THERAPY OF ENDOCRINE DISEASE

Outcomes in patients with Cushing's disease undergoing transsphenoidal surgery: systematic review assessing criteria used to define remission and recurrence

Stephan Petersenn, Albert Beckers¹, Diego Ferone², Aart van der Lely³, Jens Bollerslev⁴, Marco Boscaro⁵, Thierry Brue^{6,7}, Paolo Bruzzi⁸, Felipe F Casanueva⁹, Philippe Chanson^{10,11,12}, Annamaria Colao¹³, Martin Reincke¹⁴, Günter Stalla¹⁵ and Stelios Tsagarakis¹⁶

ENDOC Center for Endocrine Tumors, Altonaer Strasse 59, 20357 Hamburg, Germany, ¹Department of Endocrinology, CHU de Liège, Domaine Universitaire du Sart-Tilman, 4000 Liège, Belgium, ²Endocrinology Unit, Department of Internal Medicine and Medical Specialties (DiMI), Center of Excellence for Biomedical Research, IRCCS AOU San Martino–IST, University of Genova, Genova, Italy, ³Department of Medicine, Erasmus University MC, PO Box 2040, 3000 CA Rotterdam, The Netherlands, ⁴Section of Specialized Endocrinology, Faculty of Medicine, Oslo University Hospital, University of Oslo, Oslo, Norway, ⁵Division of Endocrinology, Department of Medicine (DIMED), University of Padua, Padua, Italy, ⁶Aix-Marseille Université, CNRS, CRN2M UMR 7286, 13344 Marseille Cedex 15, France, ⁷APHM, Hôpital Timone, Service d'Endocrinologie, Diabète et Maladies Métaboliques, 13385 Marseille Cedex 15, France, ⁸Department of Epidemiology and Prevention, IRCCS AOU San Martino–IST, Genova, Italy, ⁹Santiago de Compostela University and CIBERObn, Santiago de Compostela, Spain, ¹⁰Univ Paris-Sud, Faculté de Médecine Paris-Sud, UMR-S1185, Le Kremlin Bicêtre, F-94276, France, ¹¹Assistance Publique–Hôpitaux de Paris, Hôpitaux Universitaires Paris-Sud, Hôpital de Bicêtre, Service d'Endocrinologie et des Maladies de la Reproduction, Le Kremlin Bicêtre, F-94275, France, ¹²Institut National de la Santé et de la Recherche Médicale U1185, Le Kremlin Bicêtre, F-94276, France, ¹³Dipartimento di Medicina Clinica e Chirurgia, Sezione di Endocrinologia, Università Federico II di Napoli, Naples, Italy, ¹⁴Medizinische Klinik und Poliklinik IV–Innenstadt, University Hospital Munich, D-80336 Munich, Germany, ¹⁵Department of Endocrinology, Max Planck Institute of Psychiatry, Munich, Germany and ¹⁶Department of Endocrinology, Diabetes and Metabolism, Evangelismos Hospital, Athens, Greece

Correspondence should be addressed to S Petersenn
Email
 stephan.petersenn@endoc-med.de

Abstract

Objective: A number of factors can influence the reported outcomes of transsphenoidal surgery (TSS) for Cushing's disease – including different remission and recurrence criteria, for which there is no consensus. Therefore, a comparative analysis of the best treatment options and patient management strategies is difficult. In this review, we investigated the clinical outcomes of initial TSS in patients with Cushing's disease based on definitions of and assessments for remission and recurrence.

Methods: We systematically searched PubMed and identified 44 studies with clear definitions of remission and recurrence. When data were available, additional analyses by time of remission, tumor size, duration of follow-up, surgical experience, year of study publication and adverse events related to surgery were performed.

Results: Data from a total of 6400 patients who received microscopic TSS were extracted and analyzed. A variety of definitions of remission and recurrence of Cushing's disease after initial microscopic TSS was used, giving broad ranges of remission (42.0–96.6%; median, 77.9%) and recurrence (0–47.4%; median, 11.5%). Better remission and recurrence outcomes were achieved for microadenomas vs macroadenomas; however, no correlations were found with other parameters, other than improved safety with longer surgical experience.

Conclusions: The variety of methodologies used in clinical evaluation of TSS for Cushing's disease strongly support the call for standardization and optimization of studies to inform clinical practice and maximize patient outcomes. Clinically significant rates of failure of initial TSS highlight the need for effective second-line treatments.

*European Journal of
Endocrinology*
(2015) 172, R227–R239

Introduction

Cushing's disease is the consequence of chronic hypercortisolism caused by an adrenocorticotrophic hormone (ACTH)-secreting pituitary corticotroph adenoma (1), and is the most common cause of endogenous Cushing's syndrome. As such, Cushing's disease accounts for 70% of cases of Cushing's syndrome (2), with an annual incidence estimated at 1.2–1.7/million, and a prevalence of 39–940/million (3, 4, 5). The clinical consequences of Cushing's disease are severe (6, 7). An increased cardiovascular risk and metabolic syndrome have been associated with Cushing's disease; this increased cardiovascular risk may already manifest in early-stage disease, before clinical symptoms become apparent (8, 9, 10). In addition, residual increased risk of cardiovascular events has been also reported in patients who have achieved disease control (11). Furthermore, Cushing's disease is associated with excess mortality, reported to be double that of the general population; however, the mortality rate in patients with Cushing's disease who are in remission following treatment tends to be lower than in those who are not in remission (12).

Treatment of Cushing's disease aims to provide remission of disease and long-term control without recurrence (6). The first-line therapy for Cushing's disease is transsphenoidal surgery (TSS) to remove the tumor (6); microscopic TSS (the conventional intervention) or endoscopic TSS may be used. However, remission and recurrence rates after initial TSS in patients with Cushing's disease have been reported to vary greatly (13), while high remission rates have been reported for endoscopic TSS (14).

A number of factors may influence TSS outcomes, including size of the adenoma, dural invasion, localization on pre-operative imaging, intra-operative tumor visualization, pre-operative ACTH level, urinary free cortisol (UFC) levels, and histological confirmation of corticotroph adenomas. Higher remission rates are generally reported in patients with discrete, easily operated tumors,

with improved outcomes achieved with microadenomas vs macroadenomas (6, 13, 15, 16, 17, 18) and with adenomas identified at surgery or by radiology or histopathology vs no adenomas identified (19, 20). Other factors suggested to increase the success of initial TSS include extensive surgical experience and younger patient age (<25 years) (6). However, even in the most favorable circumstances, 5- and 10-year recurrence rates after initial TSS are up to 10 and 20% respectively (6). In cases in which initial TSS has failed, repeat surgery, radiotherapy, bilateral adrenalectomy, and increasingly medical therapy are options (6).

Although hypocortisolism after TSS has been shown to be a reliable prognostic factor for success of surgery (21, 22, 23), indicating remission and a lower risk of recurrence, there is currently no consensus on predictors of these outcomes. The broad range of remission and recurrence rates reported in the literature may be due to different remission and recurrence criteria used in the studies. In addition, as there is no agreement on the definitions of these outcomes, the comparative evaluation of treatment options and patient management strategies from clinical studies is rather complicated. Remission can be defined by clinical and/or biochemical outcomes, including the reversal of clinical features and normalization of biochemical changes. Although several biochemical tests are widely used for the initial diagnosis of Cushing's disease, none is fully able to distinguish all cases in normal and/or obese individuals (24). While morning serum cortisol and UFC tests may be recommended to assess remission (6), there is no general agreement on their standard use in providing markers of treatment outcomes, further complicating patient management.

We conducted a systematic review of the literature to investigate clinical outcomes in patients with Cushing's disease undergoing initial microscopic TSS, with a focus on the influence of definitions and assessments of remission and recurrence.

Subjects and methods

An initial PubMed search was conducted to identify published articles reporting studies of TSS in patients with Cushing's disease using the following keywords: 'transsphenoidal AND surgery AND Cushing's AND disease'. There were no restrictions on publication period or language, and review articles identified in the initial search were examined for additional references not identified in PubMed. The literature search was stopped in November 2012.

Studies identified in the initial search were then screened for inclusion in the systematic review. To select the most robust studies, we included those conducted in at least 40 adult patients that reported the results of initial TSS (regardless of the technique used, i.e., microscopy or endoscopy) and were published in English. Studies identified in the initial search as conducted in patients undergoing repeat TSS (i.e. after failure of initial surgery) were excluded.

Data collection

For the quantitative synthesis, data were extracted from the studies using only microscopic TSS; data extraction was performed independently (Agnieszka Rarok and Sandrine Buisson, see 'Acknowledgements' section). The principal summary measures used for the quantitative synthesis were biochemical, clinical, and both biochemical and clinical definitions of remission and recurrence, as used in the studies included in the systematic review. For the biochemical definitions, these included measures of serum cortisol level (morning and midnight assessments), UFC, and response to low-dose dexamethasone suppression test (LDDST).

For the quantitative analysis, we extracted the percentage of patients in remission and the percentage of patients with recurrence from each study, and we report here the ranges of the remission and recurrence rates thus obtained. We then extracted and pooled the total number of patients included in the final analysis in each study, the numbers of patients in remission to calculate the overall remission rate, and the numbers of patients with recurrence to calculate the overall recurrence rate. If rates for both early and late remission or for multiple years were reported, then the initial remission rate was used in the overall analysis. Studies in which only remission rates by microadenoma and macroadenoma were reported were not included in the overall analysis, but were used in the analyses of outcome by tumor size

(see below). For both remission and recurrence, mean rates and associated 95% CIs are presented for comparison between the different types of biochemical assays used in the studies included in this analysis.

In order to provide more comprehensive information, additional data comparisons applying Wilcoxon's test were conducted as follows: time of remission, early (≤ 6 months) vs late (> 6 months) remission; size of tumor, microadenoma vs macroadenoma; duration of follow-up (categories from 0–12 to 169–180 months); surgical experience at operating center (number of patients operated per year; categories 0–5 to 31–35 patients/year) measured by number of patients in the study divided by study period (estimated number of years' study duration); and year of study publication (categories from 1980–1990 to 2011–19th October 2012). Possible correlations of interest were tested using linear regression methods and correlation analysis (Spearman), as appropriate.

Results

Literature search results

A total of 491 publications were identified in the initial search, of which 43 fulfilled the pre-selected inclusion criteria. Of these, 30 were published in endocrinology journals and 13 in journals focused on neurosurgery. [Figure 1](#) summarizes the studies identified, screened, and eligible for inclusion. Interestingly, only one publication reported outcomes of endoscopic TSS in patients with Cushing's disease. [Table 1](#) summarizes the studies included in the quantitative data synthesis and provides the key data extracted from all studies reporting the outcomes of microscopic TSS in patients with Cushing's disease. A total of 6400 patients were treated in these studies.

Remission rates

A variety of definitions of remission of Cushing's disease after initial microscopic TSS is used in the literature: symptoms of hypercortisolism remitted ([25](#)), a continuous need for corticosteroid replacement for > 6 months after TSS ([26](#)), no need for additional treatment because of clinical remission of the disease ([27](#)), resolution of symptoms and signs of hypercortisolism ([28](#)) or of clinical features ([16, 19](#)), clinical evidence of eucortisolemia ([23](#)), appearance of clinical signs of adrenal insufficiency ([29](#)), regression of the clinical signs ([30](#)), presence of clinical and laboratory signs of adrenal insufficiency ([17, 22](#)), and reversal of the clinical stigmata ([31](#)). Clinical parameters

Figure 1

Flow chart of studies included for literature analysis.

were never used alone to define remission; clinical evaluation was always combined with serum cortisol, UFC, and/or LDDST biochemical tests (Table 1). The most frequently used biochemical tests were serum cortisol and serum cortisol combined with UFC. When defined, serum cortisol levels were assessed only in the morning.

Where remission was defined using biochemical tests including morning cortisol levels, a variety of morning cortisol cut-off was used. Although these ranged from 50 to 275.9 nmol/l, the cut-off of 50 nmol/l was most consistently used when morning serum cortisol was measured without any other biochemical assay to define remission. Among the 18 studies using morning cortisol in definitions of remission, the cut-off was not stated in one study (25) and only a 'normal range' was used as the definition in another study (32). A positive correlation was observed between the morning cortisol cut-off values and remission rates, with higher remission rates reported with

less stringent cut-off values for morning cortisol ($r=1.0$, $P<0.05$; albeit data for cut-off values of 100, 220, and 275.9 nmol/l were each reported in only one study).

In total, 22 studies reported remission using biochemical assays only and 16 used a combination of clinical and biochemical endpoints (Table 1). Despite the variety of biochemical assays used, similar remission rates were reported across the studies. Remission rates of 77.0% were achieved for those using biochemical assays only (2014/2614 patients; range 52.1–96.6%) and 79.5% for those using a combination of clinical and biochemical endpoints (1428/1796 patients; range 65.0–88.6%). An overall remission rate of 78% was calculated (Fig. 2).

With regard to the additional comparisons, similar rates were reported for early remission (≤ 6 months) and late remission (> 6 months). Six studies reported both early and late remission rates (6, 27, 34, 40, 42, 44, 47), with an early remission rate of 75.6% (476/639 patients; range 66.7–89.0%) compared with a late remission rate of 72.3% (342/473 patients; range 50.0–96.9%; $P=\text{not significant (NS)}$). The effect of tumor size on remission outcomes of initial microscopic TSS was available from 18 and 16 studies for microadenomas and macroadenomas respectively. A significantly higher remission rate (82.2%; 1203/1463 patients; range 46.5–94.0%) was achieved in patients with microadenoma compared with those with macroadenoma (60.1%; 187/311 patients; range 17.0–91.7%; $P<0.01$). The duration of follow up for identification of remission rates ranged from 13 to 96 months, with 25 studies following patients for between 37 and 72 months (Table 1). Remission rates did not vary significantly with length of follow-up, although a slight downward trend in remission rate by duration of follow-up could be observed ($r=-0.12$; $P=\text{NS}$; Fig. 3). With regard to outcomes analyzed by surgical experience, the highest remission rate (96.6%) was achieved when 36–40 patients were operated per year of study duration (Fig. 4), with a slight upward trend in remission rates observed with increasing surgical experience (evaluated by patient numbers/year) ($r=0.37$; $P=\text{NS}$). No change in remission rate was observed by decade of publication date ($r=-0.2$; $P=\text{NS}$). Most articles (28) were published between 2001 and 2010, with remission rates ranging from 65.0 to 96.6% (Table 1). Three articles published between 1980 and 1990 gave remission rates of 84.9–92.4%, and eight published between 1991 and 2000 gave remission rates of 52.1–87.0% (Table 1).

Of note, most studies reported the rate of patients who did not meet the set criteria for remission following initial TSS (often defined as persistent disease). Persistence rate

Table 1 Outcomes of TSS in patients with Cushing's disease. Studies listed here are original articles identified in the literature selection based on the search and inclusion criteria.

References	Study period (estimated years, n)	Patients (n)	Patients/ years (n)	Macro- adenomas (%)	Micro- adenomas (%)	Mean or median follow-up (range) (months)	Remission endpoints	Remission rate (%)	Recurrence endpoints	Recurrence rate (%)	Mean or median time to recurrence (range) (months)
(25)	Jan 1997–Dec 2005 (9)	44	5	23		49 (19–102)	Clinical+morning SC+UFC	89	Clinical+morning SC+UFC	7.7	54.6 (30–84)
(26)	1991–2006 (15)	79	5	27	53	84 (6–197)	Clinical+morning SC+UFC+DEX	65		20	16.5 (7–121)
(33)	Jan 2000–Dec 2009 (10)	81	8			40.8	Undefined SC	66.7		18.5	34.8
(34)	Jan 1979–Dec 2000 (20)	63	3			115.2 (12–252)	Undefined SC+ UFC+DEX	Initial: 71.4		22.2	63.6 (12–108)
(35)	NS	50				71.5 (25–219)	Undefined SC+ UFC+DEX	72		8.3	(12–60)
(36)	NS	68		7	59	57.5 (12–252)	Undefined SC+ UFC+DEX	79		21 (five of 46)	(8–84)
(27)	Jan 1975–Dec 1990 (15)	668	45	21		24 (up to 120)	Clinical+DEX	76.3		12.7 (65 of 510)	39.3 (6–104)
(28)	Feb 1974–Oct 1981 (7.75)	100	13	22	60	55.2 (20–110.4)	Clinical+unde- fined SC+DEX	92 (micro- adenomas and 45 macro- adenomas)		Two (micro- adenomas and 14 macro- adenomas)	
(37)	Jan 1996–Dec 2009 (14)	127	9			50.4 (7–99)	Morning SC	79.5	Clinical+mid- night corti- sol+UFC	21	
(38)	Jan 1996–June 2006 (10.5)	68	6	15	85	45 (6–123)	Morning SC	74	Morning SC+ UFC+DEX	14.3	51 (9–90)
(39)	1975–1995 (20)	288	15					70		15	
(19)	1980–1997 (26)	61	2	16.4	32.8	88 (7–211)	Clinical+DEX	78.7	Clinical+unde- fined SC+UFC	14.6	76.1 (22–158)
(40)	1973–1993 (20)	174	9	17 (29 of 162)	92 (133 of 162)	≤60		79			(6–48)
(23)	Since Sept 1998	40		22.5	57.5	33 (14–65)	Clinical+morning SC	79.5		3.1	
(41)	1990–1996 (5)	147	29	15.6		61 (14–123)	Morning SC	93		5.6	
(42)	Jan 1996–Jan 2007 (11)	40	4	30	70	86	UFC	65	Clinical+UFC	9.4	(18–96)
(32)	1978–1985 (6)	64	11	10	80	24 (6–84)	Morning SC+UFC	70	UFC	10.0	(24–36)
(16)	Feb 1975–Mar 1998 (22)	289	13			133.2 (7.2–289.2)		82		8.7	58.5 (13.2–133.2)
(43) ^a	1988–2009 (11)	80	7			55.2	Morning SC	83 (early remission) and 72 (cure)	Clinical+UFC+ DEX	13.3	25.2 (15.6–37.2)
(44)	Mar 1997–Sept 2004 (7.5)	100	13	15	35	18.8 (3–86)	Undefined SC+ DEX	75 (micro- adenomas; 81.2% and macroado- mas: 46.7%)		4.8	18.8 (3–86)
(18)	Jan 1971–Oct 2004 (34.8)	426	12	10.6	89.4	72.3 (3–300)	DEX	75.9		15.0	
(45)	Jun 1998–Jun 2011 (13)	83	6	13.3	86.7	38.2 (3–156)	Clinical+UFC+ DEX	84.3 (microade- nomas: 87.5% and macro- adenomas: 63.6%)		Microadenoma- mas: 7.4% and macroa- denomas: 0%	37.0 (20–56)

Table 1 Continued

References	Study period (estimated years, n)	Patients (n)	Patients/ years (n)	Macro- adenomas (%)	Micro- adenomas (%)	Mean or median follow-up (range) (months)	Remission endpoints	Remission rate (%)	Recurrence endpoints	Recurrence rate (%)	Mean or median time to recurrence (range) (months)
(29)	NS (20)	288	14			(6–180)	Clinical+morning SC+UFC	69		17.0	115 (6–120)
(46)	Jan 1990–Mar 2007 (7.25)	261	36			84 (12–215)	Morning SC+UFC	96.5		2.3	56 (5–129)
(47)	1987–Apr 2005 (8.3)	193	23			62	Undefined SC+ UFC+DEX	80.8	Morning SC+ UFC+DEX	13.5	57.6 (8.4–148.8)
(48)	Jan 1984–Dec 2010 (28)	54	2		83.3	50.7 (11.4–174.2)	Clinical+UFC	70.3	Undefined SC+ UFC+DEX	47.4	57.2 (13–148)
(49)	1980–1991 (10)	310	31			43		85.2		11.0	18.8 (3–86)
(50)	Feb 1977–Apr 1984 (7.2)	100	14	18.3	81.7	38.4		92.4		9.3	44
(51)	1992–2006 (14)	215	15			45 (6–166)	Clinical+UFC	85.6		17.4	39 (3–134)
(30)	1978–2002 (24)	78	3			86 (12–288)	Clinical+UFC+ DEX	72	Clinical+UFC+ DEX	9.0	84
(20) ^b	Jul 1992–Dec 2005 (8.5)	167	20	0	100	39 (6–157)	Clinical+UFC	88.6		12.8	50 (12–117)
(15)	Jan 1980–Nov 2000 (10.8)	54	5			72 (6–252)	Morning SC	77	Clinical+morn- ing SC+UFC	5.0	(13–36)
(22)	NS	48		18.4		57.6 (4–170)	Clinical+morning SC+DEX	87.5		4.2	(54–66)
(17)	Since 1989	103		22.3	57.3	72	Clinical+morning SC+DEX	85.4 (micro- adenomas: 94.9 and macro- adenomas: 73.9)		6.8	(24–66)
(52)	1996–2002 (6)	54	9	0	70.4	19.9 (1–89)	Morning SC+ UFC+DEX	66.7	Morning SC+ UFC	19.5	
(53)	1990–2000 (10)	74	7	4.1	95.9	50.4	Morning SC+ UFC+DEX	78.4		5.2	(24–60)
(54)	NS (20)	103	5			72 (24–192)	Clinical+UFC+ DEX	76.7	Clinical+UFC+ DEX	NS	
(55)	1960–2001 (40)	183	5	16.3 (21 of 129)	83.7 (108 of 129)	NS	Morning SC	Microadenomas: 78 and macro- adenomas: 48	Clinical+mid- night SC+DEX	Microadenomas: 21.4 (18 of 84) and macro- adenomas: 33.3 (four of 12)	68.4 (12–132)
(56)	1978–1996 (18)	154	9	11	89	96 (12–240)	Morning SC+UFC	(Cure) microade- nomas: 90 and macroade- nomas: 64.7		7.0	
(31)	1977–1988 (11)	56	5	13	62	58 (2–142)	Clinical+unde- fined SC+UFC	84.9		2.0	
(57)	1985–1990 (5)	48	10			40 (15–70)	Morning SC	42		0	66
(58)	1982–2007 (25)	620	25	17.1	82.9	(1–300)	Morning SC+UFC	Immediate control: 70.5	Morning SC+ UFC	13.0	
(59)	1969–1988 (19)	97	5	11.6	88.4	92 (6–348)	Morning SC+UFC	68.5 (microade- nomas: 63.2)	Morning SC+ UFC+DEX	11.5	36.3 (6–60)

SC, serum cortisol; UFC, urinary free cortisol; DEX, low-dose dexamethasone suppression test.

^aIn this study, 16.3% (14/86) of patients with Cushing's disease received endoscopic TSS.^bIn this study, 2% (3/167) of patients received endoscopic TSS.

Figure 2

Remission rates by type of assessment. Data are represented as mean remission rate (95% CIs) for any type of assessment (dotted line) and by each type of assessment.

was variable and ranged from 3.4 to 35.0%, with a mean rate of 21.9%; one study (28) reported a persistence rate of 39% for macroadenoma, reflecting the poorer outcomes observed with larger tumors.

Recurrence rates

A more limited variety of definitions of recurrence than of remission of Cushing's disease after initial microscopic TSS is used in the literature. As with remission, clinical parameters (reappearance of signs and symptoms) were never used alone to define recurrence; clinical evaluation was combined with serum cortisol, UFC, and/or LDDST biochemical tests. The most frequently used biochemical test was the assessment of 24-h UFC level. When used, the serum cortisol test was mostly performed in the morning; midnight cortisol level was assessed only in two studies, including one using either serum or saliva.

In total, seven studies reported recurrence using biochemical assays only and ten used a combination of

clinical and biochemical endpoints (Table 1). Recurrence rates of 15.7% (128/815 patients) and 14.4% (81/561 patients) were reported, respectively, with a range of 11.5–47.4% for those using biochemical assays only and

Figure 3

Patient follow-up after TSS.

Figure 4

Surgical experience in Cushing's disease.

5.0–20.8% for those using a combination of clinical and biochemical endpoints. An overall recurrence rate of 15.2% was calculated (Fig. 5), with a mean time to recurrence (from the 23 studies in which this was reported) being 50.8 months (range 3–158 months) (Table 1). Interestingly, the combination of UFC with LDDST resulted in lower recurrence rates compared with UFC

alone regardless of whether recurrence was defined using biochemical assays only (5.8% for UFC alone vs 11.5% for UFC with LDDST) or clinical parameters and biochemical assays (16.2% for UFC alone vs 11.2% for UFC with LDDST) (Fig. 5). This was also observed with UFC combined with serum cortisol vs UFC alone when clinical parameters and biochemical assays were used to evaluate recurrence (14.4% vs 16.2% respectively; Fig. 5).

The effect of tumor size on recurrence outcomes after microscopic TSS was available from 11 articles. As with remission, slightly better outcomes were seen with microadenomas than with macroadenomas; a slightly higher but not statistically significant recurrence rate (17.6%; 19/108 patients; range 0.0–80%) was reported in patients with macroadenomas compared with those with microadenomas (13.4%; 101/752 patients; range 2.0–35%). The duration of follow-up for identification of recurrence rates ranged from 13 to 96 months in 32 studies and recurrence rates did not vary with length of follow-up ($P=NS$; Table 1): a rate of 12.1% was found for five studies with a follow-up of 13–36 months, and a rate of 11.2% was found for four studies with a follow-up of 85–96 months.

Figure 5

Recurrence rates by type of assessment. Data are represented as mean recurrence rate (95% CIs) for any type of assessment (dotted line) and by each type of assessment.

Review	S Petersenn and others	Initial surgery outcomes for Cushing's disease	172:6	R235
--------	------------------------	--	-------	------

With regard to the outcomes analyzed by surgical experience, the highest recurrence rate (13.6%) was seen when ten or fewer patients were operated per year of study duration (in 18 studies), while the lowest rate (6.7%) was seen when 31–40 patients were operated per year of study duration ($r = -0.3$; $P = \text{NS}$; albeit these data are from only two studies (29, 48)). In contrast to remission, a trend toward an increase in recurrence rate could be noted over time, with the upper limit of recurrence rate ranges increasing steadily by decade of study publication, suggesting poorer outcomes or better reporting of recurrence rates ($r = 0.8$; $P = \text{NS}$; Table 1). For the decade 1980–1990, the rate range was 2.2–9.3%, for 1991–2000 it was 0.0–17.0%, and for 2001–2010 it was 2.3–24.4; the most recently published studies (from 2011 to 19th October 2012) had a recurrence rate range of 6.7–47.4% (Table 1).

Safety

Of the 43 articles included in the systematic review, 32 reported whether the TSS procedure resulted in complications (with details provided in 30 of the publications). From those with details, adverse events (AEs) related to surgery were reported in 18.4% of patients (1179/6397 patients). The most common were results of abnormal hormonal states (e.g. hypocortisolism (of note, may not necessarily be considered as an AE but as a sign of efficacy), hypogonadism, syndrome of inappropriate antidiuretic hormone secretion), with 429 incidences reported in a total of 2491 patients (17.2%; range 0–99). In addition, there were 316 cases of diabetes insipidus (9.4%; range 0–75). A total of 130 cases of cerebrospinal fluid leakage were also reported (4.5%; range 0–13.1). Less commonly, there were 47 reports of meningitis (1.9%; range 0–7.9) and 19 cardiovascular complications (1.2%; range 0.0–7.6); 177 other AEs were reported (including visual disturbance, other infection, nasal discharge/bleeding, cacosmia (i.e. perception of a malodorous smell when none exists), fat and/or fascia lata grafting, hematoma at graft site, cranial nerve palsy, epistaxis, septal perforation, blocked lacrimal duct, mesenteric infarction, numbness associated with maxillary fracture, perforated sigmoid diverticulum).

Interestingly, there was a trend toward or even a negative correlation between the number of patients developing AEs after initial TSS and the center's surgical experience, with fewer complications reported with increasing surgical experience (hypoendocrine state: $r = -0.29$, $P = \text{NS}$; diabetes insipidus: $r = -0.54$, $P < 0.05$; cerebrospinal fluid leakage: $r = -0.74$, $P < 0.001$;

meningitis: $r = -0.54$, $P < 0.05$; and cardiovascular complications: $r = -0.51$, $P = \text{NS}$).

Deaths occurred mostly during the follow-up period and were reported in 19 studies. Overall, the mortality rate was relatively low (1.7%; range 0.0–18.1%); there was no correlation with remission rate or the center's surgical experience. Six studies reported deaths related to surgery (defined as 'complications during operation or occurring within 1 month following surgery'); the mean perioperative mortality rate was 1.5% (20/1340 patients; range 1.0–1.9%).

Discussion

This systematic analysis of the outcomes of initial microscopic TSS for Cushing's disease reveals noteworthy results of relevance to healthcare providers involved in the management of patients with Cushing's disease. As previously reported, remission rates were higher in patients with microadenomas vs macroadenomas and recurrence outcomes were worse in patients with macroadenomas compared with microadenomas (6). Interestingly, duration of follow-up had no influence on recurrence rates in our analysis, while it has been previously reported that the risk for recurrence increased with long-term follow-up (51). This suggests that certain types of tumor may be more aggressive than others and may recur early during the follow-up period. Conversely, less aggressive tumors would recur later. The factors that may trigger early or late recurrence are so far unknown. Improved outcomes could be suggested with improved surgical experience. Our finding that surgical experience does not have a significant influence on remission rates conflicts with previous reports (6, 15), but may reflect publication-to-publication differences in assessing this parameter (e.g. those centers with small number of patients with Cushing's disease may operate a larger number of patients with other pituitary tumors, thereby being highly qualified). In addition, the number of operations per individual surgeon was not available in most studies, although it better reflects the impact of surgical experience on the final outcome. Of note, however, we did find a correlation between greater surgical experience and improved safety outcomes.

Our systematic review was restricted to studies using microscopic TSS; however, TSS can also be performed endoscopically. A review of the outcomes of endoscopic TSS in Cushing's disease revealed similar outcomes to those achieved by the conventional microscopic technique (14). A remission rate of 77% (defined

Review	S Petersenn and others	Initial surgery outcomes for Cushing's disease	172:6	R236
--------	------------------------	--	-------	------

biochemically) was reported; this compares with a rate of 87% found in our review of microscopic TSS. Tumor size was also an important predictor of outcome after endoscopic TSS: only 14% of patients in remission had macroadenomas, while macroadenomas were confirmed in 25% of patients with unsuccessful initial endoscopic surgery (14).

The most commonly used biochemical assays to determine remission in the studies included in this review were assessment of morning serum cortisol level alone or combined with UFC level; recurrence was most commonly measured biochemically using morning serum cortisol with UFC, UFC alone, or UFC with LDDST. The type of biochemical assay used seemed to influence recurrence rates, while remission rates did not differ markedly. These differences may be explained by variability in the cut-off thresholds used for each biochemical assay. Most of these assessments are included in the first-line screening tests used in the diagnosis of Cushing's disease (24), and thus reflect current common practice for assessing the disease state. However, a variety of assessments and methods was used to determine the outcomes; this may have contributed to the broad ranges of remission (52.1–96.6%) and recurrence (5.0–47.4%) observed. Despite the fact that the criteria for remission and recurrence varied, all of those used are widely accepted and included in current guidelines (7). Of note, none of the studies included in this systematic review used salivary cortisol to evaluate recurrence in patients with Cushing's disease following TSS, despite the increasing scientific evidence that late-night salivary cortisol is a simple and noninvasive biomarker that may be more reliable than UFC (60).

The evidence from this review is strengthened by recent data. Tritos *et al.* (13) reported a maximum rate of remission of 99%; similarly, we found a maximum reported rate of 96.6%. However, these maximum rates of remission can be considered to be overestimations of the true outcomes of Cushing's disease after initial microscopic TSS, because the potential for relapse remains high. In this review, the reported rates of recurrence ranged from 5.0 to 47.4%; similarly, rates of 5–36% were also reported in a recent publication (61). The wide range of rates of remission and recurrence observed highlight the fact that statistics for treatment outcomes are dependent on the criteria used to define those outcomes.

Limitations

Although we established pre-selected criteria for inclusion of studies in our review, most of the studies included were

retrospective, and we have not confirmed the data extracted with the principal investigators of the studies included. We only included large series in our review; exclusion of studies including <40 patients may have skewed the results in favor of positive outcomes as a result of surgical experience. Finally, no formal assessment of risk of bias in this study, including of publication bias, is a limitation.

This review reveals the variety of study designs and methods used in the clinical evaluation of TSS outcomes in Cushing's disease and confirms the better outcomes (higher remission, lower recurrence) achieved with microadenomas vs macroadenomas. Similar outcomes have been reported by other studies, and our findings thus add to the body of evidence suggesting that a consensus should determine the most appropriate definitions of remission and recurrence, the best biochemical assays to determine these outcomes, and the most patient-relevant time to assess remission of disease.

As with other reports, clinically significant rates of failure of initial TSS were recorded, highlighting the need for effective second-line therapies. A number of interventions are available if initial TSS fails. However, none is ideal. With repeat TSS, remission rates are lower than with first surgery and reoperation carries a significant higher risk of pituitary insufficiency (6). Radiotherapy may lead to remission in approximately half of patients within 5 years, but also impairs normal pituitary function (6). Most radically, bilateral adrenalectomy provides a definitive cure of disease. However, it results in permanent hypo-adrenalism, which requires life-long glucocorticoid and mineralocorticoid replacement therapy, and carries the risk of Nelson's syndrome. Medical therapy of Cushing's disease is also an option after surgical failure. Traditionally, most pharmaceutical interventions were directed to the adrenal gland. Recently pituitary-directed medical therapies are being developed for adults with Cushing's disease in whom pituitary surgery is not an option or has not been curative.

In conclusion, this systematic review highlights the need for standardization of definitions of remission and recurrence and the methods of determining these outcomes. With standardized and optimized methodology, clinical trial results can be confidently compared to inform clinical practice and maximize patient outcomes.

Declaration of interest

All authors have served on an advisory board for Novartis. S Petersenn has received speaker fees from Novartis. A Beckers has received research grants

from Novartis, Ipsen, and Pfizer. D Ferone has received lecture fees from Novartis and Ipsen, and has served on a clinical trial steering committee for Novartis. A van der Lely has received financial support for investigator-initiated research and unrestricted grants from Novartis, Pfizer, and Ipsen. A Colao has received unrestricted grants and lecture fees from Novartis. P Chanson has received unrestricted research and educational grants and lecture fees from Novartis. S Tsagarakis has received honoraria and travel grants from Novartis. J Bollerslev, T Brue, P Bruzzi, F Casanueva, M Reincke, and G Stalla declare that aside from participating in the advisory board, there are no conflicts of interest.

Funding

This work was supported by Novartis Pharma AG (Basel, Switzerland).

Author contribution statement

S Petersenn, A Beckers, D Ferone, and A van der Lely have contributed to the selection of the studies included in this systematic review, the generation of data extracted from these studies, and the preparation of this manuscript, and have read and commented on drafts of this article. J Bollerslev, M Boscaro, T Brue, P Bruzzi, F Casanueva, P Chanson, A Colao, M Reincke, G Stalla, and S Tsagarakis have judged the quality of the evidence and strength of the data extracted from the studies, have contributed to the design and purpose of the review, and have read and commented on the final draft of this manuscript.

Acknowledgements

Authors received editorial support in the preparation of this article, specifically copyediting for language and format, generation of figures and tables, and incorporating critical revisions to the article before acceptance, from Sandrine Buisson, PhD (Excerpta Medica). Based on criteria established by the authors, Agnieszka Rarok, PhD, and Sandrine Buisson, PhD (both Excerpta Medica) performed the literature search and extracted data from published articles. The authors were fully responsible for all content and editorial decisions for this manuscript and for the approval of the final manuscript for submission.

References

- Praw SS & Heaney AP. Medical treatment of Cushing's disease: overview and recent findings. *International Journal of General Medicine* 2009 **2** 209–217.
- Newell-Price J, Bertagna X, Grossman AB & Nieman LK. Cushing's syndrome. *Lancet* 2006 **367** 1605–1617. (doi:10.1016/S0140-6736(06)68699-6)
- Etxabe J & Vazquez JA. Morbidity and mortality in Cushing's disease: an epidemiological approach. *Clinical Endocrinology* 1994 **40** 479–484. (doi:10.1111/j.1365-2265.1994.tb02486.x)
- Lindholm J, Juul S, Jørgensen JO, Astrup J, Bjerre P, Feldt-Rasmussen U, Hagen C, Jørgensen J, Kosteljanetz M, Kristensen L *et al.* Incidence and late prognosis of Cushing's syndrome: a population-based study. *Journal of Clinical Endocrinology and Metabolism* 2001 **86** 117–123.
- Daly AF, Rixhon M, Adam C, Dempegioti A, Tichomirowa MA & Beckers A. High prevalence of pituitary adenomas: a cross-sectional study in the province of Liege, Belgium. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 4769–4775. (doi:10.1210/jc.2006-1668)
- Biller BM, Grossman AB, Stewart PM, Melmed S, Bertagna X, Bertherat J, Buchfelder M, Colao A, Hermus AR, Hofland LJ *et al.* Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 2454–2456. (doi:10.1210/jc.2007-2734)
- Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM & Montori VM. The diagnosis of Cushing's syndrome: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 1526–1527. (doi:10.1210/jc.2008-0125)
- Tauchmanová L, Rossi R, Biondi B, Pulcrano M, Nuzzo V, Palmieri EA, Fazio S & Lombardi G. Patients with subclinical Cushing's syndrome due to adrenal adenoma have increased cardiovascular risk. *Journal of Clinical Endocrinology and Metabolism* 2002 **87** 4872–4878.
- Pivonello R, Faggiano A, Lombardi G & Colao A. The metabolic syndrome and cardiovascular risk in Cushing's syndrome. *Endocrinology and Metabolism Clinics of North America* 2005 **34** 327–339. (doi:10.1016/j.ycl.2005.01.010)
- Chanson P & Salenave S. Metabolic syndrome in Cushing's syndrome. *Neuroendocrinology* 2010 **92** (Suppl 1) 96–101. (doi:10.1159/000314272)
- Pivonello R, De Martino MC, De Leo M, Tauchmanova L, Faggiano A, Lombardi G & Colao A. Cushing's syndrome: aftermath of the cure. *Arquivos Brasileiros de Endocrinologia e Metabologia* 2007 **51** 1381–1391. (doi:10.1590/S0004-27302007000800025)
- Clayton RN, Raskauskiene D, Reulen RC & Jones PW. Mortality and morbidity in Cushing's disease over 50 years in Stoke-on-Trent, UK: audit and meta-analysis of literature. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** 632–642. (doi:10.1210/jc.2010-1942)
- Tritos NA, Biller BM & Swearingen B. Management of Cushing disease. *Nature Reviews. Endocrinology* 2011 **7** 279–289. (doi:10.1038/nrendo.2011.12)
- Netea-Maier RT, van Lindert EJ, den Heijer M, van der Eerden A, Pieters GF, Sweep CG, Grotenhuis JA & Hermus AR. Transsphenoidal pituitary surgery via the endoscopic technique: results in 35 consecutive patients with Cushing's disease. *European Journal of Endocrinology* 2006 **154** 675–684. (doi:10.1530/eje.1.02133)
- Rees DA, Hanna FW, Davies JS, Mills RG, Vafidis J & Scanlon MF. Long-term follow-up results of transsphenoidal surgery for Cushing's disease in a single centre using strict criteria for remission. *Clinical Endocrinology* 2002 **56** 541–551. (doi:10.1046/j.1365-2265.2002.01511.x)
- Hammer GD, Tyrrell JB, Lamborn KR, Applebury CB, Hannegan ET, Bell S, Rahl R, Lu A & Wilson CB. Transsphenoidal microsurgery for Cushing's disease: initial outcome and long-term results. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 6348–6357. (doi:10.1210/jc.2003-032180)
- Rollin G, Ferreira NP & Czepielewski MA. Prospective evaluation of transsphenoidal pituitary surgery in 108 patients with Cushing's disease. *Arquivos Brasileiros de Endocrinologia e Metabologia* 2007 **51** 1355–1361. (doi:10.1590/S0004-27302007000800022)
- Hofmann BM, Hlavac M, Martinez R, Buchfelder M, Müller OA & Fahlbusch R. Long-term results after microsurgery for Cushing disease: experience with 426 primary operations over 35 years. *Journal of Neurosurgery* 2008 **108** 9–18. (doi:10.3171/JNS/2008/108/01/0009)
- Chee GH, Mathias DB, James RA & Kendall-Taylor P. Transsphenoidal pituitary surgery in Cushing's disease: can we predict outcome? *Clinical Endocrinology* 2001 **54** 617–626. (doi:10.1046/j.1365-2265.2001.01261.x)
- Prevedello DM, Pouratian N, Sherman J, Jane JA Jr, Vance ML, Lopes MB & Laws ER Jr. Management of Cushing's disease: outcome in patients with microadenoma detected on pituitary magnetic resonance imaging. *Journal of Neurosurgery* 2008 **109** 751–759. (doi:10.3171/JNS/2008/109/10/0751)
- Simmons NE, Alden TD, Thorner MO & Laws ER Jr. Serum cortisol response to transsphenoidal surgery for Cushing disease. *Journal of Neurosurgery* 2001 **95** 1–8. (doi:10.3171/jns.2001.95.1.0001)
- Rollin GA, Ferreira NP, Junges M, Gross JL & Czepielewski MA. Dynamics of serum cortisol levels after transsphenoidal surgery in a cohort of patients with Cushing's disease. *Journal of Clinical*

Review	S Petersenn and others	Initial surgery outcomes for Cushing's disease	172:6	R238
--------	------------------------	--	-------	------

- Endocrinology and Metabolism* 2004 **89** 1131–1139. (doi:10.1210/jc.2003-031170)
- 23 Esposito F, Dusick JR, Cohan P, Moftakhar P, McArthur D, Wang C, Swerdloff RS & Kelly DF. Clinical review: Early morning cortisol levels as a predictor of remission after transsphenoidal surgery for Cushing's disease. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 7–13. (doi:10.1210/jc.2005-1204)
 - 24 Arnaldi G, Angeli A, Atkinson AB, Bertagna X, Cavagnini F, Chrousos GP, Fava GA, Findling JW, Gaillard RC, Grossman AB *et al.* Diagnosis and complications of Cushing's syndrome: a consensus statement. *Journal of Clinical Endocrinology and Metabolism* 2003 **88** 5593–5602. (doi:10.1210/jc.2003-030871)
 - 25 Acebes JJ, Martino J, Masuet C, Montanya E & Soler J. Early post-operative ACTH and cortisol as predictors of remission in Cushing's disease. *Acta Neurochirurgica* 2007 **149** 471–477 (discussion 477–479). (doi:10.1007/s00701-007-1133-1)
 - 26 Alwani RA, de Herder WW, van Aken MO, van den Berge JH, Delwel EJ, Dallenga AH, De Jong FH, Lamberts SW, van der Lely AJ & Feelders RA. Biochemical predictors of outcome of pituitary surgery for Cushing's disease. *Neuroendocrinology* 2010 **91** 169–178. (doi:10.1159/000258677)
 - 27 Boichichio D, Losa M & Buchfelder M. Factors influencing the immediate and late outcome of Cushing's disease treated by transsphenoidal surgery: a retrospective study by the European Cushing's Disease Survey Group. *Journal of Clinical Endocrinology and Metabolism* 1995 **80** 3114–3120.
 - 28 Boggan JE, Tyrrell JB & Wilson CB. Transsphenoidal microsurgical management of Cushing's disease. Report of 100 cases. *Journal of Neurosurgery* 1983 **59** 195–200. (doi:10.3171/jns.1983.59.2.0195)
 - 29 Invitti C, Pecori Giralaldi F, de Martin M & Cavagnini F. Diagnosis and management of Cushing's syndrome: results of an Italian multicentre study. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 440–448.
 - 30 Pereira AM, van Aken MO, van Dulken H, Schutte PJ, Biermasz NR, Smit JW, Roelfsema F & Romijn JA. Long-term predictive value of postsurgical cortisol concentrations for cure and risk of recurrence in Cushing's disease. *Journal of Clinical Endocrinology and Metabolism* 2003 **88** 5858–5864. (doi:10.1210/jc.2003-030751)
 - 31 Tindall GT, Herring CJ, Clark RV, Adams DA & Watts NB. Cushing's disease: results of transsphenoidal microsurgery with emphasis on surgical failures. *Journal of Neurosurgery* 1990 **72** 363–369. (doi:10.3171/jns.1990.72.3.0363)
 - 32 Guilhaume B, Bertagna X, Thomsen M, Bricaire C, Vila-Porcile E, Olivier L, Racadot J, Derome P, Laudat MH, Girard F *et al.* Transsphenoidal pituitary surgery for the treatment of Cushing's disease: results in 64 patients and long term follow-up studies. *Journal of Clinical Endocrinology and Metabolism* 1988 **66** 1056–1064. (doi:10.1210/jcem-66-5-1056)
 - 33 Ammini AC, Bhattacharya S, Sahoo JP, Philip J, Tandon N, Goswami R, Jyotsna VJ, Khadgawat R, Chumber S, Seth A *et al.* Cushing's disease: results of treatment and factors affecting outcome. *Hormones* 2011 **10** 222–229. (doi:10.14310/horm.2002.1312)
 - 34 Atkinson AB, Kennedy A, Wiggam MI, McCance DR & Sheridan B. Long-term remission rates after pituitary surgery for Cushing's disease: the need for long-term surveillance. *Clinical Endocrinology* 2005 **63** 549–559. (doi:10.1111/j.1365-2265.2005.02380.x)
 - 35 Bakiri F, Tatai S, Aouali R, Semrouni M, Derome P, Chitour F & Benmiloud M. Treatment of Cushing's disease by transsphenoidal, pituitary microsurgery: prognosis factors and long-term follow-up. *Journal of Endocrinological Investigation* 1996 **19** 572–580. (doi:10.1007/BF03349020)
 - 36 Barbetta L, Dall'Asta C, Tomei G, Locatelli M, Giovanelli M & Ambrosi B. Assessment of cure and recurrence after pituitary surgery for Cushing's disease. *Acta Neurochirurgica* 2001 **143** 477–481 (discussion 481–482). (doi:10.1007/s007010170077)
 - 37 Bou Khalil R, Baudry C, Guignat L, Carrasco C, Guibourdenche J, Gaillard S, Bertagna X & Bertherat J. Sequential hormonal changes in 21 patients with recurrent Cushing's disease after successful pituitary surgery. *European Journal of Endocrinology* 2011 **165** 729–737. (doi:10.1530/EJE-11-0424)
 - 38 Carrasco CA, Coste J, Guignat L, Groussin L, Dugué MA, Gaillard S, Bertagna X & Bertherat J. Midnight salivary cortisol determination for assessing the outcome of transsphenoidal surgery in Cushing's disease. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 4728–4734. (doi:10.1210/jc.2008-1171)
 - 39 Cavagnini F & Pecori Giralaldi F. Epidemiology and follow-up of Cushing's disease. *Annales d'Endocrinologie* 2001 **62** 168–172.
 - 40 Chen JC, Amar AP, Choi S, Singer P, Couldwell WT & Weiss MH. Transsphenoidal microsurgical treatment of Cushing disease: post-operative assessment of surgical efficacy by application of an overnight low-dose dexamethasone suppression test. *Journal of Neurosurgery* 2003 **98** 967–973. (doi:10.3171/jns.2003.98.5.0967)
 - 41 Flitsch J, Knappe UJ & Lüdecke DK. The use of postoperative ACTH levels as a marker for successful transsphenoidal microsurgery in Cushing's disease. *Zentralblatt für Neurochirurgie* 2003 **64** 6–11. (doi:10.1055/s-2003-37145)
 - 42 Fomekong E, Maiter D, Grandin C & Raftopoulos C. Outcome of transsphenoidal surgery for Cushing's disease: a high remission rate in ACTH-secreting macroadenomas. *Clinical Neurology and Neurosurgery* 2009 **111** 442–449. (doi:10.1016/j.clineuro.2008.12.011)
 - 43 Hassan-Smith ZK, Sherlock M, Reulen RC, Arlt W, Ayuk J, Toogood AA, Cooper MS, Johnson AP & Stewart PM. Outcome of Cushing's disease following transsphenoidal surgery in a single center over 20 years. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 1194–1201. (doi:10.1210/jc.2011-2957)
 - 44 Hofmann BM & Fahlbusch R. Treatment of Cushing's disease: a retrospective clinical study of the latest 100 cases. *Frontiers of Hormone Research* 2006 **34** 158–184.
 - 45 Honegger J, Schmalisch K, Beuschlein F, Kaufmann S, Schnauder G, Naegele T & Psaras T. Contemporary microsurgical concept for the treatment of Cushing's disease: endocrine outcome in 83 consecutive patients. *Clinical Endocrinology* 2012 **76** 560–567. (doi:10.1111/j.1365-2265.2011.04268.x)
 - 46 Jagannathan J, Smith R, DeVroom HL, Vortmeyer AO, Stratakis CA, Nieman LK & Oldfield EH. Outcome of using the histological pseudocapsule as a surgical capsule in Cushing disease. *Journal of Neurosurgery* 2009 **111** 531–539. (doi:10.3171/2008.8.JNS08339)
 - 47 Jehle S, Walsh JE, Freda PU & Post KD. Selective use of bilateral inferior petrosal sinus sampling in patients with adrenocorticotropin-dependent Cushing's syndrome prior to transsphenoidal surgery. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 4624–4632. (doi:10.1210/jc.2008-0979)
 - 48 Kim JH, Shin CS, Paek SH, Jung HW, Kim SW & Kim SY. Recurrence of Cushing's disease after primary transsphenoidal surgery in a University Hospital in Korea. *Endocrine Journal* 2012 **59** 881–888. (doi:10.1507/endocrj.EJ12-0109)
 - 49 Knappe UJ & Lüdecke DK. Persistent and recurrent hypercortisolism after transsphenoidal surgery for Cushing's disease. *Acta Neurochirurgica. Supplement* 1996 **65** 31–34.
 - 50 Nakane T, Kuwayama A, Watanabe M, Takahashi T, Kato T, Ichihara K & Kageyama N. Long term results of transsphenoidal adenomectomy in patients with Cushing's disease. *Neurosurgery* 1987 **21** 218–222. (doi:10.1227/00006123-198708000-00015)
 - 51 Patil CG, Prevedello DM, Lad SP, Vance ML, Thorner MO, Katznelson L & Laws ER. Late recurrences of Cushing's disease after initial successful transsphenoidal surgery. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 358–362. (doi:10.1210/jc.2007-2013)
 - 52 Salenave S, Gatta B, Pecheur S, San-Galli F, Visot A, Lasjaunias P, Roger P, Berge J, Young J, Tabarin A *et al.* Pituitary magnetic resonance imaging findings do not influence surgical outcome in adrenocorticotropin-secreting microadenomas. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 3371–3376. (doi:10.1210/jc.2003-031908)
 - 53 Shimon I, Ram Z, Cohen ZR & Hadani M. Transsphenoidal surgery for Cushing's disease: endocrinological follow-up monitoring of

Review	S Petersenn and others	Initial surgery outcomes for Cushing's disease	172:6	R239
--------	------------------------	--	-------	------

- 82 patients. *Neurosurgery* 2002 **51** 57–61 (discussion 61–62). (doi:10.1097/00006123-200207000-00008)
- 54 Sonino N, Zielesny M, Fava GA, Fallo F & Boscaro M. Risk factors and long-term outcome in pituitary-dependent Cushing's disease. *Journal of Clinical Endocrinology and Metabolism* 1996 **81** 2647–2652.
- 55 Storr HL, Alexandraki KI, Martin L, Isidori AM, Kaltsas GA, Monson JP, Besser GM, Matson M, Evanson J, Afshar F *et al.* Comparisons in the epidemiology, diagnostic features and cure rate by transsphenoidal surgery between paediatric and adult-onset Cushing's disease. *European Journal of Endocrinology* 2011 **164** 667–674. (doi:10.1530/EJE-10-1120)
- 56 Swearingen B, Biller BM, Barker FG II, Katznelson L, Grinspoon S, Klibanski A & Zervas NT. Long-term mortality after transsphenoidal surgery for Cushing disease. *Annals of Internal Medicine* 1999 **130** 821–824. (doi:10.7326/0003-4819-130-10-199905180-00015)
- 57 Trainer PJ, Lawrie HS, Verhelst J, Howlett TA, Lowe DG, Grossman AB, Savage MO, Afshar F & Besser GM. Transsphenoidal resection in Cushing's disease: undetectable serum cortisol as the definition of successful treatment. *Clinical Endocrinology* 1993 **38** 73–78. (doi:10.1111/j.1365-2265.1993.tb00975.x)
- 58 Valassi E, Biller BM, Swearingen B, Pecori Giralardi F, Losa M, Mortini P, Hayden D, Cavagnini F & Klibanski A. Delayed remission after transsphenoidal surgery in patients with Cushing's disease. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 601–610. (doi:10.1210/jc.2009-1672)
- 59 Yap LB, Turner HE, Adams CB & Wass JA. Undetectable postoperative cortisol does not always predict long-term remission in Cushing's disease: a single centre audit. *Clinical Endocrinology* 2002 **56** 25–31. (doi:10.1046/j.0300-0664.2001.01444.x)
- 60 Carroll TB, Javorsky BR & Findling JW. Late-night salivary cortisol for the diagnosis of recurrent Cushing's disease: evidence of clinical benefit from early detection. *Presented at the 2014 Endocrine Society's Annual Meeting (ENDO 2014)*, OR02-2.
- 61 Feelders RA, Pulgar SJ, Kempel A & Pereira AM. The burden of Cushing's disease: clinical and health-related quality of life aspects. *European Journal of Endocrinology* 2012 **167** 311–326. (doi:10.1530/EJE-11-1095)

Received 16 October 2014

Revised version received 15 December 2014

Accepted 15 January 2015