Repeated transsphenoidal pituitary surgery (TS) via the endoscopic technique: a good therapeutic option for recurrent or persistent Cushing’s disease (CD)


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Summary

Background No data on results of repeated transsphenoidal surgery via the endoscopic technique for patients with persistent or recurrent Cushing’s disease are available.

Design and patients We retrospectively evaluated the remission rates and complications of repeated transsphenoidal surgery via the endoscopic technique in 14 patients with persistent (N = 6) or recurrent (N = 8) Cushing’s disease treated in our centre between 1999 and 2007.

Main outcomes Remission was defined as the disappearance of symptoms of hypercortisolism with basal plasma cortisol level ≤ 50 nmol/l 24–48 h after glucocorticoid withdrawal and/or suppression of plasma cortisol level ≤ 50 nmol/l after 1 mg dexamethasone overnight within the first 3 months after transsphenoidal surgery.

Results With repeated endoscopic transsphenoidal surgery a remission rate of 10/14 (71%) was achieved. No patient had a relapse during a median follow-up of 24 months. Cerebrospinal fluid leakage was the most frequent complication (6 patients) and 11 patients required hormonal substitution after surgery. The success of repeated transsphenoidal surgery could not be predicted by visualization of an adenoma on MRI before first or second surgery, histopathological confirmation of an ACTH secreting adenoma after first or second surgery, treatment with cortisol lowering agents before first or second surgery, the operation technique used during the first surgery, persistent vs. recurrent disease after the first surgery, age, gender and interval between the two surgeries.

Conclusion Repeated transsphenoidal surgery via the endoscopic technique is a good treatment option for selected patients with recurrent or persistent Cushing’s disease following primary pituitary surgery.
Between 1999 and 2007 a total of 24 patients were treated for persistent or recurrent CD. Besides the 14 patients who underwent endoscopic repeated TS, 5 patients underwent conventional pituitary radiotherapy, 4 patients underwent stereotactic radiosurgery and 1 patient underwent a bilateral adrenalectomy. A multidisciplinary team of neurosurgeons, endocrinologists and a radiotherapist decided which therapy for persistent or recurrent CD was the optimal therapy for each individual patient, taking into account the invasiveness of the adenoma, findings at previous surgery, the physical condition of the patient and the patient’s preference.

**Diagnostic evaluation before the first and second TS**

The initial diagnosis of hypercortisolism was based on clinical symptoms and biochemical tests, including 24-h urinary free cortisol measurements, assessment of the plasma cortisol and ACTH circadian rhythm and an overnight low dose dexamethasone suppression test (1 mg at 11 pm). A CRH-test (100 μg human CRH i.v.) and a high-dose dexamethasone suppression test was performed in most patients. In addition pituitary imaging by contrast enhanced magnetic resonance imaging (MRI) was performed in all patients, except in one patient where contrast enhanced computed tomography

### Patients and methods

**Patients**

Between 1999 and 2007, 68 endoscopic TS were carried out for CD in our hospital. Fourteen of these operations were repeated TS, for persistent CD in six patients and recurrent CD in eight patients. The medical records of these patients were retrospectively reviewed. There were five males and nine females and age at time of the second surgery was 37.2 ± 10.3 years (Table 1).

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(CT) scanning was used, to search for a pituitary adenoma. Eight patients underwent bilateral inferior petrosal sinus sampling with i.v. stimulation with 100 μg human CRH, which confirmed the pituitary origin of hypercortisolism in all eight patients. All repeated pituitary operations in this series were performed via an endoscopic binostril endonasal transphenoidal technique. This technique was introduced in our hospital in 1994, and first used for CD in 1997. From 1998 onward practically all TS were performed endoscopically. The surgeries were exclusively performed by two neurosurgeons. The technique is very similar to the technique that Jho et al. and Cappabianca et al. have described previously. However, a binostril, transsphenoidal, endoscopic approach to the sella turcica during which the endoscope is handheld was used.

For endoscopic transnasal TS 0° and 30° rigid endoscopes with a lens diameter of 4 mm with a separate shaft were used, which allow easy and comfortable holding, while offering a suction-irrigation-system for cleaning the lens (Karl Storz GmbH, Tuttingen, Germany). The instruments used are principally the same as with the microsurgical technique. The technique of repeated surgery is in no way different from primary surgery. In two recent cases electromagnetic neuronavigation was used for orientation and localization of a very small tumour.

In patients with recurrent CD a selective adenomectomy was performed if MRI identified the tumour. In case of negative MRI investigations a hemihypophysectomy was performed based on intra-operative findings. In patients with persistent CD after first TS, a total hypophysectomy was performed during repeated TS. Although this term suggests complete removal of all contents of the sella, it is never the intention to remove all pituitary tissue. Total hypophysectomy indicates the surgical exploration of the complete contents of the sella and removal of all anterior pituitary tissue that might harbour adenoma tissue. As soon as this goal seems to be achieved further surgery is discontinued and thus pituitary tissue may be left in place.

Postoperative evaluation after first and second TS

On the seventh day postoperatively early biochemical evaluation was carried out, consisting of measurement of fasting (8 am) plasma cortisol. If it was lower than 200 nmol/l substitution therapy with hydrocortisone, 30 mg a day, or cortisone acetate, 37.5 mg daily, was prescribed. Patients were re-evaluated every 2–4 weeks during the first 3 months after surgery and then at 2–3 months intervals during the first year. Thereafter they were evaluated at least once a year.

The fasting plasma cortisol concentration was measured at each visit. In addition an overnight 1 mg dexamethasone suppression test was carried out in 1 and 3 months postoperatively, and thereafter in patients who were in remission once yearly or earlier in case of clinical suspicion of relapse. If a patient received glucocorticoid substitution postoperatively, the dose was reduced gradually and stopped, if possible, between 3 and 12 months after surgery. Thereafter the integrity of the hypothalamic–pituitary–adrenal axis was assessed by an insulin-hypoglycaemia test. The thyrotrophic, gonadotrophic and somatotropic axis were checked regularly.

Criteria for remission and relapse

Remission was defined as disappearance of clinical symptoms of hypercortisolism with basal plasma cortisol level ≤ 50 nmol/l after glucocorticoid withdrawal for 24–48 h and/or suppression of plasma cortisol level ≤ 50 nmol/l after overnight 1 mg dexamethasone within the first 3 months after surgery. Relapse was defined as development of clinical symptoms of hypercortisolism and inadequate suppression of plasma cortisol level after an overnight 1 mg dexamethasone suppression test in patients who were in remission after the first surgery according to the previously mentioned criteria.

Statistics

Statistical analyses were performed using Pearson’s χ²-tests (P) and Wilcoxon’s two sample tests (P*). Statistical significance was defined as P < 0·05 (two tailed).

Results

Remission rates after repeated TS (Fig. 1)

The individual clinical data of the 14 patients are shown in Tables 1 and 2. The mean interval between the first and the second TS was 59 months (median 39, range 2–185).

After repeated TS remission was achieved in 10 patients. Nevertheless, patients 1 and 9 received additional therapy. Patient 1 was concerned that hypercortisolism would recur and asked for additional radiotherapy. Patient 9 was the only patient with an invasive macro-adenoma that could not entirely be removed during the second surgery. Therefore the patient received additional gamma knife surgery although he was clinically and biochemically in remission.

None of the patients who were in remission after the second TS had a relapse during follow-up of mean 34 months (median 24,
Repeated endoscopic transsphenoidal surgery in CD

Fig. 1 Results of repeated transsphenoidal pituitary surgery via the endoscopic technique in patients with persistent or recurrent Cushing’s disease (1999–2007). ADX, bilateral adrenalectomy.

Table 2. Substitution therapy and follow-up after second pituitary surgery (1999–2007)

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Substitution after first TS*</th>
<th>Substitution after second TS**</th>
<th>Result second surgery</th>
<th>Additional therapy</th>
<th>Cortisol at last follow-up (nmol/l)</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–</td>
<td>–</td>
<td>R</td>
<td>CR (45 Gy)</td>
<td>0·46</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>–</td>
<td>T, GH</td>
<td>R</td>
<td>–</td>
<td>0·57</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>–</td>
<td>T</td>
<td>F</td>
<td>ADX</td>
<td>–</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>–</td>
<td>A, GH, G</td>
<td>R</td>
<td>–</td>
<td>0·15</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>–</td>
<td>T</td>
<td>T</td>
<td>CR (50 Gy), K</td>
<td>–</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>–</td>
<td>T</td>
<td>F</td>
<td>CR (50 Gy)</td>
<td>–</td>
<td>28</td>
</tr>
<tr>
<td>7</td>
<td>–</td>
<td>T, G</td>
<td>R</td>
<td>–</td>
<td>0·13</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>–</td>
<td>T</td>
<td>F</td>
<td>CR (45 Gy), K</td>
<td>–</td>
<td>15</td>
</tr>
<tr>
<td>9</td>
<td>–</td>
<td>A</td>
<td>R</td>
<td>RS</td>
<td>0·10</td>
<td>17</td>
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<td>10</td>
<td>–</td>
<td>T</td>
<td>R</td>
<td>–</td>
<td>0·18</td>
<td>15</td>
</tr>
<tr>
<td>11</td>
<td>T</td>
<td>T, GH</td>
<td>R</td>
<td>–</td>
<td>0·26</td>
<td>15</td>
</tr>
<tr>
<td>12</td>
<td>–</td>
<td>G</td>
<td>R</td>
<td>–</td>
<td>0·40</td>
<td>13</td>
</tr>
<tr>
<td>13</td>
<td>–</td>
<td>G</td>
<td>R</td>
<td>–</td>
<td>0·06</td>
<td>13</td>
</tr>
</tbody>
</table>

*At last evaluation before relapse was diagnosed or in case of persistent Cushing’s disease immediately before second TS; **At last follow-up; A, androgens; D, desmopressin; E, estrogens; G, glucocorticoids; GH, growth hormone; T, levothyroxine; CR, conventional radiotherapy; RS, radiosurgery; ADX, bilateral adrenalectomy; K, ketoconazole; Cortisol at last follow-up, fasting plasma cortisol level at 0800 h and plasma cortisol level at 0800 h after 1 mg dexamethasone overnight, measured in January 2008 in patients who are clinically in remission after 2nd surgery.

At last follow-up plasma cortisol was not suppressed to ≤ 50 nmol/l after 1 mg dexamethasone overnight in patients 1, 2, 7 and 10 (Table 2), but they had no clinical symptoms of hypercortisolism and 24-h urinary free cortisol excretion was not elevated. Four patients had persistent CD after the second TS. Patient 3 underwent a bilateral adrenalectomy and patients 5, 6 and 8 received conventional radiotherapy.

There were no statistically significant differences between the patients who underwent successful or unsuccessful repeated TS with respect to the following parameters: visualization of an adenoma on MRI before first or second TS, histopathological confirmation of an ACTH secreting adenoma after first or second TS, treatment with cortisol lowering agents before first or second TS, the operation technique used during the first TS, persistent vs. recurrent disease after the first TS, age, gender and interval between the two TS.

Complications of repeated TS

Six of the 14 patients had mild transient diabetes insipidus. Six patients had cerebrospinal fluid (CSF) leakage, 4 intra-operatively.
(closed with a fat graft) and 2 postoperatively. All six patients with CSF leakage were treated successfully with an external lumbar drain. Two patients required a reoperation to close the leak. More serious complications occurred in two patients. Patient 5 had blood loss from the right cavernous sinus during second TS. Damage of the internal carotid artery was excluded via an angiogram. Surgery was terminated before any tissue was removed and a tampon was placed that was removed via reexploration 1 week later. A few hours after the reexploration the patient developed a hemiparesis, due to occlusion of the left internal carotid artery just above the bifurcation. This was very unlikely a direct complication of the TS because the site of occlusion of the internal carotid artery was lower than the operation area. Although the patient improved significantly during the revalidation process, permanent disabilities remain. Patient 11 had postoperative bleeding from the sphenopalatine artery. Reexploration was required with successful coagulation of the artery. The patient recovered within a few days without other complications.

Only three patients required hormonal substitution after the first TS. After the second TS 11 patients required long-term hormonal substitution (Table 2). Of all patients, 8 required levothyroxine, 4 glucocorticoids, 4 GH and 2 androgens and one oestrogens after repeated TS.

The remission rate of 71% achieved in this study compares favourably with the remission rates previously reported after repeated TS via the conventional microscopic technique, which vary between 37% and 73%, with a 0–25% relapse rate\textsuperscript{19–24} (Table 3). When comparing the reported remission rates, it is important to note that the studies were carried out in different patient groups. Three studies included patients with both persistent and recurrent CD,\textsuperscript{19–21} whereas other studies reported on patients with either persistent\textsuperscript{22,23} or recurrent\textsuperscript{24} CD. Criteria for remission also differed. In three studies immediate repeated TS was performed in case of persistent CD,\textsuperscript{21–23} However, this strategy ignores the fact that some patients who do not have a low early postoperative basal plasma cortisol level do achieve remission, so by using this strategy some patients will unnecessarily undergo immediate repeated TS.\textsuperscript{4} Overall, the remission rates reported after second TS in persistent or recurrent CD seem to be slightly lower than the remission rates reported after first TS which vary from 50% to 90%, but are mostly 70–85%.\textsuperscript{3–9} Nevertheless, the majority of the patients with persistent or recurrent CD can still instantly be cured by repeated TS, and the remission rate we achieved via the endoscopic technique seems to be at least as good as the remission rate achieved by repeated TS via the conventional microscopic technique.

In this study 57% of the patients had a perioperative complication of the repeated TS. Although most complications in our series were mild and transient more serious complications occurred in two patients: one patient had a cerebrovascular accident postoperatively and another patient had postoperative bleeding from the sphenopalatine artery. The latter complication is not a rare complication of microscopic TS, occurring in 3–4% of all cases. Vascular complications of endoscopic TS and microscopic TS are identical.\textsuperscript{38} We previously reported a complication rate of 29% in our study on results of primary endoscopic TS in patients with CD,\textsuperscript{3} which is similar to the complication rates reported in studies of primary microscopic TS in patients with CD. The studies on repeated TS in patients with persistent or recurrent CD report complication rates varying between 0% and 91%.\textsuperscript{19–24} Although complication rates are influenced substantially by differences in definitions, the complication rate of repeated TS seems to be higher than the complication rate of primary TS.

Especially CSF leakage has been reported to occur more frequently during repeated TS than during the first TS, probably because of postoperative changes such as scar tissue but also as a result of a more aggressive surgical procedure in a usually small sella with a concave

### Table 3. Overview of previously published results of repeated TS in patients with persistent or recurrent CD

<table>
<thead>
<tr>
<th>Population</th>
<th>Criteria remission</th>
<th>Remission (%)</th>
<th>Relapse (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friedman et al. (1989)</td>
<td>33 persistent + recurrent</td>
<td>Morning C &lt; 6 μg/dl and UFC &lt; 90 μg/day</td>
<td>73</td>
</tr>
<tr>
<td>Ram et al. (1994)</td>
<td>17 persistent*</td>
<td>Morning C &lt; 5 μg/dl and UFC &lt; 90 μg/day</td>
<td>71</td>
</tr>
<tr>
<td>Knappe et al. (1996)</td>
<td>10 persistent*/17 recurrent</td>
<td>Not defined</td>
<td>71/56</td>
</tr>
<tr>
<td>Benveniste et al. (2005)</td>
<td>44 persistent + recurrent</td>
<td>Not defined</td>
<td>57</td>
</tr>
<tr>
<td>Locatelli et al. (2005)</td>
<td>12 persistent*</td>
<td>Clinical symptoms of hypocortisolism and morning C ≤ 2 μg/dl</td>
<td>67</td>
</tr>
<tr>
<td>Hofman et al. (2006)</td>
<td>16 recurrent</td>
<td>C &lt; 2 μg/dl after 2 mg dexamethasone and morning C 10–21 μg/dl</td>
<td>37</td>
</tr>
</tbody>
</table>

TS, transsphenoidal pituitary surgery; CD, Cushing’s disease; *, immediate reoperation; C, plasma cortisol; UFC, urinary free cortisol excretion.
diaphragm.\textsuperscript{22,28,30} CSF leakage occurred in 43% of the patients in this study, intra-operatively in four patients and postoperatively in two patients. Previously, we reported a CSF leakage rate of 8.5% in primary endoscopic TS in patients with CD operated on by the same neurosurgeons that operated the patients in this study.\textsuperscript{3} When comparing rates of CSF leakage it is important to note that most studies only report on the rates of postoperative CSF leakage. The rate of postoperative CSF leakage is lower (1–4% during first TS) than the rate of intra-operative CSF leakage (9–25% during first TS).\textsuperscript{29,40} Because intra-operative CSF leakage, which is usually not regarded as a complication, also occurs frequently during the first TS and the risk of meningitis is minimal if patients are given a lumbar drain,\textsuperscript{41} we believe that the higher chance of CSF-leakage during repeated TS should not be a reason to refrain from repeated TS.

The chance of hypopituitarism after repeated TS is higher than after the first TS. Reported percentages of hormonal deficiencies in patients with CD after the first TS vary from 2% to 48%, but are mostly around 20%. Ram \textit{et al.}\textsuperscript{2} and Friedman \textit{et al.}\textsuperscript{29} reported rates of hormonal deficiencies after repeated TS in 41% and 50% of the patients. Locatelli \textit{et al.} found an extremely high rate of hormonal deficiencies (100%), but all patients underwent a total hypophysectomy.\textsuperscript{22} Hofmann \textit{et al.}\textsuperscript{24} and Knappe \textit{et al.}\textsuperscript{21} report on new hormonal deficiencies in 0% and 8%. In the present series the percentage of patients with hormonal deficiencies was 78% after the second TS, with six patients having only one hormonal deficiency. The rate of hormonal deficiencies was 48% in our earlier study on results of first endoscopic TS in patients with CD.\textsuperscript{3} The higher rates of hypopituitarism after repeated TS compared to after the first TS can be expected because additional pituitary tissue is removed. Even so, the risk of hypopituitarism after second TS seems to be lower than reported rates of hypopituitarism several years after radiotherapy.\textsuperscript{9,11}

The success rate of repeated TS for persistent or recurrent CD depends on the correct selection of patients. In our opinion TS is a good treatment option if there is a reasonable chance that it will be successful. CD can be controlled instantly with the possibility to normalize cortisol circadian rhythm and keep the pituitary adrenal axis intact. Radiotherapy, however, is a good option if an adenoma is invasive.

Success rates of TS also critically depend on the skills and the experience of the neurosurgeons.\textsuperscript{42} Repeated TS is an even more difficult procedure than a first TS and repeated TS is infrequently performed. Thus it is advised to concentrate repeated TS for CD in a limited number of specialized centres.

In conclusion, repeated transsphenoidal pituitary surgery (TS) is a good therapeutic option for selected patients with persistent or recurrent Cushing’s disease (CD), with the potential to achieve remission in the majority of patients. The remission rate of 71% we achieved via the endoscopic technique of repeated TS compares favourably with the remission rate of repeated TS via the conventional microscopic technique previously described in the literature. The excellent view of the surgical field during endoscopic TS provides an advantage in case of altered anatomy due to previous surgery. However, only a randomized trial can definitively assess whether the endoscopic or the microscopic technique of TS is the preferred technique for repeated surgery in patients with persistent or recurrent CD.

\textbf{References}