Long-term remission and recurrence rates after first and second transsphenoidal surgery for Cushing’s disease: care reality in the Munich Metropolitan Region

C Dimopoulou1,2, J Schopohl2, W Rachinger3, M Buchfelder4, J Honegger5, M Reincke2,* and G K Stalla1,*

1Department of Endocrinology, Max Planck Institute of Psychiatry, Kraepelinstrasse 2-10, 80804 Munich, Germany, 2Medizinische Klinik und Poliklinik IV, Ludwig-Maximilians-University, Munich, Germany, 3Department of Neurosurgery, Klinikum Grosshadern, University of Munich, Munich, Germany, 4Department of Neurosurgery, University of Erlangen-Nürnberg, Erlangen, Germany and 5Department of Neurosurgery, University of Tuebingen, Tuebingen, Germany

*(M Reincke and G K Stalla contributed equally to this work)

Correspondence should be addressed to C Dimopoulou

Email dimopoulou@mpipsykl.mpg.de

Abstract

Objective: Transsphenoidal surgery (TSS) presents the treatment of choice for Cushing’s disease (CD). Remission and recurrence rates vary dependent on tumor size, extension, adenoma visibility on magnetic resonance imaging, and neurosurgical expertise. Other than published from single-surgeon neurosurgical series so far, we have aimed to describe long-term remission and recurrence rates of CD in a series incorporating different neurosurgeons, trying to reflect care reality in the Munich Metropolitan Region, which is accommodated by three tertiary university and multiple, smaller neurosurgical centers.

Design: We conducted a retrospective analysis of 120 patients who underwent first and 36 patients who underwent second TSS as treatment for CD between 1990 and 2012.

Methods: Patients were divided into three groups according to remission status. Potential risk factors for recurrence, pituitary function, and strategy in persistent disease were assessed.

Results: Three outcome groups were identified according to remission status after first TSS (mean follow-up 79 months): remission, 71% (85/120), disease persistence, 29% (35/120), and disease recurrence, 34% (29/85) (mean time to recurrence 54 months). After second TSS (n = 36, mean follow-up 62 months), we documented remission in 42% (15/36), disease persistence in 58% (21/36), and disease recurrence in 40% (6/15) (mean time to recurrence 42 months). Postoperative hypocortisolism after first, though not after second, TSS was associated with a lower risk of suffering disease recurrence (risk = 0.72; 95% CI 0.60–0.88; exact significance (two-sided) P = 0.035).

Conclusions: Our study shows higher recurrence rates of CD after first TSS than previously reported. Second TSS leads an additional 8% of the patients to long-term CD remission.

Introduction

Cushing’s disease (CD), caused by an adrenocorticotropin (ACTH)-secreting pituitary adenoma, is a rare condition associated with increased morbidity and mortality (1, 2). According to the present treatment algorithm, transsphenoidal surgery (TSS) presents the treatment of choice for CD (3). Dependent on tumor size and extension, adenoma
visibility on preoperative magnetic resonance imaging (MRI), and neurosurgical expertise, remission rates after first TSS range from 70 to 90% (4, 5, 6, 7). Remission rates in patients having macroadenomas are lower (8, 9). Despite successful first TSS, the 10-year recurrence rates of CD range between 20 and 25% (mean time to relapse 49 months) (4); microscopic remnants of the corticotroph adenoma are suggested to be involved in CD persistence or recurrence (10). In that case, further therapeutic options comprise second TSS leading only 50–70% of patients to remission (11), radiotherapy, medical therapy, and bilateral adrenalectomy.

Main characteristics and outcomes of previous, single-surgeon studies on remission and recurrence rates after TSS for CD are presented in Table 1.

The aim of our study was to analyze long-term remission and recurrence rates of CD after first ($n = 120$) and second TSS ($n = 36$) in the Munich Metropolitan Region (3.27 million, population as by ESPON 2007), which is accommodated by three major tertiary university neurosurgical centers and multiple, smaller neurosurgical centers, reflecting care reality in this region. We hypothesized that remission rates might be lower and recurrence rates might be higher in our series incorporating different neurosurgeons, when compared with remission and recurrence rates published from single-surgeon expert neurosurgical series. Moreover, we focused on the role of second TSS in the current therapeutic regimen for CD, attempted a correlation between postoperative hypocortisolism and risk of recurrence and described our therapeutic strategy in patients with persistent disease after TSS.

### Subjects and methods

#### Patients

We report on a series of 120 CD patients: 53 treated at the Department of Endocrinology, Max Planck Institute of Psychiatry, Munich and 67 treated at the Medizinische Klinik und Poliklinik IV, Ludwig-Maximilians-University, Munich, both cooperating partners of the Network of Excellence for Neuroendocrine Tumors Munich (NeoExNET). All patients underwent TSS as initial treatment for CD between 1990 and 2012 and had a documented follow-up of at least 6 months. Medical records were analyzed to obtain demographic data, laboratory values, tumor characteristics, comorbidities, previous and current therapy, therapy outcome, pituitary function, and duration of postoperative hypocortisolism. Baseline characteristics of the study population are presented in Table 2.

### Table 1

Main characteristics and outcomes of previous, single-surgeon studies on remission and recurrence rates after transsphenoidal surgery for Cushing’s disease. All studies included 50 or more patients and were published since 2000.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Number of patients</th>
<th>Follow-up (in months)</th>
<th>Overall remission rate (% patients)</th>
<th>Recurrence rate (% patients)</th>
<th>Time to relapse (mean/median in months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(22)</td>
<td>2001</td>
<td>61</td>
<td>88</td>
<td>79</td>
<td>15</td>
<td>76</td>
</tr>
<tr>
<td>(36)</td>
<td>2001</td>
<td>300</td>
<td>NA</td>
<td>70</td>
<td>15</td>
<td>70</td>
</tr>
<tr>
<td>(32)</td>
<td>2002</td>
<td>89</td>
<td>92</td>
<td>69</td>
<td>11</td>
<td>36</td>
</tr>
<tr>
<td>(20)</td>
<td>2002</td>
<td>53</td>
<td>72</td>
<td>77</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>(37)</td>
<td>2003</td>
<td>174</td>
<td>60</td>
<td>82</td>
<td>14</td>
<td>28</td>
</tr>
<tr>
<td>(38)</td>
<td>2003</td>
<td>147</td>
<td>61</td>
<td>98</td>
<td>6</td>
<td>44</td>
</tr>
<tr>
<td>(39)</td>
<td>2003</td>
<td>78</td>
<td>86</td>
<td>72</td>
<td>9</td>
<td>84</td>
</tr>
<tr>
<td>(17)</td>
<td>2004</td>
<td>289</td>
<td>133</td>
<td>82</td>
<td>9</td>
<td>59</td>
</tr>
<tr>
<td>(40)</td>
<td>2006</td>
<td>100</td>
<td>19</td>
<td>75</td>
<td>5</td>
<td>NA</td>
</tr>
<tr>
<td>(41)</td>
<td>2007</td>
<td>103</td>
<td>72</td>
<td>85</td>
<td>7</td>
<td>44</td>
</tr>
<tr>
<td>(14)</td>
<td>2008</td>
<td>215</td>
<td>45</td>
<td>86</td>
<td>17</td>
<td>39</td>
</tr>
<tr>
<td>(5)</td>
<td>2008</td>
<td>426</td>
<td>72</td>
<td>69</td>
<td>15</td>
<td>73</td>
</tr>
<tr>
<td>(42)</td>
<td>2008</td>
<td>167</td>
<td>40</td>
<td>80</td>
<td>13</td>
<td>50</td>
</tr>
<tr>
<td>(6)</td>
<td>2009</td>
<td>261</td>
<td>84</td>
<td>92</td>
<td>2</td>
<td>56</td>
</tr>
<tr>
<td>(7)</td>
<td>2010</td>
<td>620</td>
<td>NA</td>
<td>71</td>
<td>13</td>
<td>66</td>
</tr>
<tr>
<td>(31)</td>
<td>2011</td>
<td>331</td>
<td>132</td>
<td>89</td>
<td>12</td>
<td>38</td>
</tr>
<tr>
<td>(34)</td>
<td>2012</td>
<td>80</td>
<td>55</td>
<td>72</td>
<td>11</td>
<td>25</td>
</tr>
<tr>
<td>(43)</td>
<td>2013</td>
<td>131</td>
<td>184</td>
<td>68</td>
<td>24</td>
<td>63</td>
</tr>
<tr>
<td>(2)</td>
<td>2013</td>
<td>346</td>
<td>76</td>
<td>89</td>
<td>21</td>
<td>70</td>
</tr>
<tr>
<td>This study</td>
<td>2013</td>
<td>120</td>
<td>79</td>
<td>71</td>
<td>34</td>
<td>54</td>
</tr>
</tbody>
</table>

NA, not applicable.
Initial testing for hypercortisolism was performed using one of the following tests: urine free cortisol (UFC; at least two measurements), late-night salivary cortisol (two measurements), or 1 mg overnight dexamethasone suppression test (DST) (low-dose DST, LDDST) (12). Criteria confirming hypercortisolism were UFC greater than the normal range for the assay, serum cortisol $0.5 \text{ mg/dl}$ after LDDST, and late-night salivary cortisol $0.145 \text{ ng/dl}$.

Once the diagnosis of hypercortisolism was established, subtype determination was performed in all patients by the measurement of plasma ACTH, 8 mg overnight DST (high-dose DST, HDDST), and a corticotropin-releasing hormone (CRH) stimulation test (100 $\mu$g human CRH i.v.) (13). As a cutoff for diagnosis of CD, we used plasma ACTH values $> 20 \text{ pg/ml}$, a 35% increase in plasma ACTH and a 20% increase in serum cortisol during the CRH stimulation test and/or a more than 50% suppression of cortisol during HDDST (13). Additional inferior petrosal sinus sampling (IPSS) was recommended in all cases of no visible adenoma on preoperative MRI ($n \geq 30$); out of these, 25 patients (21%) received IPSS and five patients rejected it. Pituitary origin of hypercortisolism was confirmed in all the patients who received IPSS ($n = 25$).

Preoperative imaging

Preoperative imaging included thin-section MRI (2 mm) of the pituitary comprising dynamic sequences. Radiological findings – interpreted both by radiologists and neurosurgeons in all centers – were divided into three groups: i) diagnosis of a clearly visible microadenoma ($\leq 10 \text{ mm}$); ii) diagnosis of a macroadenoma ($> 10 \text{ mm}$); and iii) no visible adenoma.

Neurosurgical centers, surgical technique, and histopathological findings

The Munich Metropolitan Region is accommodated by three major tertiary university referral centers for neurosurgery: Klinikum Grosshadern, Munich (operator W. R), University of Erlangen-Nürnberg (operator M. B), and University of Tuebingen (operator J. H) (number of pituitary surgeries per surgeon/year and total number of pituitary surgeries at center are presented in Table 3).

Biochemical criteria for CD

Initial testing for hypercortisolism was performed using one of the following tests: urine free cortisol (UFC; at least two measurements), late-night salivary cortisol (two measurements), or 1 mg overnight dexamethasone suppression test (DST) (low-dose DST, LDDST) (12). Criteria confirming hypercortisolism were UFC greater than the normal range for the assay, serum cortisol $> 5 \mu\text{g/dl}$ after LDDST, and late-night salivary cortisol $> 145 \text{ ng/dl}$.

Table 3 Neurosurgical centers where first and second TSS were performed.

<table>
<thead>
<tr>
<th>Center</th>
<th>First TSS $(n = 120)$</th>
<th>Second TSS $(n = 36)$</th>
<th>Number of pituitary surgeries per surgeon/year</th>
<th>Total number of pituitary surgeries at center (single surgeon)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klinikum Grosshadern, Munich</td>
<td>46 (38%)</td>
<td>8 (22%)</td>
<td>80–90</td>
<td>850</td>
</tr>
<tr>
<td>University of Erlangen-</td>
<td>19 (16%)</td>
<td>10 (28%)</td>
<td>250–300$^a$</td>
<td>2000</td>
</tr>
<tr>
<td>Nürnberg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University of Tuebingen</td>
<td>12 (10%)</td>
<td>2 (6%)</td>
<td>100</td>
<td>1100</td>
</tr>
<tr>
<td>Other centers</td>
<td>43 (36%)</td>
<td>16 (44%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$Number of pituitary surgeries per surgeon/year in University of Erlangen-Nürnberg since 2005.
The majority of the study population underwent TSS in one of the above-mentioned neurosurgical centers (first TSS: 77/120, 64%; second TSS: 20/36, 56%). Forty-three of 120 (36%) and 16 of 36 patients (44%) underwent first and second TSS, respectively, in a smaller neurosurgical center (Table 3).

All patients underwent surgery by microscopic transsphenoidal approach.

Pathology reports of the surgically excised specimens were available for the patients operated upon in a tertiary university referral center. Comparable with the literature (14), an ACTH-staining adenoma was confirmed in 75.3 and 75% of patients after first and second TSS respectively. In the remaining cases, no abnormality (= normal pituitary tissue) could be detected.

Postoperative biochemical evaluation

Postoperatively, patients were administered hydrocortisone only after adrenal insufficiency was confirmed (serum cortisol <5 μg/dl). The first outpatient postoperative evaluation was performed 4–6 weeks after TSS. Patients were seen in clinic, off hydrocortisone replacement for 2 days, and serum cortisol levels were measured. In case of postoperative hypocortisolism (serum cortisol <5 μg/dl), hydrocortisone supplementation was resumed. Duration of postoperative hypocortisolism was confirmed by repeated serum cortisol measurements. Other patients underwent a one-sample UFC or a LDDST to establish remission status. Remission was defined as 24-h UFC values below or within normal range for the assay used or serum cortisol below 5 μg/dl during a LDDST. Persistent disease or disease recurrence after remission was defined as an elevated 24-h UFC above the upper limit of the range for the assay used or a lack of cortisol suppression below 5 μg/dl during LDDST with clinical symptoms consistent with CD. Perioperative management including timing of hydrocortisone initiation postoperatively and hydrocortisone withdrawal 2 days before assessment of hypocortisolism was similar over all participating centers. Evaluation of further pituitary axes comprised basal fasting measurements of insulin-like growth factor 1 (IGF1), thyrotropin (TSH), free thyroxine, total triiodothyronine, luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, and testosterone (in men) or estradiol (in women) in all patients (15). In case of low serum IGF1, diagnosis of growth hormone deficiency was established by dynamic testing via the insulin tolerance test (ITT) or the growth hormone-releasing hormone-arginine test (16).

Final follow-up was defined as the last patient’s contact with the endocrinological referral center including patients after first and/or second TSS, radiation therapy, bilateral adrenalectomy, and medical therapy.

Statistical analysis

Statistical analysis was performed using PASW Statistics Version 18 for Windows. Data for descriptive statistics including mean age, mean follow-up time, and mean time to recurrence are presented as mean ± S.D. (range). Kaplan–Meier analysis for recurrence was performed using the product-limit method. Differences in recurrence rates between patient groups (positive preoperative MRI vs negative MRI; patients who underwent surgery in different university referral centers, patients with postoperative hypocortisolism vs patients with postoperative eucortisolism) were assessed using χ² analysis. A P value of <0.05 was considered statistically significant.

Results

First TSS

Remission rates ► The overall remission rate following primary surgery was 71% (n = 120). In the microadenoma group (n = 58), a remission rate of 79% was achieved; in the macroadenoma group (n = 32), remission rate after first TSS was 69%. In cases of no visible adenoma (n = 30), remission rate was 57% (Table 4).

Recurrence rates ► Mean follow-up after first TSS was 79±67 (range 252) months. Overall recurrence rate after successful first TSS was 34% (22% of patients with microadenoma, 59% of patients with macroadenoma, and 35% of patients with no visible adenoma; P = 0.007). The time to recurrence after first TSS ranged from 5 to 205 months, with a mean of 54±54 months.

Second TSS

According to the current algorithm for the management of CD (4), second TSS was considered in all cases of persistent or recurrent CD after first TSS (n = 64). Reasons for not performing second TSS (n = 28) included patients with ACTH-secreting macroadenomas with tumor invasion into the cavernous sinus or sphenoid (n = 8), who might not benefit from a second TSS, patients’ unwillingness to undergo second TSS (n = 12), and other contraindications to surgery (n = 8).
Remission rates

Thirty-six of 120 CD patients (30%) underwent second TSS. Second TSS was carried out by the same surgeon, in the same neurosurgical center where first TSS took place in 64% (23/36), suggesting patients’ satisfaction. After second TSS, overall remission rate of CD was 42% (36% of patients with microadenoma, 29% of patients with macroadenoma, and 75% of patients with no visible adenoma).

Recurrence rates

Mean follow-up after second TSS was 62 ± 54 (range 18–7 months). Overall recurrence rate after successful second TSS was 40% (40% of patients with microadenoma, 75% of patients with macroadenoma, and 17% of patients with no visible adenoma). The time to recurrence after second TSS was shorter (mean 27 ± 29, range 3–76 months). Kaplan–Meier analysis of CD recurrence after successful first and/or second TSS is shown in Fig. 1.

No adenoma visibility on preoperative MRI

In this analysis, 30 patients with no visible tumor on preoperative MRI underwent first TSS; a pituitary adenoma could be detected during surgery in 16/30 cases (53%). In the remaining cases (n=14), a systematic dissection of the pituitary gland was performed; only one patient received total hypophysectomy. Regarding second TSS, of the eight patients with no visible tumor preoperatively, a pituitary adenoma was visualised during surgery in 2/8 cases (25%). A systematic dissection of the pituitary gland was performed in the remaining six patients; one patient received a hemi-hypophysectomy.

Hemi-hypophysectomy was performed on the side on which an adenoma was most likely suspected or on the side with a suspicious area on MRI. If IPSS was available, then hemi-hypophysectomy would be performed on the side with greater ACTH values. Remission rates after first and second TSS when definite tumor was not found during surgery were 50 and 100% respectively.

Role of neurosurgical center, cavernous sinus invasion, and IPSS

Analysis of outcomes at each participating center showed that remission and recurrence rates after first and after second TSS were not significantly different (Table 5). There were no significant differences in remission and recurrence rates between tumors with and without cavernous sinus invasion (CSI) neither after first (P=0.237 and P=0.846 respectively) nor after second TSS (P=0.335 and P=0.306 respectively).

There were no significant differences in remission and recurrence rates after first and second TSS and at the final follow-up between the group of patients who received IPSS (n=25) and those who did not.

Postoperative hypocortisolism and risk of recurrence

Diagnosis of postoperative hypocortisolism was based in all patients on biochemical testing while in hospital (serum cortisol < 5 μg/dl).

First TSS

After first TSS, 65/120 CD patients (54%) were presented with postoperative hypocortisolism (64% in the...
microadenoma group, 47% in the macroadenoma group, and 43% in the group of no visible adenoma) (mean duration 45 ± 60, range 252 months). Patients who had postoperative hypocortisolism after first TSS were 0.7 times less likely to suffer disease recurrence than patients with postoperative eucortisolism (risk = 0.72; 95% CI 0.60–0.88; exact significance (two-sided) P = 0.035). Longer duration of postoperative hypocortisolism did not prevent CD recurrence (48 ± 64 vs 32 ± 22 months; P = 0.186).

Second TSS ▶ After second TSS, overall frequency of postoperative hypocortisolism was 33% (12/36 patients) (36% in the microadenoma group, 29% in the macroadenoma group, and 63% in the group of no visible adenoma) (mean duration 15 ± 16, range 56 months). Neither the presence of postoperative hypocortisolism after second TSS (risk = 0.83; 95% CI 0.25–2.73; exact significance (two-sided) P = 1.000), nor its longer duration (17 ± 17 vs 5 months; P = 0.55) prevented patients from disease recurrence.

Strategy in patients with persistent disease after first and/or after second TSS

Strategy in patients with persistent disease after first and/or after second TSS is shown in Fig. 2a and b. Overall incidence of Nelson’s syndrome in our series was 23% (five of 22 bilaterally adrenalectomized patients).

Final follow-up

Remission rates ▶ Of the 120 CD patients included in this analysis, 92% were in remission at final follow-up (100% in the group of no visible adenoma, 97% in the microadenoma, and 75% in the macroadenoma group). Overall, 8% of the CD patients suffered from disease persistence at final follow-up (Table 4). Nine patients were lost to follow-up (n = 8 after first TSS, n = 1 after second TSS).

Pituitary function ▶ At final follow-up, 81 of 120 (68%) patients presented with deficiency of at least one pituitary hormone, with ACTH being affected in the majority of cases with 51% (isolated ACTH deficiency in 29%). Frequencies of LH/FSH, TSH, and GH deficiencies accounted for 29, 22, and 22% respectively. Posterior pituitary deficiency was less frequent with 8%.

Table 5 Remission rates, disease persistence, and recurrence rates after first and second TSS according to neurosurgical center. Comparisons between groups were calculated using χ² analysis.

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Klinikum Grosshadern Munich</th>
<th>University of Erlangen-Nürnberg</th>
<th>University of Tuebingen</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First TSS</td>
<td>n = 77</td>
<td>n = 46</td>
<td>n = 19</td>
<td>n = 12</td>
<td>0.409</td>
</tr>
<tr>
<td>Remission</td>
<td>56 (72%)</td>
<td>35 (76%)</td>
<td>12 (63%)</td>
<td>9 (75%)</td>
<td>0.557</td>
</tr>
<tr>
<td>Disease persistence</td>
<td>21 (28%)</td>
<td>11 (24%)</td>
<td>7 (37%)</td>
<td>3 (25%)</td>
<td>0.061</td>
</tr>
<tr>
<td>Recurrence</td>
<td>13/56 (23%)</td>
<td>12/35 (34%)</td>
<td>1/12 (8%)</td>
<td>0/9 (0%)</td>
<td></td>
</tr>
<tr>
<td>Second TSS</td>
<td>n = 20</td>
<td>n = 8</td>
<td>n = 10</td>
<td>n = 2</td>
<td></td>
</tr>
<tr>
<td>Remission</td>
<td>8 (40%)</td>
<td>3 (38%)</td>
<td>4 (40%)</td>
<td>1 (50%)</td>
<td>0.949</td>
</tr>
<tr>
<td>Disease persistence</td>
<td>12 (60%)</td>
<td>5 (62%)</td>
<td>6 (60%)</td>
<td>1 (50%)</td>
<td>0.949</td>
</tr>
<tr>
<td>Recurrence</td>
<td>2/8 (25%)</td>
<td>1/3 (33%)</td>
<td>1/4 (25%)</td>
<td>0/1 (0%)</td>
<td>0.870</td>
</tr>
</tbody>
</table>
First TSS

Remission rates following TSS for CD vary between 69 and 98%, as reported since 1995 (mean follow-up 65 months) (4). Several factors including tumor size and extension, adenoma visibility on preoperative MRI, during the operation or in pathology as well as neurosurgical expertise have been suggested to influence pituitary surgery outcome (8, 17, 18, 19, 20, 21, 22, 23). Here, we report an overall remission rate of 71% after first TSS comparing favorably with the literature, against our study hypothesis.

Remission rates in macroadenomas are reported to be lower, possibly mediated by CSI and maximum tumor diameter (8, 9, 24). Our results were again in accordance with published series, as patients with macroadenomas experienced after first TSS lower remission rates compared with those with microadenomas (69 vs 79%). Of course, we have to concede that our cohort harbored a high prevalence of macroadenomas (27%) when compared with other series (20, 21, 25); this might be due to the fact that our endocrinology departments serve as referral centers for difficult, complicated cases.

Lack of consensus regarding remission criteria of CD has led to a broad range of recurrence rates reported (25). A comprehensive review of large clinical studies reveals a recurrence rate of 20–25% 10 years after surgery (4). It is well established that the longer the period of follow-up, the higher the incidence of recurrence (short-term recurrence rates 0–13%, long-term recurrence rates of 5–27%) (26, 27, 28, 29). In our study, we documented an overall recurrence rate of CD of 34% after first TSS, which falls at the higher end of the published range so far, supporting our study hypothesis. This might be partially attributable to the high proportion of macroadenomas in our series and to our long follow-up period in excess of 6 years.

Second TSS

Second TSS should be considered in patients with refractory or recurrent CD. In the literature, remission rates after second TSS are lower than after first TSS, leading only 50–70% of patients to remission (11, 30). In our series, about one-third of the patients received second TSS, leading to a low remission rate of 42% and confirming the study hypothesis. We have to take into account that here we report not on a single-, but on a multiple-surgeon series involving different neurosurgical skills and reflecting care reality in the Munich Metropolitan Region. Besides, our series harbored one-quarter of macroadenoma patients, our follow-up period was long (>5 years), and our departments serve as referral centers for complicated cases, all factors of potential negative impact on surgical outcome (3).

Interestingly, after second TSS: i) there were no significant differences in remission rates between patients with macroadenomas compared with those with microadenomas (29 vs 36%; P=0.124); ii) unlike a number of studies published so far (20, 21), patients with no visible...
tumor on preoperative MRI seemed to benefit from the more radical procedure, e.g. hemi-hypophysectomy performed at second TSS showing a paradox high remission rate of 75%; iii) overall CD recurrence rate after second TSS was similar to that after first TSS (40 vs 34%), recurrence occurred though sooner (42 vs 54 months); and iv) total long-term CD remission after second TSS was 54.2% (65/120 patients), meaning that performance of second TSS led an additional 9/120 patients to disease remission (long-term CD remission after first TSS 46.7%, 56/120 patients).

Although CSI has been reported in the literature to be the most important unfavorable preoperative factor affecting operative results in CD, in our series, we could not detect any significant differences in remission and recurrence rates between tumors with and without CSI neither after first nor after second TSS. As we do not question the significance of CSI regarding surgical results, we rather believe that this finding might be explained by our small sample size with CSI (11%).

Final follow-up

In our series, overall remission rate of 92% at final follow-up compared favorably with the literature, against our study hypothesis. Of course, we have to take into account that final follow-up in our series was defined as the last patient contact with the endocrinological referral center, including patients after first and/or second TSS, radiation therapy, bilateral adrenalectomy, and medical therapy. Nine patients were lost to final follow-up.

Postoperative hypocortisolism and risk of recurrence

Factors that have been associated with low risk of CD recurrence comprise undetectable or low serum level of cortisol in the early morning, low plasma levels of ACTH, and prolonged (>1 year) requirement for glucocorticoid replacement after pituitary surgery and have been thoroughly discussed in the literature (31). Patil et al (14) demonstrated that patients who had postoperative serum cortisol of >2 μg/dl were 2.5 times more likely to have a recurrence than patients with a serum cortisol of ≤2 μg/dl within 72 h after surgery; however, undetectable postoperative cortisol does not always predict long-term remission of CD (32). In our series, presence of postoperative hypocortisolism after first, though not after second, TSS was associated with a lower risk of CD recurrence; duration of postoperative hypocortisolism did not seem to prevent from disease recurrence.

Strategy in patients with persistent disease after second TSS

Alternative second line therapies for CD comprise radiotherapy, medical therapy, and bilateral adrenalectomy. In our series, second line therapies for CD led 17/27 of active patients to remission; management of therapy-refractory CD in the remaining 10/27 patients might be challenging, incorporating new medical therapies with improved efficacy. Incidence of Nelson’s syndrome in our series (23%) was comparable with published rates in the literature (23–47%) (33).

Pituitary function

In our series, frequencies of hypopituitarism of any degree (68%), ACTH (51%) (isolated ACTH deficiency 29%), and LH/FSH deficiencies (29%) at final follow-up were compared favorably with those reported in previous large studies (34, 35). Interestingly, our rates of TSH (22%) and GH (22%) deficiencies are rather lower than those described so far (20, 34, 35), possibly in part mediated by longer follow-up time accompanied by normal thyrotropic or somatotropic axis function recovery.

Conclusion

In our series incorporating different neurosurgeons, remission rates after first TSS were comparable with available literature, whereas recurrence rates both after first and second TSS fell at the higher end of the published single-surgeon series so far, supporting our study hypothesis. Second TSS leads an additional 8% of the patients to long-term CD remission. The presence of postoperative hypocortisolism after first TSS, though not its duration, was associated with a lower risk of CD recurrence. Hypopituitarism of any degree persisted in a subset of patients at final follow-up.

In summary, our results confirm the necessity of long-term, lifelong follow-up in patients with initially successfully treated CD, enlightening the role of second TSS in the current treatment algorithm and reflecting long-term care reality in the Munich Metropolitan Region from the endocrinologist’s point of view.

Declaration of interest

C Dimopoulou received lecture fees from Pfizer Pharma GmbH and Novartis Pharma GmbH. J Schopohl received lecture fees from Pfizer Pharma GmbH, Ipsen International GmbH and Novartis Pharma GmbH. W Rachinger has
nothing to disclose. M Buchfelder received travel grants and fees for invited lectures from Pfizer Pharma GmbH. J Honegger received lecture fees from Pfizer Pharma GmbH and Novartis Pharma GmbH. M Reincke received lecture fees from Pfizer Pharma GmbH, Ipsen International GmbH, and Novartis Pharma GmbH. In addition, M Reincke received financial support from Novartis Pharma GmbH for a clinical trial. G K Stallar received lecture fees from Pfizer Pharma GmbH, Novo Nordisk Pharma GmbH, Ipsen International GmbH, and Novartis Pharma GmbH.

Funding
NeoExNET (Network of Excellence for Neuroendocrine Tumors in Munich) is a national database for the evaluation of diagnostics, treatment and outcome in neuroendocrine tumors. NeoExNET is supported by the German Federal Ministry of Education and Research (BMBF; 04MUR02); by an unrestricted educational grant of Novartis Pharma GmbH, Nürnberg, Germany. Members of the NeoExNET – Study group include: Principal investigator: G K Stalla (Max Planck Institute of Psychiatry, Munich). Steering Committee: Felix Beuschlein (Ludwig Maximilian University, Munich), Christoph Auernhammer (Ludwig Maximilian University, Munich), Klaus A Kuhn (Technische Universität München, Munich). This project was partly funded by an Else Kröner-Fresenius grant (2012_A103).

Acknowledgements
The authors thank Caroline Sievers and Marcus Ising for valuable statistical advice, Marily Theodoropoulou for help with artwork, and Stefanie Held, Ferengis Knerr, Sylvia Lang, Anne Mickisch, and Andrea Osswald for helping to process the patient data.

References


**Received 1 August 2013**

**Revised version received 25 October 2013**

**Accepted 11 November 2013**