Endoscopic transsphenoidal pituitary surgery: a good and safe primary treatment option for Cushing’s disease, even in case of macroadenomas or invasive adenomas

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Abstract
Context: Although the endoscopic technique of transsphenoidal pituitary surgery (TS) has been widely adopted, reports on its results in Cushing’s disease (CD) are still scarce and no studies have investigated long-term recurrence rates. This is the largest endoscopic series published till now.
Objective: To gain insight into the role of endoscopic TS as a primary treatment option for CD, especially in patients with magnetic resonance imaging (MRI)-negative CD and (invasive) macroadenomas.
Design: Retrospective cohort study.
Patients and methods: The medical records of 86 patients with CD who underwent endoscopic TS were examined. Data on preoperative and postoperative evaluation, perioperative complications, and follow-up were collected. Remission was defined as disappearance of clinical symptoms with a fasting plasma cortisol level \(< 50 \text{ nmol/l either basal or after 1 mg dexamethasone.}

Results: The remission rate in different adenoma subclasses varied significantly: 60% in MRI-negative CD (n=20), 83% in microadenomas (n=35), 94% in noninvasive macroadenomas (n=16), and 40% in macroadenomas that invaded the cavernous sinus (n=15). The recurrence rate was 16% after 71±39 months of follow-up (mean±s.d., range 10–165 months).

Conclusions: Endoscopic TS is a safe and effective treatment for all patients with CD. Recurrence rates after endoscopic TS are comparable with those reported for microscopic TS. Our data suggest that in patients with noninvasive and invasive macroadenomas, the endoscopic technique of TS should be the treatment of choice as remission rates seem to be higher than those reported for microscopic TS, although no comparative study has been performed.

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Introduction
Persisting Cushing’s disease (CD) after unsuccessful treatment is associated with a four- to fivefold increased standardized mortality ratio and substantial morbidity (1, 2, 3). Successful treatment of CD is therefore crucial. Since Hardy introduced the operating microscope to selectively remove ACTH-secreting microadenomas via the transsphenoidal route in 1963, transsphenoidal surgery (TS) has become the treatment of choice for CD (4). Over the years, a large number of reports on the results of microscopic TS in patients with CD have been published. These reports show that, in experienced hands, excellent remission rates of over 80% can be achieved if a microadenoma is visualized on preoperative imaging (5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16). Furthermore, CD relapses in up to 25% of the patients. Therefore, it has been suggested that TS is the optimal primary treatment for only a subset of patients with CD (17).

In the 1990s, the purely endoscopic technique of TS was introduced as an alternative to the conventional microscopic technique. The endoscopic technique offers a panoramic view with increased illumination of the operating field. Furthermore, different angles can be used making it possible to reach the suprasellar and parasellar regions. Owing to these advantages, the endoscopic technique has been widely adopted (18, 19, 20, 21, 22). Compared with historical microscopic series, the endoscopic technique seems to result in improved outcome rates in macroadenomas (18, 19, 20, 21, 22). However, reports on the results of endoscopic TS in CD are still scarce, and in studies that have been published (including our own report on...
the results in the first 35 patients), all patients have a short follow-up period, so no statements about recurrences can be made (23, 24, 25). Furthermore, it is still unclear whether the endoscopic technique has advantages or disadvantages in patients with very small microadenomas (<5 mm), which occur frequently in patients with CD (26, 27). Therefore, some neurosurgeons are reluctant to use this technique in patients with CD (27).

To gain more insight into the role of endoscopic TS as a primary treatment option for patients with CD, especially in patients with MRI-negative CD or (invasive) macroadenomas, we evaluated the results of endoscopic TS in the first 86 patients treated in our center. Furthermore, we evaluated the recurrence rates after initial remission.

Subjects and methods

Patients

From 1998 onward, all TS in our hospital was performed endoscopically. All patients who underwent endoscopic TS as a primary treatment for CD between January 1998 and December 2011 (n=86) were identified for this retrospective cohort study. The medical records of these 86 consecutive patients were examined. Data on preoperative and early postoperative evaluation, perioperative complications, and follow-up were collected according to the guidelines of our local medical ethics committee. Seventy-two percent of all patients were female. At the time of endoscopic TS, the age of the patients was 42.3 ± 14.9 years (mean ± S.D.) and BMI was 30.5 ± 7.2 kg/m². The initial results of endoscopic TS in the first 35 patients have been published previously (23).

Diagnostic evaluation

At presentation, all patients had symptoms of active hypercortisolism. The clinical diagnosis of hypercortisolism was confirmed by standard biochemical investigations (elevated 24-h urinary free cortisol (UFC) excretion, decreased diurnal variation of plasma and/or salivary cortisol levels, and failure to suppress plasma cortisol after 1 mg dexamethasone overnight) (28). ACTH dependency was confirmed by normal or elevated ACTH values. The diagnosis of pituitary-dependent CD was confirmed as follows: pituitary imaging by MRI scanning with intravenous contrast (gadolinium) was performed in all patients. If no adenoma was seen on the MRI scan (MRI-negative CD, n = 20) or if the adenoma was < 6 mm (n = 21), inferior petrosal sinus sampling (IPSS) was performed (n = 22) or (if IPSS could not be performed because of technical reasons, co-morbidity, or refusal by the patient) a corticotropin-releasing hormone (CRH) test (100 μg human CRH, i.v.) and a high-dose dexamethasone suppression test (DST; 7 mg dexamethasone in 7 h, i.v.) were performed (n = 19).

Perioperative treatment

Eighty-seven percent of all patients received cortisoldowering medication (ketoconazole in 48 patients, metyrapone in 22 patients, and a combination of both drugs in eight patients) before TS for 3.6 ± 1.8 months. One hour before surgery, administration of glucocorticoids (prednisolone, 25 mg i.v. every 8 h) was started, and after surgery the dose was tapered rapidly.

Surgical procedures

The endoscopic technique of TS was introduced in our hospital in 1994 and was first used for the treatment of CD in 1998 (n = 2). Thereafter, an increasing number of patients with CD were operated endoscopically, reaching an average of eight patients per year from 2003 onward. The technique of endoscopic TS has been described earlier (22, 23, 29). In short, a binostril, transphenoidal, endoscopic approach to the sella turcica during which the endoscope is handheld was used. Until 2010, endoscopic TS was exclusively performed by two neurosurgeons and thereafter by three neurosurgeons.

A selective adenomectomy was performed if an adenoma could be localized during TS (n = 76). In five patients, no adenoma could be localized preoperatively and a hemi-hypophysectomy was performed (based on the results of IPSS). In one patient, the whole pituitary gland seemed abnormal and a resection of the total anterior pituitary gland was performed. In four patients, only debulking of the adenoma was performed because it was clear that it was impossible to remove the total adenoma based on preoperative imaging. However, these patients required an operation because of local mass effects of the adenoma. All material removed during TS was examined histopathologically and immunohistochemical staining for pituitary hormones was performed to confirm the diagnosis of ACTH-secreting pituitary adenoma.

A complication of TS was defined as any event occurring during or in the month after TS that required treatment. As intraoperative cerebrospinal fluid (CSF) leakage, which occurred in 11 patients and was closed with a fat graft preoperatively, is inherent to the surgical procedure, this was not regarded as a complication.

Postoperative evaluation

On the fourth day postoperatively, biochemical evaluation was carried out (after glucocorticoid substitution had been stopped for at least 24 h) by measurement of fasting (0800 h) plasma cortisol, ACTH, thyrotropin,
The proportion of the different adenoma classes varied significantly over the years, with a higher percentage of patients with MRI-negative CD in the first 5 years and a higher percentage of invasive macroadenomas in the last 5 years ($P<0.01$). As investigated with a stepwise logistic regression analysis, adenoma classification was the only preoperative variable that significantly influenced the chance of remission ($P<0.01$).
Evidence of an ACTH-producing pituitary adenoma was found during immunohistochemical investigation in 79% of the patients who were in remission of CD after TS compared with 54% of the patients with persistent CD \( (P = 0.02) \). The follow-up period of the total patient group was 71 ± 39 (5–164) months. After 42 ± 27 (10–98) months, CD recurred in 10 of the 62 patients who were initially in remission (16%).

The probability of recurrence-free survival, as estimated with a Kaplan–Meier analysis, was 98% 1 year after successful primary TS, 84% after 5 years, and 73% after 8 or more years (Fig. 3A). The chance of recurrence significantly increased with a larger adenoma classification: probability of recurrence-free survival after successful primary TS was 91.7% after a mean of 100 months in the MRI-negative CD group, 66.8% after 45 months in the microadenoma group, 60.9% after 43 months in the noninvasive macroadenoma group, and 37.5% after 35 months in the invasive macroadenoma group \( (P = 0.04, \text{Fig. 3B}) \).

**Complications of endoscopic TS and influence on pituitary hormone secretion**

In this series, all complications of endoscopic TS were relatively mild and did not cause any permanent damage. The most severe complication, which occurred in one patient, was postoperative bleeding originating from the sphenopalatine artery. This directly required reoperation. One patient with persistent CD after TS developed a pulmonary embolism 2 weeks after surgery. Ten patients (11.6% of all patients) had mild epistaxis controlled with nasal tampons. Four patients (4.6%) had postoperative CSF leakage, which was successfully treated with an external lumbar drain (ELD). Four patients (4.6%) developed transient diabetes insipidus (polyuria for more than 2 days and <6 months requiring desmopressin substitution), which resolved spontaneously in the first few weeks after surgery. Ten patients (11.6%) developed transient hyponatremia of <130 mmol/l postoperatively, caused by inappropriate ADH secretion and/or (relative) glucocorticoid deficiency. Three patients (3.4%) had an infection postoperatively and were treated with antibiotics: two patients due to a local urinary tract infection and one patient due to a local infection at the entry point of the ELD.

**Figure 1** Results of endoscopic pituitary surgery in 86 patients with Cushing’s disease (1998–2011). ADX, adrenalectomy; RT, radiation therapy; †deceased.

**Figure 2** Overview of the remission rates of Cushing’s syndrome after endoscopic pituitary surgery for the different adenoma classes. *Indicates significant difference between the two groups.
Thirteen patients (15%) already received substitution therapy for deficiencies of one or more pituitary hormones before surgery. After TS, six patients who received hormonal substitution before TS no longer needed any hormonal substitution and 22 patients started with substitution therapy. So at the last follow-up (or at the follow-up visit before additional treatment was initiated), 35% of all patients received one or more hormonal substitution therapies. Twenty-two percent of all patients received substitution with levothyroxine, 14% received long-term glucocorticoid substitution (for a minimum duration of 2 years), 6% received GH, and 3.5% received androgens (Table 1).

**Additional treatment for persistent and recurrent CD**

Figure 1 shows how patients with persistent and recurrent CD were treated. Four of the 24 patients with persistent CD did not receive any additional treatment. The persisting CD is subclinical in three of these patients and the fourth patient refused further treatment. Eleven patients with persistent CD were treated with repeat endoscopic TS, which was only successful in three patients. Seven patients with persistent CD were treated with radiation therapy (RT), which was successful in six patients. In the seventh patient, the pituitary tumor turned out to be a pituitary carcinoma. The patient died of metastatic disease. Two patients with persistent CD were treated with a bilateral adrenalectomy.

Five of the ten patients with recurrent CD were treated with a second endoscopic TS, which was successful in four patients. In the fifth patient, the intention of repeat TS was to debulk the adenoma that had grown very rapidly in a short period of time and also turned out to be a pituitary carcinoma. Three patients (30%) with recurrent CD were treated with RT and two patients have not yet received additional treatment.

**Discussion**

This study reports on the results of endoscopic TS in 86 patients with CD treated at the Radboud University Nijmegen Medical Centre between 1998 and 2011. To our knowledge, this is the largest series on the results of endoscopic TS in CD published till now, with the longest follow-up time. In addition, in contrast to the most previously published series on the results of both endoscopic and microscopic TS, we included a relatively large number of patients with macroadenomas, including invasive macroadenomas.

The most important finding of our study is the high remission rate of 94% achieved in patients with noninvasive macroadenomas. This compares favorably with previously reported remission rates after microscopic TS in patients with ACTH-secreting macroadenomas which are on average 60%, despite the fact that most studies used less strict criteria for remission than we used (Table 2) (5, 7, 8, 9, 10, 13, 14, 15, 16, 34, 35, 36). In line with our results, Starke et al. recently reported a high remission rate of 87% in patients with ACTH-secreting macroadenomas (n = 15, of which six were invasive), achieved with endoscopic TS. Furthermore, the remission rates after endoscopic TS also seem to be higher in patients with a GH-secreting or a nonfunctioning macroadenoma (18, 19, 20, 21, 22). We therefore believe that the endoscopic technique of

![Figure 3](image-url)  

**Table 1** Influence of TS on hormonal substitution therapy in 86 patients with Cushing’s disease.

<table>
<thead>
<tr>
<th></th>
<th>Levothyroxine substitution</th>
<th>Androgen substitution</th>
<th>Glucocorticoid substitution</th>
<th>GH substitution</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinued after TS</td>
<td>5</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Continued after TS</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Started after TS</td>
<td>13</td>
<td>1</td>
<td>12</td>
<td>5</td>
<td>31</td>
</tr>
</tbody>
</table>

TS, transsphenoidal surgery.
### Table 2 Remission and recurrence rates of Cushing’s disease in micro- and macroadenomas after primary transphenoidal pituitary surgery: a selection* of recently published single-center series.

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Remission criteria</th>
<th>Remission percentage</th>
<th>Recurrence percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Microscopic series</strong></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
| (16)      | 154 | Basal cortisol <138 nmol/l  
UFC <55 nmol/l  | Overall, 87%  
Microadenomas (n=137), 90%  
Macroadenomas (n=17), 65% | 7% follow-up  
Mean 8.7 years |
| (13)      | 54  | Overall, 70%  
MRI-negative CD (n=16), 69%  
Microadenomas (n=23), 100% | 5% follow-up  
Mean 7 years |
| (15)      | 77  | Normal UFC  
Cortisol <138 nmol/l after 48-h DST  | Overall, 78%  
MRI-negative CD (n=10), 80%  
Microadenomas (n=3), 33% | 5% follow-up  
Mean 4.2 years |
| (34)      | 97  | Basal cortisol <50 nmol/l  | Overall, 68.5%  
MRI-negative CD (n=34)  
Microadenomas (n=45)  
Macroadenomas (n=10) | 11.5% follow-up  
Mean 7.6 years |
| (6)       | 174 | Cortisol <83 nmol/l  
after a 1 mg DST  | Overall, 79%  
Microadenomas (n=133), 92%  
Macroadenomas (n=29), 17% | 6.5% follow-up  
Mean 5 years |
| (9)       | 200  | Overall, 85%  
Cortisol <140 nmol/l  
after a 1 mg DST  | Overall, 85%  
Cortisol <140 nmol/l  
after a 1 mg DST  | 9% follow-up  
Median 11.1 years |
| (8)       | 39  | Basal cortisol <140 nmol/l  | Overall, 79%  
MRI-negative CD (n=8), 50%  
Microadenomas (n=23), 91%  
Macroadenomas (n=8), 75% | 6% follow-up  
Mean 2.8 years |
| (14)      | 108 | Glucocorticoid dependence  
Cortisol <82.8 nmol/l  
after a 1 mg DST  | Overall, 85%  
MRI-negative CD (n=21), 71%  
Microadenomas (n=59), 95%  
Macroadenomas (n=23), 74% | 7% follow-up  
Mean 6 years |
| (35)      | 40  | Normal UFC  
Glucocorticoid dependence  | Overall, 65%  
MRI-negative CD (n=3), 0%  
Microadenomas (n=25), 64%  
Macroadenomas (n=12), 83% | 11.5% follow-up  
Mean 7 years |
| (5)       | 79  | Normal UFC  
Cortisol <50 nmol/l  
after a 1 mg DST  | Overall, 65%  
MRI-negative CD (n=14), 57%  
Microadenomas (n=44), 77%  
Macroadenomas (n=21), 43% | 21% follow-up  
Median 7 years |
| (7)       | 136 | Basal cortisol <138 nmol/l  | Overall, 85%  
Microadenomas (n=123), 90%  
Macroadenomas (n=13), 31% | 9.7% follow-up  
Mean 5.7 years |
| (10)      | 83  | Normal UFC  
Cortisol <55 nmol/l  
after a 1 mg DST  | Overall, 84%  
MRI-negative CD (n=20), 77%  
Microadenomas (n=46), 93%  
Macroadenomas (n=5), 100%  
Invasive macroadenomas (n=7), 43% | 7% follow-up  
Mean 3.2 years |
| **Endoscopic series** |  |  |  |  |
| (25)      | 25  | Basal cortisol <100 nmol/l  
Suppression of cortisol  
after a 1 mg DST  
Normal UFC  | Overall, 80%  
MRI-negative CD (n=5), 60%  
Microadenomas (n=13), 100%  
Macroadenomas (n=5), 80%  
Invasive macroadenomas (n=2), 0% | 0% follow-up  
Median 1.4 years |
| (24)      | 62  | Overall, 95%  
MRI-negative CD (n=16), 100%  
Microadenomas (n=30), 97%  
Macroadenomas (n=15), 87% | 10% follow-up  
Mean 2.3 years |
| **This series** |  |  |  |  |
| 86        | Basal cortisol <50 nmol/l  
Cortisol 50 nmol/l  
after a 1 mg DST  | Overall remission, 72%  
MRI-negative CD (n=20), 60%  
Microadenomas (n=35), 83%  
Macroadenomas (n=16), 94%  
Invasive macroadenomas (n=15), 40% | 16% follow-up  
Mean 5.6 years |

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*n, number of patients; DST, dexamethasone suppression test; UFC, 24-h urinary free cortisol; MRI, magnetic resonance imaging scan; CD, Cushing’s disease.  
*Only single-center studies with clear criteria for remission and relapse and in which remission rates were mentioned or could be calculated for different adenoma subclasses were included in this literature overview.  
*For a few patients, the operation was the second operation.
TS should be the treatment of choice in patients with an ACTH-secreting macroadenoma.

It is of interest that in the previously published series on microscopic TS, only a few patients with ACTH-secreting macroadenomas that invaded the cavernous sinus were included, probably because it was believed to be virtually impossible to achieve remission in these patients. Remission was nevertheless achieved in 40% of the patients with an invasive macroadenoma in the current series, of whom one patient even had a total encasement of the intracavernous carotid artery (KNOSP grade 4). This relatively good result can be explained by the fact that compared with the microscopic technique of TS, the endoscopic technique enables the use of different operating angles, which makes it possible to effectively reach suprasellar and parasellar portions of the lesion, including the cavernous sinus (37). In our opinion, invasion of the adenoma in the cavernous sinus should therefore not be a reason to refrain from surgery, especially because at present TS remains the only treatment that potentially restores normal physiology and all other treatment options for CD have major disadvantages.

In patients with an intrasellar ACTH-secreting microadenoma, we achieved a remission rate of 83%, which is in concordance with the remission rates previously reported in both conventional microscopic and endoscopic series (Table 2). Thus, in patients with a microadenoma, the technique of TS is probably equivocal, as long as TS is performed by an experienced neurosurgeon. Furthermore, the number and type of complications, the complication rates, and the rates of postoperative hormonal deficiencies that are reported are similar in both the techniques (18, 19). The preference of the neurosurgeon and/or the patient should therefore determine the technique of TS that is used in patients with a microadenoma.

In MRI-negative CD, the remission rate we achieved was 60%, which is significantly lower than that achieved in microadenomas that could be visualized on preoperative MRI. This is in concordance with most conventional microscopic series that also report lower remission rates in MRI-negative CD (Table 2). Interestingly, Starke et al. achieved remission in 100% of patients with MRI-negative CD with the endoscopic technique (21). More data are needed in order to determine the real value of endoscopic TS in patients with MRI-negative CD.

This is the first study that reports on long-term recurrence rates after endoscopic TS in CD. We found that after a mean of 5.6 years of follow-up, 16% of the patients who were initially in remission after endoscopic TS developed a recurrence. All patients were actively investigated for recurrence and a strict definition of recurrence was used in order to obtain a good insight into actual recurrence rates. There are only a few previously published microscopic series that carefully analyzed patients for recurrence (3, 5, 38, 39), and these series also report relatively high recurrence rates varying between 13 and 21%. Therefore, recurrence rates of CD after endoscopic TS seem to be comparable with those after microscopic TS. Because most recurrences occur in the first 5 years after TS and more recurrences occur in larger/invasive adenomas (Fig. 3), the cause of a recurrence is most likely a small adenoma remnant left behind during TS.

We previously reported that endoscopic TS seems to be a good therapeutic option for recurrent or persistent CD, after analyzing the outcome in 14 patients (29). At that time, we did not separately analyze the results of persistent and recurrent CD, but remission was achieved in seven of eight patients with recurrent CD and three of six patients with persistent CD. This study confirms that repeated endoscopic TS seems to be a good therapeutic option for patients with recurrent CD with remission achieved in four of five patients. However, repeated endoscopic TS seems to be of less value for patients with persistent CD as remission was only achieved in three of 11 patients.

A limitation of this study is that, although the total patient group is relatively large, the number of patients in the different adenoma subclasses is relatively small. Another limitation of this study is its retrospective nature. Ideally, a comparison between the microscopic and endoscopic technique of TS in CD would be made via a randomized controlled trial, with one or two neurosurgeons performing both operations. However, because CD is a rare disease, it is very difficult to organize such a trial. Furthermore, only a few neurosurgeons have extensive experience with both techniques of TS. Thus, the only way that the results of the microscopic and endoscopic technique of TS in CD can currently be compared in a large number of patients is via a meta-analysis. However, at present, it is difficult to compare the remission rates between different studies as remission criteria vary immensely between different studies (Table 2). It is therefore of the greatest importance that a good consensus statement is established about the definition of remission and recurrence of CD after TS for future research purposes.

In conclusion, endoscopic TS is a safe and effective treatment for all patients with CD. Recurrence rates after endoscopic TS are comparable with those reported for microscopic TS. Our data suggest that in patients with noninvasive and invasive macroadenomas, the endoscopic technique of TS should be the treatment of choice as remission rates seem to be higher than those reported for microscopic TS, although no formal comparative study has been performed. In MRI-negative CD or microadenomas, the preference of the neurosurgeon and/or the patient should determine the technique of TS that is used because remission and complication rates that are reported in microscopic TS and endoscopic TS are comparable.
Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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