (p = 0,0008). **Conclusions :** Une réintervention était le facteur de prédiction d'une rémission incomplète dans la MC. Compte tenu de la puissance limitée d'une étude effectuée sur un échantillon de cette taille, nous n'avons pas constaté de différence entre le résultat de la chirurgie endoscopique et celui de la chirurgie microscopique. Les résultats chirurgicaux devraient être revus en parallèle avec les critères de rémission que nous avons utilisés.

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Cushing's Disease (CD) is the commonest cause of endogenous hypercortisolemia<sup>1</sup> and is associated with significant morbidity and mortality.<sup>2-4</sup> Transsphenoidal pituitary surgery remains the first line treatment for this condition with reported remission rates of 52% to 89%.<sup>5-19</sup> Many attempts have been made to identify factors that would predict sustained remission after surgical intervention. Suggested factors include smaller adenomas and the confirmation of adenoma intra-operatively.<sup>18,20</sup> The question of whether the newer endoscopic surgical technique (endo TSS)<sup>21</sup> has improved results compared to the older microscopic technique (micro TSS) remains to be answered. The aim of this report is to study the outcomes of

transsphenoidal surgery in Cushing's disease secondary to magnetic resonance imaging (MRI) identifiable adenomas with both techniques and analyze the impact of this and other

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variables on the outcomes, including sustained remission. We excluded adenomas with frank cavernous sinus invasion since remission in this subgroup is difficult regardless of technique. We also elected to use the current strict remission criteria determined by the endocrine literature.<sup>22</sup>

## METHODS

### *Endocrine criteria for diagnosis and remission*

Cushing's syndrome was diagnosed based on the appropriate clinical presentation and a combination of laboratory investigations, including: (1) eight a.m. serum cortisol >50 nmol/L after administering one mg of dexamethasone at midnight the night before; (2) elevated 24-hour urinary free cortisol (24-h UFC) (often four-fold above the upper limit of normal for the assay); and/or (3) elevated midnight salivary or serum cortisol.<sup>23</sup> Cushing's disease was confirmed by an unsuppressed serum ACTH level and the suppression of eight AM serum cortisol by more than 80-90% of baseline after administering eight mg of dexamethasone the night before.<sup>24</sup> Enhanced MRI with dynamic sequences of the sella was done in all cases. In cases where the sellar MRI was negative or showed a tumor less than six mm, inferior petrosal sinus sampling (IPSS) was done. A diagnosis of Cushing's disease was confirmed based on an ACTH central-to-peripheral gradient of >2 (>3 after Desmopressin (DDAVP) administration) and the laterality was predicted based on inter-sinus gradient > 1.4.<sup>25-27</sup> Remission was defined as normal postoperative (24-h UFC), suppression of morning serum cortisol to <50 nmol/L after a 1-mg low dose dexamethasone suppression test or being dependent on corticosteroid replacement.<sup>22</sup> These tests were done three and six months from surgery, and every year after that to rule out any evidence of recurrence.

### *Analysis*

A retrospective review of all cases of CD was performed. Multiple neurosurgeons performed the transsphenoidal surgeries in a single institution using either the microscopic or the endoscopic approach. The decision for the particular approach was based on the surgeon's individual preference. Information collected included patients' demographics, clinical presentation, laboratory results, radiological studies, treatment details, and remission rates. Descriptive statistics were performed to identify patterns of clinical and radiological presentation. Chi-square test was used to study any associations between the different variables. Student t-test was used to compare mean values between different groups. Statistical significance was set at 0.05.

### *Surgical Techniques*

*Microscopic Technique:* This technique was based on the standard microscopic trans-septal approach popularized by Hardy, more recently modified by a nasal transfection incision and a trans-septal approach.<sup>28,29</sup> The key points of this procedure include: 1) performed with lateral x-ray fluoroscopy; 2) submucosal trans-septal approach; 3) nasal speculum used to visualize the floor of the sphenoid sinus and opening of the sphenoid and sellar floors with an osteotome; 4) Before the dural opening, the sellar space is confirmed with a contrast adenography using contrast injection. Intra-operative frozen

sections were sent in selected cases. In all cases, permanent sections were sent for pathology. Suction trap was used to secure the pathological specimens. The whole procedure was carried under the microscope visualization.

*Endoscopic Technique:* Our standard purely endoscopic endonasal technique, originally performed in 1993 and reported in 1996, is used<sup>21</sup> with the following key points. An Ear, Nose and Throat (ENT) surgeon performs the initial part of the procedure. The whole procedure is carried using the rigid endoscope (Karl Storz, Tuttlingen, Germany). A trimanual or occasional quadrimanual binostril approach with a posterior septotomy is used without specula. Frameless stereotaxy and intraoperative doppler ultrasound are used for confirmation of critical anatomical structures such as the carotid artery. Again, intra-operative frozen sections were sent in selected cases and permanent sections were sent for pathology in all cases.

## RESULTS

### *Patient Population*

Forty-two patients with complete data and follow-up were included for the final analysis. The average age of the patients was 50-years-old (range 20-69 years). Central obesity was the commonest symptom (98%). The average duration of symptoms before diagnosis was 36 months. The MRI showed a pituitary macroadenoma in 15 cases and a microadenoma in 27 cases. Eighteen patients had IPSS study preoperatively. Twenty-five patients had the microscopic approach and 17 patients had the endoscopic one. Baseline patients' characteristics are summarized in Table 1.

### *Hospital course*

The median and average hospital stays were 5 and 5.8 days, respectively (range 2-33 days and standard deviation (SD) 5.1 days). A pituitary adenoma was identified intra-operatively in 37 cases and the surgeon performed adenectomy. Five patients underwent hypophysectomy (one total and four hemi-). There

**Table 1: Baseline patients' characteristics**

Feature	Number (%)
Gender	
Male	11 (26%)
Female	31 (74%)
MRI	
Microadenoma	27 (64%)
Macroadenoma	15 (36%)
Previous Surgery	
Primary	33 (79%)
Repeat	9 (21%)
Surgical Technique	
Microscopic	25 (60%)
Endoscopic	17 (40%)

**Table 2: Ki-67 index based on tumor size**

Size	Ki-67 (0-3%)	Ki-67 (>3%)
Microadenoma	14	1
Macroadenoma	10	3

were two cases of cerebrospinal fluid (CSF) leak with one of them requiring surgery. There were no cases of meningitis. There were eight cases of transient diabetes insipidus (DI) that resolved by hospital discharge and three cases of permanent DI (only one of the 11 patients with DI had hypophysectomy). One patient developed sinusitis that required a course of antibiotic therapy and two patients developed persistent nasal crusting and foul smell after surgery. In 22 patients, the postoperative serum cortisol dropped to below 100 nmol/L during hospitalization, and they were given glucocorticoid replacement.

### Pathology

In eight patients (19%), pathological examination could not confirm the presence of an adenoma, although in three of them, there was a resolution of the hypercortisolemia. The pathology showed a corticotroph adenoma in 28 (67%) cases, Crooke's cell adenoma in four (9.5%) cases, one case of corticotroph hyperplasia and one case of double adenoma consisting of a corticotroph adenoma and a prolactinoma. Crooke's hyaline changes in the non-tumorous corticotroph cells were identified in 20 (48%) cases. Ki-67 proliferative index was measured in 28 cases and was below 3% in 23 cases. Average and median values for Ki-67 labeling index were 4% and 3%, respectively (range 0-15%). There was no significant correlation between size and Ki-67 index (p value 0.3111) (Table 2).

### Surgical Remission

Thirty-two of the 42 patients (76%) had improvement in their presenting symptoms. Initial remission was achieved by surgery

**Table 3: Remission rates in the microscopic and endoscopic groups based on tumor size**

Results	Endo TSS	Micro TSS	
Microadenoma	6/10 (60%)	10/17 (59%)	NS*
Macroadenoma	4/7 (57%)	6/8 (75%)	0.6084

\* NS: Not significant

in 28 patients (67%). In the 33 patients who were operated for the first time, initial remission was achieved in 26 (82%) cases while two of the nine (22%) patients with repeat surgery achieved initial remission. Two patients developed recurrence during the follow-up period making the final remission rate after TSS 62%. The final remission rates for the endoscopic and the microscopic groups were 59% and 64%, respectively (p value 0.757). The remission rates for each technique based on tumor size are summarized in Table 3. There was no statistically significant difference between the two techniques in all subgroups.

Long-term remission was achieved in 16 of the 27 (59%) patients with microadenomas, 10 of the 15 (67%) patients with macroadenomas. Average follow-up duration was 33 months (range 3-102 months). Nine patients were operated upon because of failed previous transsphenoidal surgery. Only one patient (11%) in this group achieved long-term remission.

### Predictors of Remission

Patients clinical, laboratory, imaging characteristics and treatment details were reviewed to identify predictors of long-term remission (see Table 4). On univariate analysis, only repeat transsphenoidal surgery predicted lack of remission (p value 0.0008).

### Failed Surgery

Surgery failed to achieve long-term remission in 16 cases. In 14 of these 16 cases, post-operative MRI did not show residual tumor and the failure was biochemical. Factors that were

**Table 4: Analysis of predictors of remission**

Feature	Remission group	Non-remission group	P value
Gender (female)	19/26 (73%)	12/16 (75%)	0.8905
Endoscopic approach	10/26 (45%)	7/16 (31%)	0.757
Repeat surgery	1/26 (4%)	8/16 (50%)	<b>0.0008</b>
Macroadenoma	10/26 (38%)	5/16 (31%)	0.7464
Pathological confirmation of tumor	23/26 (88%)	11/16 (69%)	0.2233
Crooke's cell adenoma	2/26 (8%)	2/16 (13%)	0.6283
hypophysectomy	2/26 (8%)	4/16 (25%)	0.1798
Crooke's hyaline changes	12/26 (46%)	8/16 (50%)	0.8085

**Table 5: Summary of the failed endo TSS cases**

Case	Approach	MRI	Repeat surgery	Procedure	Comments	Evidence of recurrence
1	Endo	Macro	No	Ad*	Ki-67=6%	Biochemical
2	Endo	Macro	No	Ad	Corticotroph Adenoma Ki-67=15%	Biochemical
3	Endo	Micro	No	Ad	Corticotroph Adenoma Ki-67=3%	Biochemical
4	Endo	Micro	Yes	Ad	No tumor on pathology	Biochemical
5	Endo	Micro	No	Ad	Crooke's cell adenoma Mitotic index cannot be estimated	Biochemical
6	Endo	Micro	No	Ad	Corticotroph adenoma Ki-67= 3-8%	Biochemical
7	Endo	Macro	No	Ad	Corticotroph adenoma No mitosis	Biochemical

\*Ad: adenomectomy

identified in failed cases included repeat surgery, high mitotic index (>3%), unfavorable pathology (corticotroph hyperplasia and Crooke's cell adenoma) and failure to identify the tumor intraoperatively. High mitotic index was a common feature in failed endo TSS cases (Table 5) while repeat surgery and failure to identify the tumor intra-operatively were the commonest features in the micro TSS group (Table 6).

#### Outcomes Correlation

We studied the correlation between long-term biochemical remission and clinical symptomatic improvement and in-patient postoperative drop in morning serum cortisol below 100 nmol/L

necessitating steroid replacement. Both clinical symptomatic improvement and postoperative drop in serum cortisol predicted long-term biochemical remission (p value 0.0031 and 0.0101, respectively). At an upper limit of postoperative morning cortisol value of 100 nmol/L, the sensitivity and specificity for long-term remission were 69% and 75%, respectively. The positive and negative predictive values were 82% and 60%, respectively.

#### Endoscopic versus Microscopic Surgery

The comparison between the two techniques showed no statistically significant difference in remission rate (P=0.757)

**Table 6: Summary of the failed micro TSS cases**

Case	Approach	MRI	Repeat surgery	Procedure	Comments	Evidence of recurrence
1	Micro	Macro	Yes	Ad*	No obvious mitosis	Biochemical and MRI evidence of tumor
2	Micro	Macro	Yes	Ad	Crooke's cell adenoma. No obvious mitosis	Biochemical and MRI evidence of tumor
3	Micro	Negative	No	Ad	Corticotroph Adenoma. No obvious mitosis. Fibrous adenoma	Biochemical
4	Micro	Micro	Yes	Ad	Corticotroph Adenoma. No obvious mitosis	Biochemical
5	Micro	Micro	No	Ad	Corticotroph hyperplasia. No obvious mitosis	Biochemical
6	Micro	Micro	Yes	Hyp**	No tumor on pathology	Biochemical
7	Micro	Negative	Yes	Hyp	No tumor on pathology	Biochemical
8	Micro	Negative	Yes	Hyp	No tumor on pathology	Biochemical
9	Micro	Negative	Yes	Hyp	No tumor on pathology	Biochemical

\* Ad: Adenomectomy. \*\* Hyp: Hypophysectomy

**Table 7: Comparison between the endoscopic and microscopic groups**

Feature	Endoscopic (n=17)	Microscopic (n=25)	P value
Microadenoma	10/17 (59%)	17/25 (68%)	P=0.7438
Macroadenoma	7/17 (41%)	8/25 (32%)	P=NS*
Tumor consistency (fibrous)	0/17 (0%)	2/25 (8%)	P= 0.5064
Female Gender	14 (82%)	17 (68%)	P=0.4767
Mean age (years)	44.68	48.64	P= 0.3783
Mean surgical time (minutes)	265	228	P= 0.0797
Hospital stay (days)	4.67	6.42	P=0.3414
Repeat surgery	2/17 (12%)	7/25 (28%)	P= 0.2708
Mean follow up (months)	32	35	P=0.3196
Remission	10/17 (59%)	16/25 (64%)	P=0.757
DI	4/17 (24%)	7/25 (28%)	P=NS
CSF leak	2/17 (12%)	0/25 (0%)	P=0.1580
Anterior pituitary deficiency	1/17 (6%)	3/25 (12%)	P= 0.6355
Rhinological complications	3/17 (18%)	0/25 (0%)	P= 0.0513

\* Not Significant

(univariate analysis). The endoscopic procedure tended to be longer than the microscopic one (265 minutes and 228 minutes, respectively, p value 0.0797). Average hospital stay was 4.67 days and 6.42 days for the endoscopic and microscopic techniques, respectively (p value 0.3414). There was a tendency for more reported nasal complications in the endoscopic group (p value 0.0513), however, only the endo TSS patients routinely saw rhinological surgeons postoperatively (Table 7).

## DISCUSSION

Cushing's disease has a significant impact on general health, quality of life and life expectancy.<sup>2-4,30,31</sup> Transsphenoidal selective adenomectomy is the first line treatment for this

condition with the hope that it achieves remission. When this treatment fails, patients can be offered hemi/total hypophysectomy, pituitary radiation or bilateral adrenalectomy. These second line treatments aim at stopping the cortisol excess with its associated impact on health. In our report, the overall long-term remission rate was 62%. The remission rates of the endoscopic and the microscopic groups were not statistically different at 59% and 64%, respectively (p= 0.757). Our series failed to show a difference in outcome between the two techniques in microadenomas or macroadenomas but this may be an effect of beta-type error.

Reported remission rates for transsphenoidal surgery range from 50% to 91%.<sup>13,16,20,32,33</sup> This is a very wide range of results

**Table 8: Summary of reported endoscopic series of CD**

Series	Remission (%)	Remission Criteria	Macroadenoma (%)	Follow up duration
Current series (endoscopic technique)	10/17 (59%)	Normal 24-hr UFC, morning cortisol <50 nmol/L after 1 mg dexamethasone or dependent on replacement	36%	Mean 32 months
Atkinson <sup>[4]</sup>	16/21 (76%)	Postoperative hypocortisolism	All micro	Median 2.5 yrs
D'Haens <sup>[17]</sup>	9/16 (56%)	Evidence of cortisol deficiency, normal 24-hr UFC or cortisol below 18 mcg/L after 1 mg of dexamethasone	38%	Mean 18 months
Netea-Maier <sup>[29]</sup>	29/35 (83%)	Serum cortisol after 1 mg of dexamethasone <50 nmol/L	17%	Median 20 months
Dehdeshi <sup>[11]</sup>	22/27 (81%)	Postoperative morning serum cortisol < 100nmol/L requiring substitutive therapy, suppression to low dose dexamethasone (no specific value) and normal 24-hour UFC	30%	Median 19 months
Hofstetter <sup>[21]</sup>	11/18 (61%)	Morning cortisol level of ≤ 50nmol/L within 48 hours after surgery or a normal of the 24-hour UFC	39%	Mean 25 months

which requires careful interpretation. It can be explained on the basis of differences between the reported cohorts in certain outcome predictors such as tumor size,<sup>22</sup> intra-operative identification of the adenoma,<sup>33</sup> cavernous sinus invasion, or pathological confirmation of the tumor.<sup>18,20,22,33-35</sup> But, it also reflects variation in the criteria used to define remission as seen in some large series that do not report their remission criteria. Furthermore, duration of follow-up is also important in determining long-term remission rates.

In a report by Atkinson et al of 21 microscopic and 21 endoscopic cases of CD, final remission rate was 76%.<sup>7</sup> Remission was defined by the presence of postoperative hypocortisolism. There was no difference between the two procedures with regard to remission rate. The median follow-up periods in that report for the microscopic and the endoscopic groups were 1 and 2.5 years, respectively. This study included only patients with MRI-depicted microadenoma where the wide panoramic view of the endoscope might not be advantageous. The remission rate is certainly going to be lower in series that include macroadenomas as our series did. D'Haens also compared the outcome in an endoscopic and a microscopic cohort of functioning pituitary adenomas.<sup>34</sup> Remission was defined as evidence of cortisol deficiency, normal 24-hr UFC or suppressed cortisol level after one mg of dexamethasone to below 18 mcg/L (50 nmol/L). The remission rates of the endoscopic and microscopic groups were 56% and 46%, respectively. The analysis showed better outcome with endoscopic surgery in non-invasive macroadenoma when all functional adenomas were combined together.

Netea-Maier reported the outcome of endoscopic surgery for CD and the overall remission rate was 83%.<sup>16</sup> In that report, strict remission criteria were used (suppression of serum cortisol after one mg of dexamethasone to <50 nmol/L). This is again a promising result for the endoscopic technique. Dehdeshi reported remission rate for CD to be 81%.<sup>32</sup> Remission in his paper was defined as postoperative serum cortisol < 100 nmol/L requiring substitutive therapy, suppression to low dose dexamethasone and normal 24-hour UFC. Hofstetter reported the outcome of an endoscopic series that contained 18 patients with CD with remission rate of 61%.<sup>35</sup> Remission in the last series was defined by cortisol below 50 nmol/L within 48 hours from surgery or normal 24-hour UFC. Hofstetter and D'Haens cohorts shared with us a relatively high percentage of macroadenomas, which may have contributed to the lower remission rates (Table 8). In a large meta-analysis of endoscopic series by Tabaei, the overall remission rate for CD was 81%.<sup>36</sup>

It is hard to draw generalized conclusions from these reports since they report different types of patients and different remission criteria are used for variable follow-up periods (Table 8). In our report, the overall long-term remission rate was 62% based on our remission criteria. Patients with borderline cortisol levels postoperatively who were observed at the time of this manuscript were considered as failed cases if they did not meet our remission criteria. Had we selected less strict criteria such as the one used by Hammer<sup>12</sup> for dexamethasone suppression test, our remission rate would have been 71%. The microscopic literature, on the other hand, reports remission rates of 65% to 91%.<sup>7,13,20,22,37</sup> The ranges of reported outcomes for the two techniques overlap. With differences in inclusion criteria,

definition of remission and follow up periods, it is hard to make definitive conclusions about the surgical technique.

The known wider visualization of the endoscopic approach has not been paralleled with similarly established superiority in biochemical remission. The superior visualization might not make a difference in adenomas with cavernous sinus invasion nor in pure intrasellar tumors that are easily visualized with either technique. Also, surgeon's experience and other tumor-related variables are important confounders that impact the outcome. This may explain the lack of difference in clinical trials between the two techniques. Future multi-centre studies or registries with very large numbers of patients should be able to show whether the endoscopic approach offers any advantage in non-invasive tumors with lateral, anterior or posterior extension, which is the group where the superior visualization is expected to make a difference.

The endo TSS group had more reports of nasal complications than the micro TSS group (p value 0.0513). However, only the endo TSS group were routinely seen and examined by expert rhinological surgeons and this may have led to a better documentation of these issues in that group. One of our patients had sinusitis, which required antibiotic treatment, and two patients had persistent crusting and foul smell. Since the rhinological part of the surgery is completely different between the two approaches, future pituitary series should also include assessment of rhinological outcome through validated patient-administered questionnaires to both groups of patients.

Having a revision surgery was the most significant predictor of poor outcome in our patients undergoing transsphenoidal surgery (p value 0.0008). This factor has been previously identified as a poor prognosticator.<sup>17,33,38</sup> Nonetheless, repeat surgery still remains as an established option in selected cases of CD after first failed surgery.<sup>39</sup> The only patient who achieved remission after repeat surgery had an identifiable non-invasive adenoma on MRI. In cases with negative MRI or tumors with CS invasion, the threshold for repeat transsphenoidal surgery should be higher especially in cases where the first surgery was done by an experienced pituitary surgeon.

We analyzed our failed cases to identify any obvious potential predictors of poor outcome. The commonest identifiable factor in the endoscopic group was high mitotic index while repeat surgery and lack of intra-operative tumor identification were the commonest factors in the microscopic group. This may suggest that the limited visualization of the microscope contributed to lack of tumor identification but the small number of cases in each group limits the strength of such conclusions.

We tried to study the correlation between different outcome measures and biochemical remission. We found that morning postoperative serum cortisol nadir below 100 nmol/L was associated with long-term remission (p value 0.0101). Given that the association between low postoperative serum cortisol and remission has also been confirmed by other studies,<sup>5,6,9,38,40,41</sup> it would appear appropriate to re-explore those patients without a nadir in the early postoperative period. The best cut-off for serum cortisol remains uncertain, though. At a cut-off value of 100 nmol/L, the sensitivity and specificity for long-term remission were 69% and 75%, respectively. Moving the cut-off value in one direction will cause paradoxical effect on these two parameters. This in concordance with the observation of Lindsay

et al<sup>41</sup> who found patients without long-term remission despite postoperative nadir value below 50 nmol/L. In our series, clinical improvement also correlated with biochemical remission (p value 0.0031).

All prior reports on assessing the benefits of endoscopic versus microscopic surgery, including ours, suffer from the methodological limitation of lack of randomization to minimize the impact of all confounding variables on outcome. Our comparison derived from the same institution over the same time interval addresses some of these confounders to an extent, better than historical controls, but will not eliminate them. We think that comparing single surgeon results with historical control where the two populations can differ significantly in baseline characteristics limits the validity of any conclusions from these comparisons. Within the limits of our population size and statistical power, our study showed the outcome to be comparable between the two techniques. We acknowledge that for the different subgroups (macro- or microadenomas), our population size is too small to draw valid conclusions. We also aimed to report the outcome of surgery with both techniques using strict remission criteria established by endocrine societies.<sup>22</sup>

Future reports of surgery for Cushing's disease should use strict remission criteria defined by endocrine societies that allow more accurate comparisons between different studies. Using less strict remission criteria may provide falsely elevated rates of disease control with subsequent increased morbidity from the cortisol excess. Our remission rate reflects, to some extent, our strict remission criteria in combination with the types of patients we included in this analysis. Although our study has a relatively long follow-up for an endoscopic series (Table 8), definitive statements can only be made when follow-ups extend in to the decades. Multi-centre prospective trials with long follow-up that help to establish the favorable biological, radiological and surgical variables will improve the management of these challenging patients in the future.

## CONCLUSIONS

In the management of patients with Cushing's disease, the endoscopic transphenoidal technique has a comparable outcome to the standard microscopic transphenoidal technique. Patients with repeat transphenoidal surgery have significantly lower remission rate. Clinical symptomatic improvement and a drop in early postoperative serum cortisol levels predict remission from the disease.

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