Pituitary (2012) 15:71–83
DOI 10.1007/s11102-011-0347-7

Clinical factors involved in the recurrence of pituitary adenomas after surgical remission: a structured review and meta-analysis

Ferdinand Roelfsema · Nienke R. Biermasz · Alberto M. Pereira

Published online: 15 September 2011

Abstract To study the currently available data of recurrence rates of functioning and nonfunctioning pituitary adenomas following surgical cure and to analyze associated predisposing factors, which are not well established. A systematic literature search was conducted using Medline, Embase, Web of Science and the Cochran Library for studies reporting data on recurrence of pituitary adenoma after surgery, in nonfunctioning adenoma (NF), prolactinoma (PRL) acromegaly (ACRO) and Cushing's disease (CUSH). Of 557 initially retrieved potential relevant studies 143 were selected. Recurrence in NFA was defined as reappearance of tumor on MRI or CT. Increase of hormone levels above normal limits as set by the authors after initial remission was used to indicate recurrence in the functioning tumor types. Remission percentage was lowest in NFA compared with other tumor types ($P < 0.001$). Surgery-related hypopituitarism was more frequent in CUSH than in the other tumors ($P < 0.001$). Recurrence, expressed as percentage of the cured population or as ratio of recurrence and total patient years of follow-up was highest in PRL ($P < 0.001$). The remission percentage did not improve over 3 decades of publications, but there was a modest decrease in recurrence rate ($P = 0.04$). Recurrences peaked between 1 and 5 years after surgery. Most of the studies with a sufficient number of recurrences did not apply multivariate statistics, and mentioned at best associated factors. Age, gender, tumor size and invasion were generally unrelated to recurrence. For functioning adenomas a low postoperative hormone concentration was a prognostically favorable factor. In NFA no specific factor predicted recurrence. Recurrence rate differs between pituitary adenomas, being highest in patients with prolactinoma, with the highest incidence of recurrence between 1 and 5 years after surgery in all adenomas. Patients with NFA have a lower chance of remission than patients with functioning adenomas. The postoperative basal hormone level is the most important predictor for recurrence in functioning adenomas, while in NFA no single convincing factor could be identified.

Keywords Pituitary adenoma · Recurrence · Relapse · Acromegaly · Non-functioning adenoma · Prolactinoma · Cushing's disease · Hypercortisolism · Pituitary surgery · Meta-analysis

F. Roelfsema (✉) · N. R. Biermasz · A. M. Pereira
Department of Endocrinology and Metabolic Diseases, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands
e-mail: f.roelfsema@lumc.nl

Introduction

Over the last four decades the preferred treatment of choice of pituitary adenomas has been transsphenoidal surgery, although primary medical treatment is currently used in most patients with prolactinoma and in selected patients with acromegaly [1–4]. The obvious advantage of surgery is the quick relief of signs and symptoms, and the arrest of permanent damage to organ systems caused by the hormonal excess. Recurrence of a pituitary adenoma after apparent cure is well recognized, but the clinical predictive factors associated with relapse have not been studied systematically and compared between different types of adenomas. The purpose of this study is to present a systematic review and meta-analysis of publications spanning the last three decades of pituitary surgery and reporting remission and recurrence of pituitary adenomas during long-term follow-up studies. Particular attention was given to clinical

factors predicting recurrence of an adenoma, also when this was not the primary goal of the reported study. Many factors may influence the proliferation of pituitary adenomas, such as angiogenesis, apoptosis, growth factors, oncogenes, tumor suppressor genes, and hormone receptors [5, 6]. However, we did not include reports investigating the association of biochemical tumor factors with the risk of recurrence of the adenoma, since the majority of these reports was not based on unselected patient groups.

Study design

Search strategy

The following databases for studies addressing the recurrence of pituitary adenomas after transsphenoidal surgery were searched: PubMed, Cochrane Library, Web of Science, EMBASE, CINAHL, PsycINFO, Academic Search Premier and Science Direct. The final search was performed on August 1, 2011. We devised a search strategy for the mentioned databases with the help of a trained clinical librarian focusing on pituitary adenomas, treatment and recurrence after treatment. All relevant keyword variations were used, including free text words. The references of the relevant articles were checked for additional articles. Original articles in the English, German, French and Dutch languages were included. Studies were eligible for inclusion in this review when they fulfilled the following criteria: more than 20 patients included with a mean follow-up period of at least 1 year. Studies were excluded when restricted to elderly patients (>80 years) or adolescents and children, when patients underwent repeat pituitary surgery, pituitary irradiation, transcranial surgery, or in the presence of rare pituitary adenomas e.g. TSH secreting adenomas or functioning gonadotropinomas, hereditary tumors, e.g. MEN I syndrome or when regrowth and recurrence of nonfunctioning adenomas were considered as equivalent entities. In case of (partial) duplication of cohorts, the paper with the longest duration of follow-up was included in the review.

Data review and analysis

Initial selection of studies by title and abstract was performed by one reviewer (FR) and these studies were retrieved for full assessment. Three reviewers independently evaluated all studies and disagreement was resolved by consensus. The retrieved documents were screened and evaluated with a question list of 60 different items, which was then used to construct the database. The list included bibliographical details, background of the study, study design, recruitment period, inclusion and exclusion criteria, details on diagnosis, type of hormone assays used, normal test values, and eventual preoperative medical treatment. Furthermore we noted the number of included patients, the total number undergoing surgery, the number lost to follow-up, deaths, duration of follow-up, surgical details, criteria of cure, details of CT and MRI investigations, immediate postoperative results, surgically induced hypopituitarism, improved hypopituitarism, used methods for diagnosis of hypopituitarism, number of recurrences in time, histology of the tumor including immunohistochemistry, presence of invasiveness, and potential tumor growth factors. Finally we looked for recurrence-associated factors, e.g. age, gender, tumor size, postoperative hormone concentrations, invasiveness (macroscopic and microscopic), surgical technique, surgical center, biological tumor factors and the used statistical analyses.

Statistical analysis

Primary outcomes of this review were short-term remission after single surgery and induced pituitary failure. To this end we used the criteria set by the authors of each publication, either biochemical or in case of nonfunctioning adenoma (NFA) CT and/or MRI evaluation. The other main primary outcome was the incidence of recurrence of the adenoma after clinical cure, as reported by the authors. In case of NFA the postoperative CT or MRI should show no tumor remnant and studies using regrowth of a tumor remnant were excluded, unless a distinction between the two cases was made clearly. In addition we carefully evaluated clinical factors associated with recurrence were carefully evaluated. Statistical comparison between groups was done with ANOVA, with selected post-hoc contrasts. Regression analysis was used for time-dependent observations. P values < 0.05 were considered significant.

Results

The initial search resulted in a total of 1,663 publications. Of these 1,106 were excluded on the basis of title and abstract. The remaining 557 articles were assessed for inclusion in this study, and a further 427 articles were excluded on the basis of reading the full text, leaving 130 studies which fulfilled the criteria of our search. Thirteen papers were identified from other sources, mainly from references cited in the read papers. Details of the search strategy with the distribution along the 4 main groups of pituitary adenomas are shown in Fig. 1.

Short-term results of pituitary surgery

Thirty studies reported results on surgery in prolactinoma patients [7–36], 31 studies in NFA [9, 37–65], 32 studies in

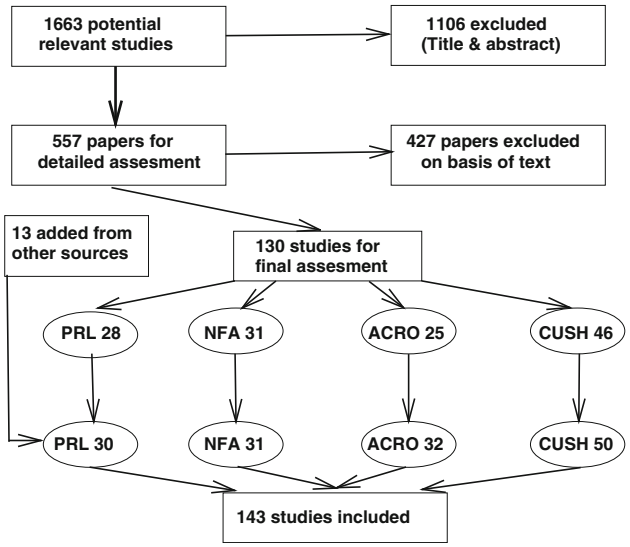

Fig. 1 Flow chart of the study assessment and used criteria. Used abbreviations are PRL: prolactinoma, NFA: nonfunctioning adenoma, ACRO: acromegaly and CUSH: M. Cushing

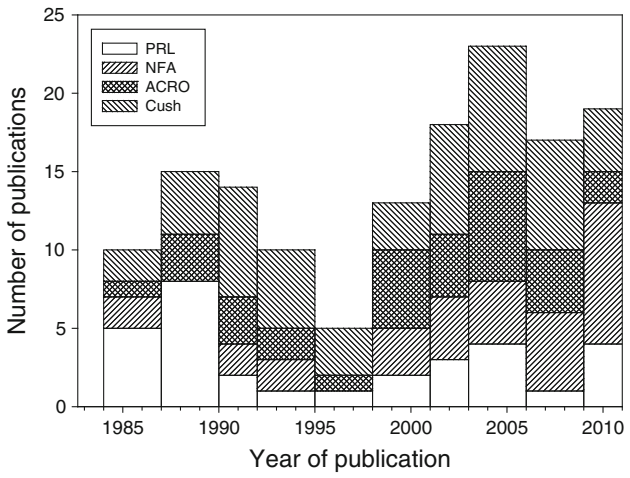

Fig. 2 Distribution of the publications on pituitary adenomas over 3 decades of transsphenoidal pituitary surgery

acromegaly [12, 18, 19, 29, 49, 66–91] and 50 studies in Cushing's disease [12, 19, 29, 92–138]. The distribution of these reports across the years is shown in Fig. 2.

The number of patients treated with a single surgical procedure for prolactinoma, NFA, acromegaly and Cushing's disease were respectively 3,152, 5,022, 3,548 and 5,787 patients. The absolute number of remission in these groups were 1,949, 2,232, 2,162 and 4,207 patients, respectively, with an overall remission percentage of respectively 61.7, 44.4, 60.9 and 72.7% (see Table 1). The remission percentage, as reported in the papers, is shown in Fig. 3. The mean remission values and (ranges) were 68.8% (27–100) in prolactinoma, 47.3% (3–92) in NFA, 61.2% (37–88) in acromegaly, and 71.3% (41–98) in Cushing's disease. The surgical results are also shown as box plots in Fig. 3. Patients with NFA had a lower remission percentage compared with the other patient groups ($P < 0.001$). Patients with Cushing's disease had a higher remission percentage than patients with acromegaly ($P = 0.01$). The overall surgical results with respect to postoperative normalization according to criteria set by the authors did not show an improvement over the last 3 decades (publication year coefficient -0.18 ± 0.17, $P = 0.29$, see Fig. 4).

The incidence of new, surgery-related pituitary deficiencies is displayed in Fig. 5. It should be noted, however, that only 55% of the studies reported data on surgery-related pituitary deficiencies, as shown on the ordinate of the figure. The incidence of pituitary insufficiency was highest in patients with Cushing's disease ($P < 0.0001$), but the incidence of (new) pituitary insufficiency in NFA patients was not higher than in patients with prolactinoma or acromegaly ($P = 0.22$).

Results of long-term follow-up

The absolute number of patients in remission after surgery who were included in follow-up studies is shown in Table 1. This table also shows the total duration of follow-up in years and the number of recurrences. The mean reported years of follow-up was 4.90 ± 0.57 in prolactinoma, 5.13 ± 0.24 in NFA, 6.36 ± 0.58 in acromegaly and 4.91 ± 0.34 in Cushing's disease. The follow-up was longer in acromegaly than in the other groups ($P < 0.01$). The percentage tumor recurrence as mentioned in the papers or calculated from available data is shown in Fig. 6. The recurrence incidence was lowest in patients with acromegaly ($P < 0.0001$). Prolactinoma patients had a higher recurrence incidence than patients with acromegaly and Cushing's disease ($P < 0.0001$), but there was no difference between patients with NFA and prolactinoma ($P = 0.17$).

Studies with a different follow-up period could be compared when recurrence was expressed as number of recurrences per total years at risk. The overall recurrence rate, related to follow-up years, could be calculated from the data shown in Table 1. This was respectively for the 4 groups 0.034, 0.022, 0.007 and 0.023 patients/years. The recurrence rate for the 4 groups, as defined above, is shown in Fig. 7. Patients with acromegaly had a better long-term outcome than patients in the other 3 groups ($P < 0.0001$), while patients with a prolactinoma had a higher recurrence rate than patients in the other groups ($P < 0.001$). There was no difference between NFA and prolactinoma patients ($P = 0.09$).

No change in recurrence incidence was observed over 3 decades of publications ($P = 0.51$), although the recurrence rate showed a modest improvement with time (coefficient -0.0007 ± 0.0003, $P = 0.04$, see Fig. 8). The

Table 1 Absolute number of patients, remission, recurrence and follow-up period

	PRL	NFA	ACRO	CUSH
Number of patients	3,152	5,022	3,548	5,787
Number of patients in remission	1,949	2,232	2,162	4,207
Number of patients in remission in follow-up	1,771	2,065	1,980	4,206
Total years of follow-up in patients in remission	9,861	10,411	14,082	21,229
Number of recurrences	339	236	98	491

PRL prolactinoma, *NFA* nonfunctioning adenoma, *ACRO* acromegaly, *Cush* Cushing's disease

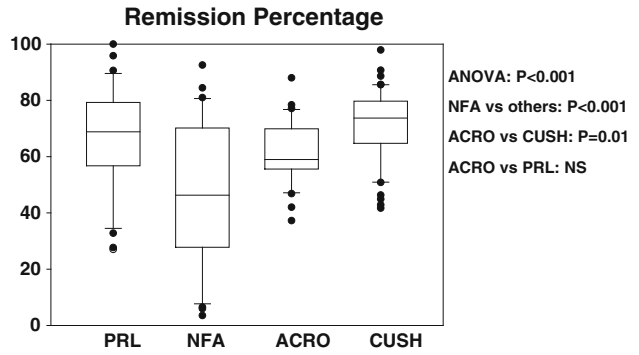

Fig. 3 Box-plots of the remission percentage after pituitary surgery in patients with prolactinoma, nonfunctioning adenoma, acromegaly and Cushing's disease

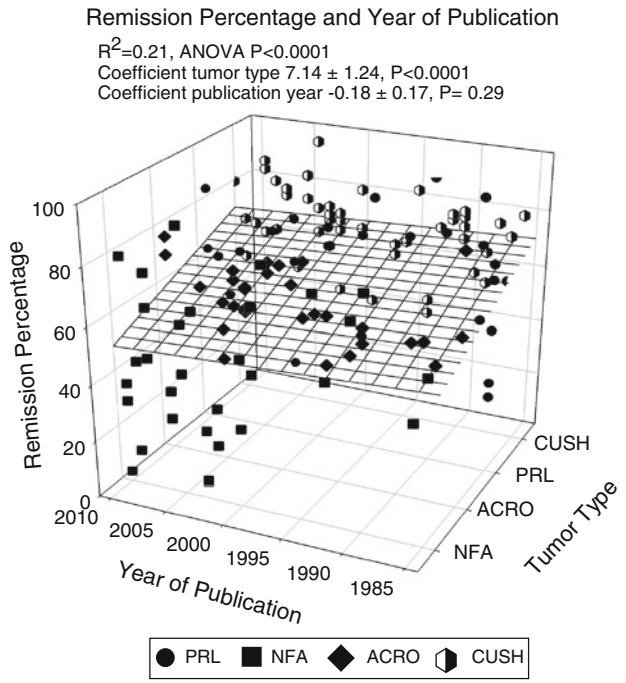

Fig. 4 Regression analysis of tumor type, year of publication and remission percentage with its regression plane

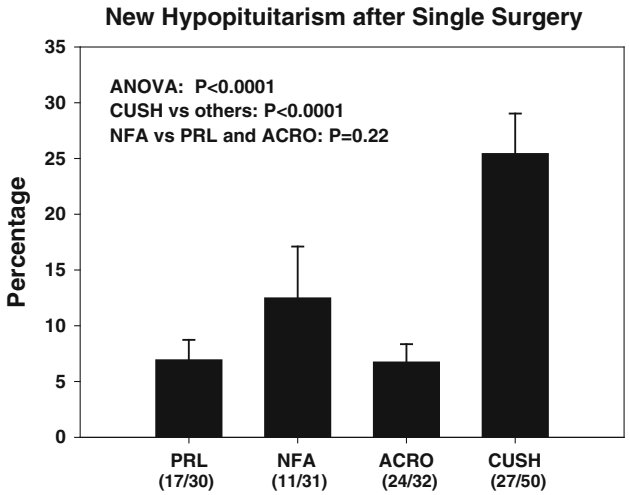

Fig. 5 The incidence of new hypopituitarism caused by pituitary surgery. The *numbers* between parentheses refer to the number of studies reporting hypopituitarism and the total number of manuscripts

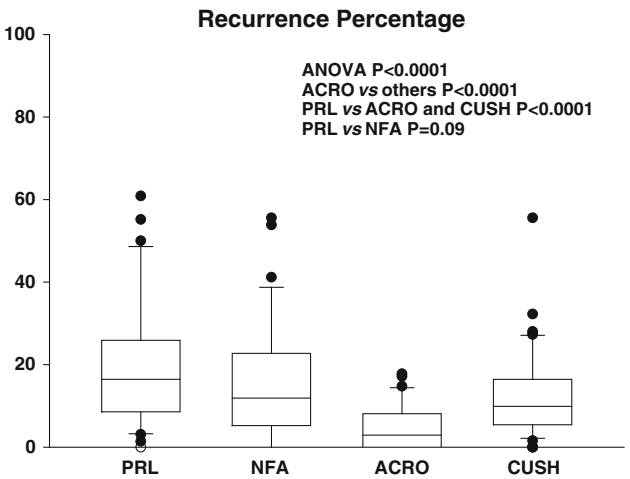

Fig. 6 Box-plots of the recurrence percentage during follow-up

majority of recurrences occurred between 1 and 5 years after surgery, although patients with acromegaly and NFA also displayed a significant number of recurrences between 5 and 10 years (Fig. 9). These data were based on papers that provided details on recurrence during follow-up (77% of the prolactinoma papers, 71% of NFA papers, 72% of acromegaly papers and 70% of papers on Cushing's disease).

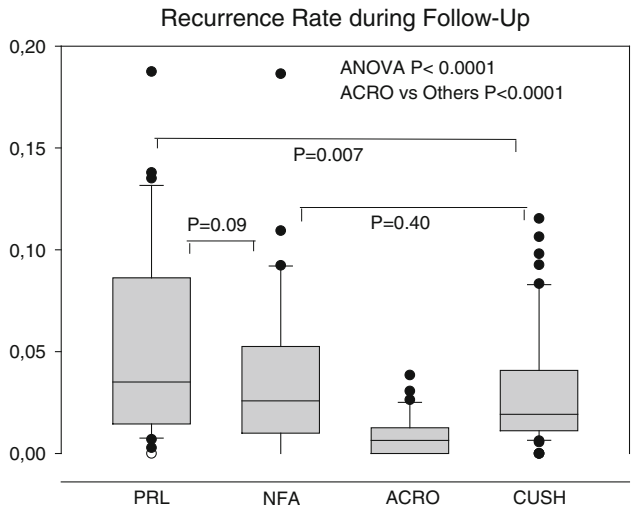

Fig. 7 Box-plots of the recurrence rate in patients treated by transsphenoidal surgery (ratio of the number of recurrences and years of follow-up in patients at risk) Note that the lowest recurrence rate was found in patients with acromegaly: *P* value versus Cushing's disease $P = 0.013$, versus NFA $P = 0.003$ and versus prolactinoma $P < 0.0001$

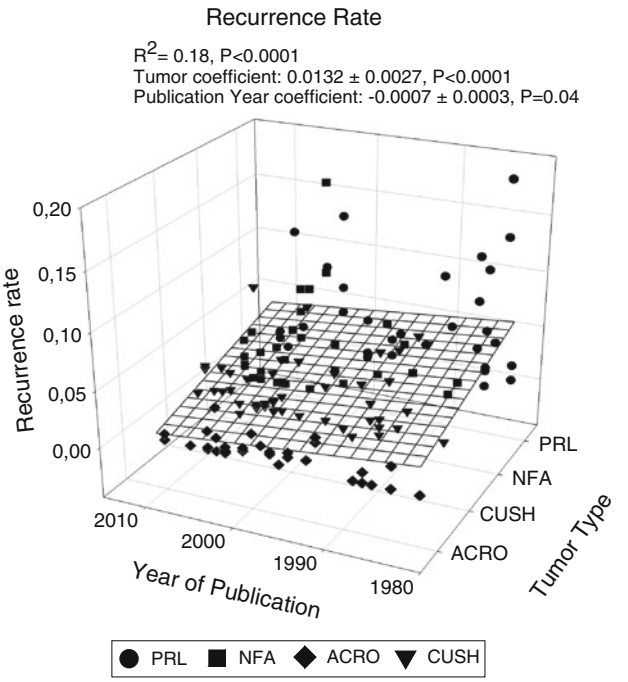

Fig. 8 Regression analysis of pituitary adenoma recurrence rate in patients after pituitary surgery over 3 decades of publications with its regression plane

There was a weak linear correlation between recurrence percentage and remission percentage ($R^2 = 0.032$, $P = 0.03$). Short-term and long-term surgical results did not differ between European and American studies.

Prognostic factors for adenoma recurrence

The search of prognostic factors involved in pituitary adenoma recurrence was hampered by several factors. Some studies reported zero recurrences during follow-up, thus logically excluding any prognostic factor. This was the case in 6 studies in NFA [37, 49, 52, 56, 60, 139], 1 study on prolactinoma [49], 12 studies in acromegaly [12, 29, 49, 68, 73, 76, 79, 89, 90, 140–142] and 3 studies in Cushing's disease [118, 120, 136]. Studies with a low absolute number of recurrences mostly did not generally provide clinical details and finally multivariate analysis was rarely performed when a sufficient number of recurrences were present. We were therefore obliged to apply a simplified approach and we selected studies where one or more factors, such as age, gender, tumor size, invasion etc., were considered to be associated with recurrence or excluded as a significant factor for it, and scored these as 'yes' and 'no', respectively, as shown in Fig. 10, with the bars representing the number of studies. The figures at the end of the bars are the absolute number of patients with relapse, and the total years of follow-up in patients at risk.

In NFA, age [40, 44, 51, 54, 55, 57, 61, 63, 143], gender [40, 44, 45, 51, 54, 57, 61, 63, 143], tumor size [40, 44, 51, 54, 55, 57, 61, 63, 143], and tumor invasion had prognostic significance in some studies[40, 41, 64], but not in others [51, 54, 57, 63]. Histology was a predictor in some studies [40, 43, 47, 57, 58], but not in others [54, 61, 64, 143].

In prolactinoma, age [15, 21, 24, 27, 144], gender [21, 23, 24, 27] and macroscopic and microscopic tumor invasion were not significant factors for recurrence [15, 21, 24, 26, 27]. Tumor size was not a convincing factor [7, 8, 10, 15, 30, 34, 144] while a low basal postoperative PRL concentration (below 10 or 6 μg/L thus much lower than the upper normal basal PRL level of 20 or 22 μg/L) [7, 15, 23, 24, 28, 30, 34, 144] and normalization of the TRH test were favorable clinical factors associated with permanent cure [10, 21, 30]. In acromegaly, tumor recurrence was unlikely in patients with a low postoperative GH concentration [69, 87, 145, 146], a low glucose-suppressed GH concentration [147, 148], or with normalization of the paradoxical GH increase after TRH infusion [149]. Tumor size [66, 69, 71, 81, 145, 146] and invasion [66, 84] were not definite prognostic factors in acromegaly. In Cushing's disease, age [98, 117, 134, 150], gender [117, 134, 150],tumor size [95, 98, 111, 117, 121, 132, 134, 150] and macroscopic tumor invasion [95, 98, 117, 134] were not prognostic factors of recurrence. Microscopic tumor invasion [29, 92, 117, 126, 134], as well as postoperative dexamethasone tests [93, 95, 96, 98, 114, 134] were undetermined factors. However, a significant positive and favorable factor was a low basal postoperative cortisol concentration in more studies [19, 29, 93, 97, 99, 104, 105, 107, 109, 112–114, 116, 121–123, 127, 129, 130, 133,

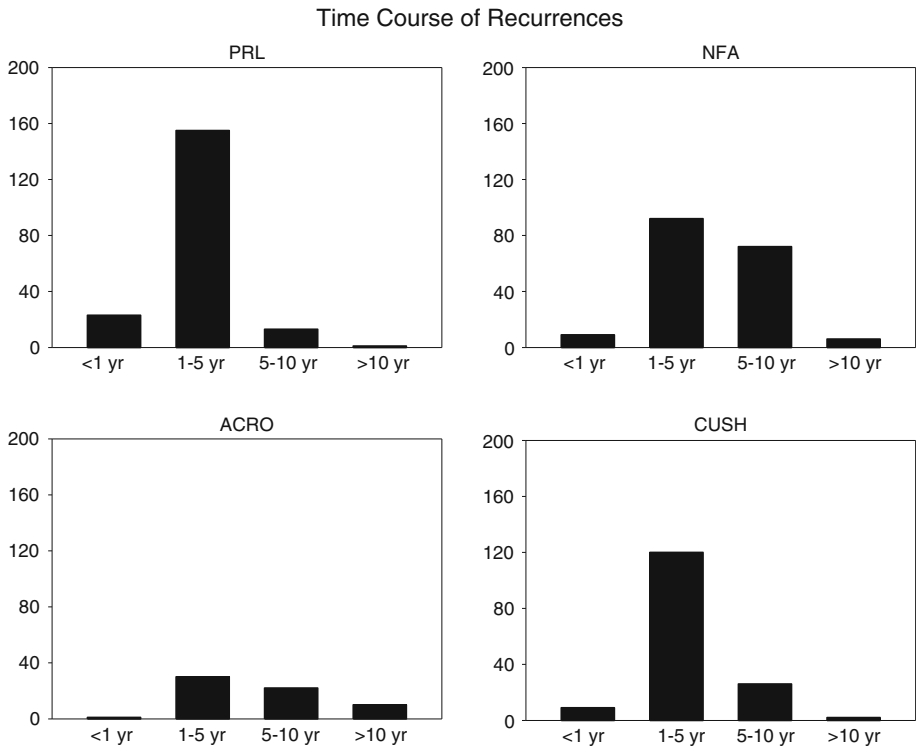

Fig. 9 Time course of tumor recurrence after surgery. Data are expressed as total number of patients

151], than in those which did not confirm this finding [92, 95, 98, 117, 134, 138].

Discussion

An important outcome of surgery of pituitary adenomas is the immediate cure rate and the impact on normal pituitary function. In our study we restricted the analysis to studies that reported both short-term and long-term results of surgery in unselected patient series. Our data analyses demonstrate that patients with NFA have a lower chance of remission, which is not too surprising, because many patients are not diagnosed until the tumor is large resulting in compression of the optic chiasm with generally substantial supra- and para-sellar extension, making curative surgery less feasible than in (functioning) adenomas restricted to the sella turcica. Indeed, many studies in acromegaly, prolactinoma and Cushing's disease, have stressed the difference in remission percentage between patients with a microadenoma and those with a macroadenoma [34, 80, 152, 153]. The overall (initial) remission in patients with prolactinoma is comparable with the remission achieved in patients with acromegaly and Cushing's disease, suggesting that the tumor type per se does not influence outcome.

Recurrence of a functioning adenoma was based on the reappearance of clinical signs and symptoms, confirmed by biochemical tests, as used by the authors. In order to allow a fair comparison with the other adenoma types, in NFA recurrence was defined as reappearance of an adenoma, thus excluding patients with growth of a tumor remnant, possible. For this review recurrence was either expressed as percentage of patients who could be followed-up and thus at risk for recurrence (thus controlling for deaths and other causes of follow-up failure) and as recurrence rate. The latter expression is the ratio of number of recurrences and total years of patients at risk, thus (partially) eliminating differences in follow-up time between studies. This study shows that patients with acromegaly had fewer recurrences than patients with other pituitary adenomas, both expressed as percentage and as recurrence rate. In contrast, patients with prolactinoma had a higher recurrence percentage and rate than patients with acromegaly or Cushing's disease. At present, this behavior of prolactinoma is largely unexplained, but may be related to definition of cure, or to more frequent microscopic tumor infiltration into normal pituitary tissue, which is not removed at surgery.

Another interesting point emerging from this study is that the remission percentage of transsphenoidal surgery did not improve over the last three decades. The majority of papers (>95%) which were included in this review were based on traditional surgery using an operation microscope, without the use of other tools, such as intraoperative blood sampling of hormones, intraoperative use of MRI, neuronavigation or the additional use of an endoscope. If earlier reports estimated the remission percentage to be too high, a publication year-dependent decrease in recurrence

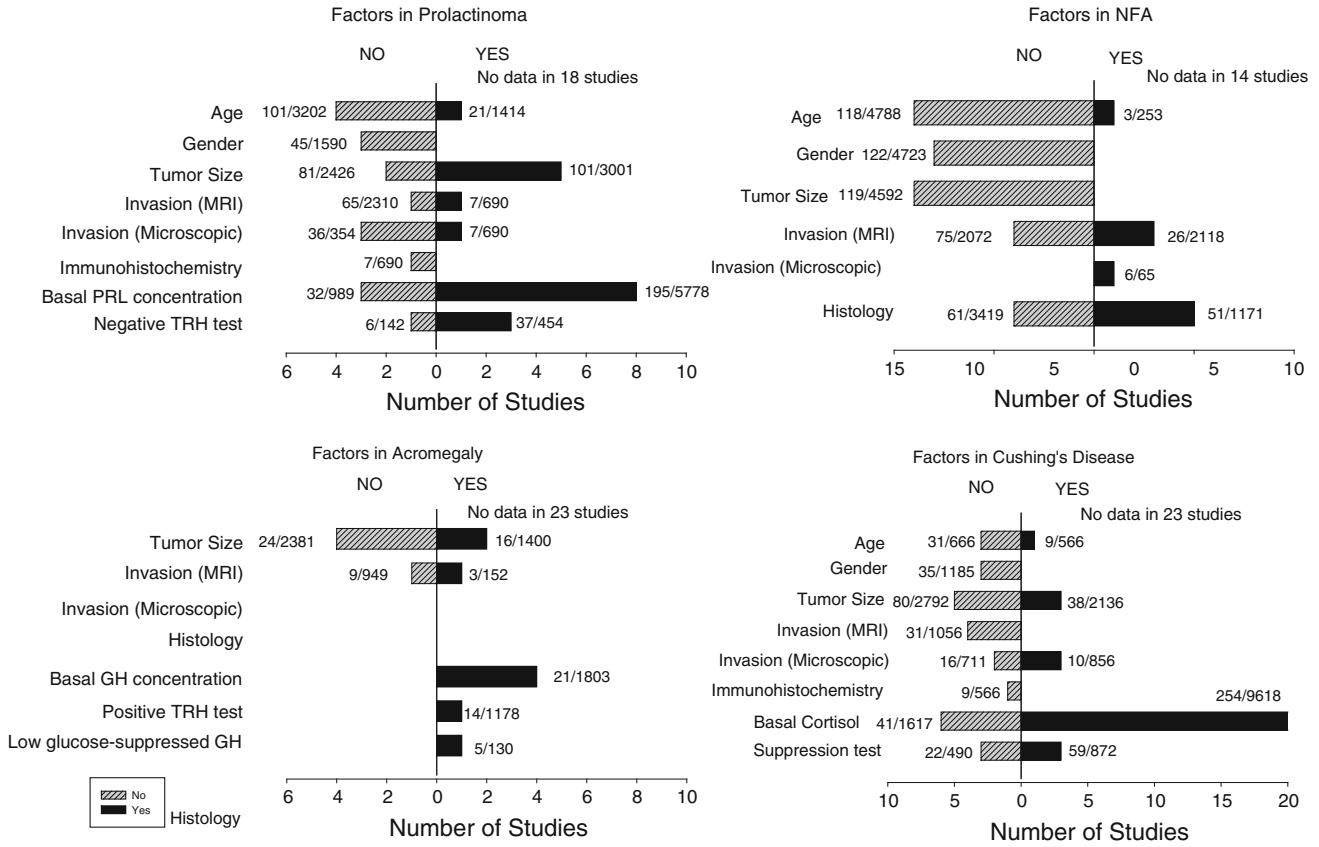

Fig. 10 Prognostic factors of tumor recurrence. The *horizontal bars* represent the number of studies reporting significant associations (*black bars*) or the absence of a statistically validated association (*gray bars*). The reported factors are listed vertically for each adenoma type. The number of studies not reporting clinical details on recurrences is also indicated in the figure. The *numbers* at the end of the *bars* reflect the total number of recurrences of that particular risk factor and the total years at risk for the group

percentage and rate would have been expected. Indeed, the review demonstrated a very moderate decrease in recurrence rate over the years, which could also be explained by improved surgical techniques, increased experience of neurosurgeons and the limitation of performance of pituitary operations to dedicated surgeons. Furthermore, a very weak correlation between remission and recurrence percentage was found, explaining only 3% of variability, indicating that remission and recurrence are largely independent phenomena. These observations, therefore, indicate that remission rates reported in earlier publications are not greatly influenced by less sensitive hormone assays in use at that time.

One might suppose that a longer follow-up period will lead to a higher recurrence rate. We investigated this hypothesis, which was only possible in studies which reported details on the time of recurrence after surgery, or gave sufficient data to calculate these data. Fortunately, the percentage of studies of the 4 tumor types reporting these details was comparable, and lying between 70 and 77%. For a meaningful comparison between studies, the time period was divided into bins of less than 1 year, between 1 and 5 years, between 6 and 10 years, and longer than 10 years. With the limitation that the majority of studies were shorter than 10 years, the incidence of recurrence peaked between 1 and 5 years, and not later. It is not unreasonable to assume that adenoma recurrences originate from tiny postoperative tumor remnants, with insufficient hormone secretion (or size) to affect biochemical tests or detection with high-resolution MRI. Apparently, the growth rates of these recurrent tumors are comparable, although recurrence of functional tumors is no guarantee that they can be detected by MRI or high resolution CT scanning.

The clinical factors of age, gender, tumor size and invasion had no predictive value in most studies, independently of the tumor type. However, there is no agreement whether silent corticotrope adenomas have a greater growth potential than NFA tumors. This matter is of some importance, since prophylactic postoperative irradiation has been advocated for this type of adenoma. However, our review indicates that this issue is still unsettled [154]. Particularly, regarding acromegaly and prolactinoma one might expect that a normalized TRH test (normalization of

a paradoxical GH increase in acromegaly and stimulatory PRL in prolactinoma) would indicate permanent cure. Indeed, in prolactinoma this was found in 3 studies, but not in another study. A comparable situation was found in acromegaly. A paradoxical TRH test in acromegaly is considered as non-diagnostic and thus clinically not useful, because it can be also present in other conditions, such as in children, anorexia nervosa, and serious liver disease [155]. Interestingly, acromegalic patients with a paradoxical response of GH to TRH express the TRH receptor in the adenoma, while TRH-negative patients do not [156], establishing the pathophysiological basis for this response. In a selected series of acromegalic patients who had a normal postoperative GH suppression (although differing in magnitude) and a normalized TRH test, only one recurrence was noted after a 14.3 years [160]. Others also found the test useful [157] but not all [158, 159]. In our experience, if an abnormal TRH test is the only biochemical abnormality observed, it may take a long time before a relapse becomes clinically obvious, thus requiring long-term observations [160]. The low number of reports in Cushing's disease and acromegaly, relating outcome of hormone suppression tests with recurrence. renders the usefulness of this parameter doubtful at this time, and careful studies, such as initiated in acromegaly by Freda are required to establish its value [148].

The most interesting predictor of recurrence was a low postoperative basal hormone concentration for functioning adenomas, and not dynamic tests, although these were not systematically investigated in most studies. Depending on the sensitivity and specificity of the assay, a low hormone concentration indicates no tumor remnant or a residual tumor mass which does not lead to clinical significant growth. Whether this latter hypothesis is correct can only be ascertained when more unselected studies with much longer follow-up become available.

New pituitary deficiencies caused by surgery were reported in only 60% of the publications. In the majority of these, only basal hormone concentrations were used, rather than dynamic tests. In addition, GH reserve was rarely investigated with stimulation tests. Nevertheless, pituitary function was most often disturbed in Cushing's disease, which can be partially explained by long-term glucocorticoid dependency and the commonly observed permanent diabetes insipidus. It is also possible that more aggressive surgery was used than in other adenomas, because of the seriousness of the condition. In many studies details were insufficient to outline the precise distribution of newly developed pituitary malfunction.

A new approach in pituitary surgery is the endoscopic technique. For this review, we only found 4 studies exclusively using the endoscopic technique and with a sufficient follow-up period for inclusion. Available studies which compared traditional transsphenoidal microsurgery with the endoscopic surgery indicate that the endoscopic technique is associated with a shorter hospital stay, less blood loss, fewer nasal complications and less frequent diabetes insipidus. Although these findings are important, till now no major improvement of direct postoperative remission has been demonstrated and long-term data are not yet available [161–163].

In summary, this analysis indicates that remission is lowest in patients with nonfunctioning adenomas, and recurrence is highest in patients with a prolactinoma. The remission rate has not improved over 3 decades of publication, but there is a modest decrease in recurrences with time. The highest incidence of tumor recurrence is between 1 and 5 years after surgery. Surgery-related hypopituitarism was highest in Cushing's disease. The most important predictor for recurrence is the postoperative basal (non-stimulated) hormone level in functioning adenomas, while in nonfunctioning adenomas no single convincing factor could be identified.

Acknowledgments We thank Johannes W. Schoones, medical librarian, for his help and advice on the structured literature search and Ashley Bryant for his help with constructing the 3-D plots in Sigmaplot. We are grateful to our colleague Dr. Neveen A. T. Hamdy for the critical reading of the manuscript.

Conflict of interest The authors have nothing to declare.

References

1. Giustina A, Bronstein MD, Casanueva FF, Chanson P, Ghigo E, Ho KK, Klibanski A, Lamberts S, Trainer P, Melmed S (2011) Current management practice for acromegaly: an international survey. Pituitary 14:125–133
2. Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, Wass JA, Endocrine Society (2011) Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 96: 273–288
3. Roelfsema F, Biermasz NR, Romijn JA, Pereira AM (2005) Treatment strategies for acromegaly. Expert Opin Emerg Drugs 10:875–890
4. Sherlock M, Woods C, Sheppard MC (2011) Medical therapy in acromegaly. Nat Rev Endocrinol 7:291–300
5. Farrell WE, Clayton RN (2000) Molecular pathogenesis of pituitary tumors. Front Neuroendocrinol 21:174–198
6. Saeger W (2005) Pituitary tumors: prognostic indicators. Endocrine 28:57–66
7. Amar AP, Couldwell WT, Chen JC, Weiss MH (2002) Predictive value of serum prolactin levels measured immediately after transsphenoidal surgery. J Neurosurg 97:307–314
8. Arafah BM, Brodkey JS, Pearson OH (1986) Gradual recovery of lactotroph responsiveness to dynamic stimulation following

surgical removal of prolactinomas: long-term follow-up studies. Metabolism 35:905–912
9. Auer LM, Clarici G (1985) The first 100 transsphenoidally operated pituitary adenomas in a non-specialised centre: surgical results and tumour-recurrence. Neurol Res 7:153–160
10. Charpentier G, de Plunkett T, Jedynak P, Peillon F, Le Gentil P, Racadot J, Visot A, Derome P (1985) Surgical treatment of prolactinomas. Short- and long-term results, prognostic factors. Horm Res 22:222–227
11. Ciccarelli E, Ghigo E, Miola C, Gandini G, Muller EE, Camanni F (1990) Long-term follow-up of 'cured' prolactinoma patients after successful adenomectomy. Clin Endocrinol (Oxf) 32: 583–592
12. Esposito V, Santoro A, Minniti G, Salvati M, Innocenzi G, Lanzetta G, Cantore G (2004) Transsphenoidal adenomectomy for GH-, PRL- and ACTH-secreting pituitary tumours: outcome analysis in a series of 125 patients. Neurol Sci 25:251–256
13. Fahlbusch R, Buchfelder M (1985) Present status of neurosurgery in the treatment of prolactinomas. Neurosurg Rev 8:195–205
14. Faria MA Jr, Tindall GT (1982) Transsphenoidal microsurgery for prolactin-secreting pituitary adenomas. J Neurosurg 56:33–43
15. Feigenbaum SL, Downey DE, Wilson CB, Jaffe RB (1996) Transsphenoidal pituitary resection for preoperative diagnosis of prolactin-secreting pituitary adenoma in women: long term follow-up. J Clin Endocrinol Metab 81:1711–1719
16. Gondim JA, Schops M, Cavalcante JP, Gomes E (2007) Rathke's cleft cyst and partial feet adactyly: an unusual association. Arq Neuropsiquiatr 65:1040–1042
17. Gordon D, Richards A, Bulloch R, Cohen HN, Semple CG, Beastall GH, Thomson JA, Teasdale G (1985) Prolactin dynamics and tumour size in the prediction of surgical outcome for prolactinoma. Q J Med 54:141–151
18. Kreutzer J, Vance ML, Lopes MB, Laws ER Jr (2001) Surgical management of GH-secreting pituitary adenomas: an outcome study using modern remission criteria. J Clin Endocrinol Metab 86:4072–4077
19. Kristof RA, Schramm J, Redel L, Neuloh G, Wichers M, Klingmuller D (2002) Endocrinological outcome following first time transsphenoidal surgery for GH-, ACTH-, and PRL-secreting pituitary adenomas. Acta Neurochir (Wien) 144: 555–561
20. Lee EJ, Ahn JY, Noh T, Kim SH, Kim TS, Kim SH (2009) Tumor tissue identification in the pseudocapsule of pituitary adenoma: should the pseudocapsule be removed for total resection of pituitary adenoma? Neurosurgery 64:62–69
21. Losa M, Mortini P, Barzaghi R, Gioia L, Giovanelli M (2002) Surgical treatment of prolactin-secreting pituitary adenomas: early results and long-term outcome. J Clin Endocrinol Metab 87:3180–3186
22. Maira G, Anile C, De Marinis L, Barbarino A (1989) Prolactin-secreting adenomas: surgical results and long-term follow-up. Neurosurgery 24:736–743
23. Massoud F, Serri O, Hardy J, Somma M, Beauregard H (1996) Transsphenoidal adenomectomy for microprolactinomas: 10 to 20 years of follow-up. Surg Neurol 45:341–346
24. Nelson PB, Goodman M, Maroon JC, Martinez AJ, Moossy J, Robinson AG (1983) Factors in predicting outcome from operation in patients with prolactin-secreting pituitary adenomas. Neurosurgery 13:634–641
25. Otten P, Rilliet B, Reverdin A, Demierre B, Berney J (1996) Pituitary adenoma secreting prolactin. Results of their surgical treatment. Neurochirurgie 42:44–53
26. Parl FF, Cruz VE, Cobb CA, Bradley CA, Aleshire SL (1986) Late recurrence of surgically removed prolactinomas. Cancer 57:2422–2426
27. Raverot G, Wierinckx A, Dantony E, Auger C, Chapas G, Villeneuve L, Brue T, Figarella-Branger D, Roy P, Jouanneau E, Jan M, Lachuer J, Trouillas J (2010) Prognostic factors in prolactin pituitary tumors: clinical, histological, and molecular data from a series of 94 patients with a long postoperative follow-up. J Clin Endocrinol Metab 95:1708–1716
28. Rodman EF, Molitch ME, Post KD, Biller BJ, Reichlin S (1984) Long-term follow-up of transsphenoidal selective adenomectomy for prolactinoma. JAMA 252:921–924
29. Santoro A, Minniti G, Ruggeri A, Esposito V, Jaffrain-Rea ML, Delfini R (2007) Biochemical remission and recurrence rate of secreting pituitary adenomas after transsphenoidal adenomectomy: long-term endocrinologic follow-up results. Surg Neurol 68:513–518
30. Schlechte JA, Sherman BM, Chapler FK, VanGilder J (1986) Long term follow-up of women with surgically treated prolactin-secreting pituitary tumors. J Clin Endocrinol Metab 62:1296–1301
31. Serri O, Hardy J, Massoud F (1993) Relapse of hyperprolactinemia revisited. N Engl J Med 329:1357
32. Thomson JA, Davies DL, McLaren EH, Teasdale GM (1994) Ten year follow up of microprolactinoma treated by transsphenoidal surgery. BMJ 309:1409–1410
33. Turner HE, Adams CB, Wass JA (1999) Trans-sphenoidal surgery for microprolactinoma: an acceptable alternative to dopamine agonists? Eur J Endocrinol 140:43–47
34. Tyrrell JB, Lamborn KR, Hannegan LT, Applebury CB, Wilson CB (1999) Transsphenoidal microsurgical therapy of prolactinomas: initial outcomes and long-term results. Neurosurgery 44:254–261
35. Webster J, Page MD, Bevan JS, Richards SH, Douglas-Jones AG, Scanlon MF (1992) Low recurrence rate after partial hypophysectomy for prolactinoma: the predictive value of dynamic prolactin function tests. Clin Endocrinol (Oxf) 36:35–44
36. Woosley RE, King JS, Talbert L (1982) Prolactin-secreting pituitary adenomas: neurosurgical management of 37 patients. Fertil Steril 37:54–60
37. Alameda C, Lucas T, Pineda E, Brito M, Uria JG, Magallon R, Estrada J, Barcelo B (2005) Experience in management of 51 non-functioning pituitary adenomas: indications for post-operative radiotherapy. J Endocrinol Invest 28:18–22
38. Baldeweg SE, Pollock JR, Powell M, Ahlquist J (2005) A spectrum of behaviour in silent corticotroph pituitary adenomas. Br J Neurosurg 19:38–42
39. Bradley KM, Adams CB, Potter CP, Wheeler DW, Anslow PJ, Burke CW (1994) An audit of selected patients with non-functioning pituitary adenoma treated by transsphenoidal surgery without irradiation. Clin Endocrinol (Oxf) 41:655–659
40. Brochier S, Galland F, Kujas M, Parker F, Gaillard S, Raftopoulos C, Young J, Alexopoulou O, Maiter D, Chanson P (2010) Factors predicting relapse of nonfunctioning pituitary macroadenomas after neurosurgery: a study of 142 patients. Eur J Endocrinol 163:193–200
41. Chang EF, Zada G, Kim S, Lamborn KR, Quinones-Hinojosa A, Tyrrell JB, Wilson CB, Kunwar S (2008) Long-term recurrence and mortality after surgery and adjuvant radiotherapy for nonfunctional pituitary adenomas. J Neurosurg 108:736–745
42. Chen L, White WL, Spetzler RF, Xu B (2011) A prospective study of nonfunctioning pituitary adenomas: presentation, management, and clinical outcome. J Neurooncol 102:129–138
43. Cho HY, Cho SW, Kim SW, Shin CS, Park KS, Kim SY (2010) Silent corticotroph adenomas have unique recurrence characteristics compared with other nonfunctioning pituitary adenomas. Clin Endocrinol (Oxf) 72:648–653
44. Comtois R, Beauregard H, Somma M, Serri O, Aris-Jilwan N, Hardy J (1991) The clinical and endocrine outcome to trans-sphenoidal

microsurgery of nonsecreting pituitary adenomas. Cancer 68:860–866
45. Dekkers OM, Pereira AM, Romijn JA (2008) Treatment and follow-up of clinically nonfunctioning pituitary macroadenomas. J Clin Endocrinol Metab 93:3717–3726
46. Ebersold MJ, Quast LM, Laws ER Jr, Scheithauer B, Randall RV (1986) Long-term results in transsphenoidal removal of nonfunctioning pituitary adenomas. J Neurosurg 64:713–719
47. Erickson D, Scheithauer B, Atkinson J, Horvath E, Kovacs K, Lloyd RV, Young WF Jr (2009) Silent subtype 3 pituitary adenoma: a clinicopathologic analysis of the Mayo Clinic experience. Clin Endocrinol (Oxf) 71:92–99
48. Ferrante E, Ferraroni M, Castrignano T, Menicatti L, Anagni M, Reimondo G, Del Monte P, Bernasconi D, Loli P, Faustini-Fustini M, Borretta G, Terzolo M, Losa M, Morabito A, Spada A, Beck-Peccoz P, Lania AG (2006) Non-functioning pituitary adenoma database: a useful resource to improve the clinical management of pituitary tumors. Eur J Endocrinol 155:823–829
49. Gondim JA, Schops M, de Almeida JP, de Albuquerque LA, Gomes E, Ferraz T, Barroso FA (2010) Endoscopic endonasal transsphenoidal surgery: surgical results of 228 pituitary adenomas treated in a pituitary center. Pituitary 13:68–77
50. Greenman Y, Ouaknine G, Veshchev I, Reider-Groswasser II, Segev Y, Stern N (2003) Postoperative surveillance of clinically nonfunctioning pituitary macroadenomas: markers of tumour quiescence and regrowth. Clin Endocrinol (Oxf) 58:763–769
51. Jaffrain-Rea ML, Derome P, Bataini JP, Thomopoulos P, Bertagna X, Luton JP (1993) Influence of radiotherapy on long-term relapse in clinically non-secreting pituitary adenomas. A retrospective study (1970-1988). Eur J Med 2:398–403
52. Kabil MS, Eby JB, Shahinian HK (2005) Fully endoscopic endonasal vs. transseptal transsphenoidal pituitary surgery. Minim Invasive Neurosurg 48:348–354
53. Lillehei KO, Kirschman DL, Kleinschmidt-DeMasters BK, Ridgway EC (1998) Reassessment of the role of radiation therapy in the treatment of endocrine-inactive pituitary macroadenomas. Neurosurgery 43:432–438
54. Losa M, Mortini P, Barzaghi R, Ribotto P, Terreni MR, Marzoli SB, Pieralli S, Giovanelli M (2008) Early results of surgery in patients with nonfunctioning pituitary adenoma and analysis of the risk of tumor recurrence. J Neurosurg 108:525–532
55. Meij BP, Lopes MB, Ellegala DB, Alden TD, Laws ER Jr (2002) The long-term significance of microscopic dural invasion in 354 patients with pituitary adenomas treated with transsphenoidal surgery. J Neurosurg 96:195–208
56. O'Sullivan EP, Woods C, Glynn N, Behan LA, Crowley R, O'Kelly P, Smith D, Thompson CJ, Agha A (2009) The natural history of surgically treated but radiotherapy-naive nonfunctioning pituitary adenomas. Clin Endocrinol (Oxf) 71:709–714
57. Park P, Chandler WF, Barkan AL, Orrego JJ, Cowan JA, Griffith KA, Tsien C (2004) The role of radiation therapy after surgical resection of nonfunctional pituitary macroadenomas. Neurosurgery 55:100–106
58. Scheithauer BW, Jaap AJ, Horvath E, Kovacs K, Lloyd RV, Meyer FB, Laws ER Jr, Young WF Jr (2000) Clinically silent corticotroph tumors of the pituitary gland. Neurosurgery 47: 723–729
59. Shone GR, Richards SH, Hourihan MD, Hall R, Thomas JP, Scanlon MF (1991) Non-secretory adenomas of the pituitary treated by trans-ethmoidal sellotomy. J R Soc Med 84:140–143
60. Soto-Ares G, Cortet-Rudelli C, Assaker R, Boulinguez A, Dubest C, Dewailly D, Pruvo JP (2002) MRI protocol technique in the optimal therapeutic strategy of non-functioning pituitary adenomas. Eur J Endocrinol 146:179–186
61. Turner HE, Stratton IM, Byrne JV, Adams CB, Wass JA (1999) Audit of selected patients with nonfunctioning pituitary adenomas treated without irradiation—a follow-up study. Clin Endocrinol (Oxf) 51:281–284
62. Webb KM, Laurent JJ, Okonkwo DO, Lopes MB, Vance ML, Laws ER Jr (2003) Clinical characteristics of silent corticotrophic adenomas and creation of an internet-accessible database to facilitate their multi-institutional study. Neurosurgery 53: 1076–1084
63. Woollons AC, Hunn MK, Rajapakse YR, Toomath R, Hamilton DA, Conaglen JV, Balakrishnan V (2000) Non-functioning pituitary adenomas: indications for postoperative radiotherapy. Clin Endocrinol (Oxf) 53:713–717
64. Yang SY, Zhu T, Zhang JN, Sun YS (1994) Transsphenoidal microsurgical management of pituitary adenomas. Microsurgery 15:754–759
65. Zhang X, Li A, Yi S, Zhang Z, Fei Z, Zhang J, Fu L, Liu W, Chen Y (1998) Transsphenoidal microsurgical removal of large pituitary adenomas. Chin Med J (Engl) 111:963–967
66. Abosch A, Tyrrell JB, Lamborn KR, Hannegan LT, Applebury CB, Wilson CB (1998) Transsphenoidal microsurgery for growth hormone-secreting pituitary adenomas: initial outcome and long-term results. J Clin Endocrinol Metab 83:3411–3418
67. Ahmed M, Rifai A, Al Jurf M, Akhtar M, Woodhouse N (1989) Classical pituitary apoplexy presentation and a follow-up of 13 patients. Horm Res 31:125–132
68. Arafah BU, Brodkey JS, Kaufman B, Velasco M, Manni A, Pearson OH (1980) Transsphenoidal microsurgery in the treatment of acromegaly and gigantism. J Clin Endocrinol Metab 50: 578–585
69. Baskin DS, Boggan JE, Wilson CB (1982) Transsphenoidal microsurgical removal of growth hormone-secreting pituitary adenomas. A review of 137 cases. J Neurosurg 56:634–641
70. Beauregard C, Truong U, Hardy J, Serri O (2003) Long-term outcome and mortality after transsphenoidal adenomectomy for acromegaly. Clin Endocrinol (Oxf) 58:86–91
71. Biermasz NR, Dekker FW, Pereira AM, van Thiel SW, Schutte PJ, van Dulken H, Romijn JA, Roelfsema F (2004) Determinants of survival in treated acromegaly in a single center: predictive value of serial insulin-like growth factor I measurements. J Clin Endocrinol Metab 89:2789–2796
72. Davis DH, Laws ER Jr, Ilstrup DM, Speed JK, Caruso M, Shaw EG, Abboud CF, Scheithauer BW, Root LM, Schleck C (1993) Results of surgical treatment for growth hormone-secreting pituitary adenomas. J Neurosurg 79:70–75
73. De P, Rees DA, Davies N, John R, Neal J, Mills RG, Vafidis J, Davies JS, Scanlon MF (2003) Transsphenoidal surgery for acromegaly in wales: results based on stringent criteria of remission. J Clin Endocrinol Metab 88:3567–3572
74. Freda PU, Post KD, Powell JS, Wardlaw SL (1998) Evaluation of disease status with sensitive measures of growth hormone secretion in 60 postoperative patients with acromegaly. J Clin Endocrinol Metab 83:3808–3816
75. Gasser RW, Spoendlin H, Finkenstedt G, Pallua AK, Aichner F, Braunsteiner H (1993) Trans-septo-sphenoidal operation for pituitary adenoma in 92 patients: results and follow-up endocrine studies. Wien Klin Wochenschr 105:204–207
76. Grisoli F, Leclercq T, Jaquet P, Guibout M, Winteler JP, Hassoun J, Vincentelli F (1985) Transsphenoidal surgery for acromegaly—long-term results in 100 patients. Surg Neurol 23:513–519
77. Krieger MD, Couldwell WT, Weiss MH (2003) Assessment of long-term remission of acromegaly following surgery. J Neurosurg 98:719–724
78. Losa M, Oeckler R, Schopohl J, Muller OA, Alba-Lopez J, von Werder K (1989) Evaluation of selective transsphenoidal adenomectomy by endocrinological testing and somatomedin-C measurement in acromegaly. J Neurosurg 70:561–567

79. Minniti G, Jaffrain-Rea ML, Esposito V, Santoro A, Tamburrano G, Cantore G (2003) Evolving criteria for post-operative biochemical remission of acromegaly: can we achieve a definitive cure? An audit of surgical results on a large series and a review of the literature. Endocr Relat Cancer 10:611–619
80. Nomikos P, Buchfelder M, Fahlbusch R (2005) The outcome of surgery in 668 patients with acromegaly using current criteria of biochemical 'cure'. Eur J Endocrinol 152:379–387
81. Osman IA, James RA, Chatterjee S, Mathias D, Kendall-Taylor P (1994) Factors determining the long-term outcome of surgery for acromegaly. QJM 87:617–623
82. Ronchi CL, Arosio M, Rizzo E, Lania AG, Beck-Peccoz P, Spada A (2007) Adequacy of current postglucose GH nadir limit (<1 microg/l) to define long-lasting remission of acromegalic disease. Clin Endocrinol (Oxf) 66:538–542
83. Ross DA, Wilson CB (1988) Results of transsphenoidal microsurgery for growth hormone-secreting pituitary adenoma in a series of 214 patients. J Neurosurg 68:854–867
84. Serri O, Somma M, Comtois R, Rasio E, Beauregard H, Jilwan N, Hardy J (1985) Acromegaly: biochemical assessment of cure after long term follow-up of transsphenoidal selective adenomectomy. J Clin Endocrinol Metab 61:1185–1189
85. Sheaves R, Jenkins P, Blackburn P, Huneidi AH, Afshar F, Medbak S, Grossman AB, Besser GM, Wass JA (1996) Outcome of transsphenoidal surgery for acromegaly using strict criteria for surgical cure. Clin Endocrinol (Oxf) 45:407–413
86. Shimon I, Cohen ZR, Ram Z, Hadani M (2001) Transsphenoidal surgery for acromegaly: endocrinological follow-up of 98 patients. Neurosurgery 48:1239–1243
87. Trepp R, Stettler C, Zwahlen M, Seiler R, Diem P, Christ ER (2005) Treatment outcomes and mortality of 94 patients with acromegaly. Acta Neurochir (Wien) 147:243–251
88. Valdemarsson S, Ljunggren S, Bramnert M, Norrhamn O, Nordstrom CH (2000) Early postoperative growth hormone levels: high predictive value for long-term outcome after surgery for acromegaly. J Intern Med 247:640–650
89. van't Verlaat JW, Nortier JW, Hendriks MJ, Bosma NJ, Graamans K, Lubsen H, Vasen HF, Thijssen JH, Croughs RJ (1988) Transsphenoidal microsurgery as primary treatment in 25 acromegalic patients: results and follow-up. Acta Endocrinol (Copenh) 117:154–158
90. van Lindert E, Hey O, Boecher-Schwarz H, Perneczky A (1997) Treatment results of acromegaly as analyzed by different criteria. Acta Neurochir (Wien) 139:905–912
91. Yamada S, Aiba T, Takada K, Ozawa Y, Shimizu T, Sawano S, Shishiba Y, Sano T (1996) Retrospective analysis of long-term surgical results in acromegaly: preoperative and postoperative factors predicting outcome. Clin Endocrinol (Oxf) 45:291–298
92. Acebes JJ, Martino J, Masuet C, Montanya E, Soler J (2007) Early post-operative ACTH and cortisol as predictors of remission in Cushing's disease. Acta Neurochir (Wien) 149: 471–477
93. 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 (2010) Biochemical predictors of outcome of pituitary surgery for Cushing's disease. Neuroendocrinology 91:169–178
94. Arnott RD, Pestell RG, McKelvie PA, Henderson JK, McNeill PM, Alford FP (1990) A critical evaluation of transsphenoidal pituitary surgery in the treatment of Cushing's disease: prediction of outcome. Acta Endocrinol (Copenh) 123:423–430
95. Atkinson AB, Kennedy A, Wiggam MI, McCance DR, Sheridan B (2005) Long-term remission rates after pituitary surgery for Cushing's disease: the need for long-term surveillance. Clin Endocrinol (Oxf) 63:549–559
96. Bakiri F, Tatai S, Aouali R, Semrouni M, Derome P, Chitour F, Benmiloud M (1996) Treatment of Cushing's disease by transsphenoidal, pituitary microsurgery: prognosis factors and long-term follow-up. J Endocrinol Invest 19:572–580
97. Barbetta L, Dall'Asta C, Tomei G, Locatelli M, Giovanelli M, Ambrosi B (2001) Assessment of cure and recurrence after pituitary surgery for Cushing's disease. Acta Neurochir (Wien) 143:477–481
98. Blevins LS Jr, Christy JH, Khajavi M, Tindall GT (1998) Outcomes of therapy for Cushing's disease due to adrenocorticotropin-secreting pituitary macroadenomas. J Clin Endocrinol Metab 83:63–67
99. Bochicchio D, Losa M, Buchfelder M (1995) 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. J Clin Endocrinol Metab 80:3114–3120
100. Boggan JE, Tyrrell JB, Wilson CB (1983) Transsphenoidal microsurgical management of Cushing's disease. Report of 100 cases. J Neurosurg 59:195–200
101. Buchfelder M, Fahlbusch R, Schott W, Honegger J (1991) Long-term follow-up results in hormonally active pituitary adenomas after primary successful transsphenoidal surgery. Acta Neurochir Suppl (Wien) 53:72–76
102. Buchfelder M, Schlaffer S (2010) Pituitary surgery for Cushing's disease. Neuroendocrinology 92(Suppl 1):102–106
103. Burke CW, Adams CB, Esiri MM, Morris C, Bevan JS (1990) Transsphenoidal surgery for Cushing's disease: does what is removed determine the endocrine outcome? Clin Endocrinol (Oxf) 33:525–537
104. Chee GH, Mathias DB, James RA, Kendall-Taylor P (2001) Transsphenoidal pituitary surgery in Cushing's disease: can we predict outcome? Clin Endocrinol (Oxf) 54:617–626
105. Chen JC, Amar AP, Choi S, Singer P, Couldwell WT, Weiss MH (2003) Transsphenoidal microsurgical treatment of Cushing disease: postoperative assessment of surgical efficacy by application of an overnight low-dose dexamethasone suppression test. J Neurosurg 98:967–973
106. Esposito F, Dusick JR, Cohan P, Moftakhar P, McArthur D, Wang C, Swerdloff RS, Kelly DF (2006) Clinical review: early morning cortisol levels as a predictor of remission after transsphenoidal surgery for Cushing's disease. J Clin Endocrinol Metab 91:7–13
107. Flitsch J, Knappe UJ, Ludecke DK (2003) The use of postoperative ACTH levels as a marker for successful transsphenoidal microsurgery in Cushing's disease. Zentralbl Neurochir 64:6–11
108. Fomekong E, Maiter D, Grandin C, Raftopoulos C (2009) Outcome of transsphenoidal surgery for Cushing's disease: a high remission rate in ACTH-secreting macroadenomas. Clin Neurol Neurosurg 111:442–449
109. Guilhaume B, Bertagna X, Thomsen M, Bricaire C, Vila-Porcile E, Olivier L, Racadot J, Derome P, Laudat MH, Girard F (1988) Transsphenoidal pituitary surgery for the treatment of Cushing's disease: results in 64 patients and long term follow-up studies. J Clin Endocrinol Metab 66:1056–1064
110. Hammer GD, Tyrrell JB, Lamborn KR, Applebury CB, Hannegan ET, Bell S, Rahl R, Lu A, Wilson CB (2004) Transsphenoidal microsurgery for Cushing's disease: initial outcome and long-term results. J Clin Endocrinol Metab 89:6348–6357
111. Hofmann BM, Hlavac M, Martinez R, Buchfelder M, Muller OA, Fahlbusch R (2008) Long-term results after microsurgery for Cushing disease: experience with 426 primary operations over 35 years. J Neurosurg 108:9–18
112. Hoybye C, Grenback E, Thoren M, Hulting AL, Lundblad L, von Holst H, Anggard A (2004) Transsphenoidal surgery in

Cushing disease: 10 years of experience in 34 consecutive cases. J Neurosurg 100:634–638
113. Imaki T, Tsushima T, Hizuka N, Odagiri E, Murata Y, Suda T, Takano K (2001) Postoperative plasma cortisol levels predict long-term outcome in patients with Cushing's disease and determine which patients should be treated with pituitary irradiation after surgery. Endocr J 48:53–62
114. Invitti C, Pecori GF, De Martin M, Cavagnini F (1999) Diagnosis and management of Cushing's syndrome: results of an Italian multicentre study. Study Group of the Italian Society of Endocrinology on the Pathophysiology of the Hypothalamic–Pituitary–Adrenal Axis. J Clin Endocrinol Metab 84:440–448
115. Lindholm J, Juul S, Jorgensen JO, Astrup J, Bjerre P, Feldt-Rasmussen U, Hagen C, Jorgensen J, Kosteljanetz M, Kristensen L, Laurberg P, Schmidt K, Weeke J (2001) Incidence and late prognosis of cushing's syndrome: a population-based study. J Clin Endocrinol Metab 86:117–123
116. Ludecke DK, Niedworok G (1985) Results of microsurgery in Cushing's disease and effect on hypertension. Cardiology 72(Suppl 1):91–94
117. Mampalam TJ, Tyrrell JB, Wilson CB (1988) Transsphenoidal microsurgery for Cushing disease. A report of 216 cases. Ann Intern Med 109:487–493
118. McCance DR, Besser M, Atkinson AB (1996) Assessment of cure after transsphenoidal surgery for Cushing's disease. Clin Endocrinol (Oxf) 44:1–6
119. Nakane T, Kuwayama A, Watanabe M, Takahashi T, Kato T, Ichihara K, Kageyama N (1987) Long term results of transsphenoidal adenomectomy in patients with Cushing's disease. Neurosurgery 21:218–222
120. Netea-Maier RT, van Lindert EJ, den Heijer M, van der Eerden A, Pieters GF, Sweep CG, Grotenhuis JA, Hermus AR (2006) Transsphenoidal pituitary surgery via the endoscopic technique: results in 35 consecutive patients with Cushing's disease. Eur J Endocrinol 154:675–684
121. Patil CG, Prevedello DM, Lad SP, Vance ML, Thorner MO, Katznelson L, Laws ER Jr (2008) Late recurrences of Cushing's disease after initial successful transsphenoidal surgery. J Clin Endocrinol Metab 93:358–362
122. Pereira AM, van Aken MO, van Dulken H, Schutte PJ, Biermasz NR, Smit JW, Roelfsema F, Romijn JA (2003) Long-term predictive value of postsurgical cortisol concentrations for cure and risk of recurrence in Cushing's disease. J Clin Endocrinol Metab 88:5858–5864
123. Pieters GF, Hermus AR, Meijer E, Smals AG, Kloppenborg PW (1989) Predictive factors for initial cure and relapse rate after pituitary surgery for Cushing's disease. J Clin Endocrinol Metab 69:1122–1126
124. Post KD, Habas JE (1990) Comparison of long term results between prolactin secreting adenomas and ACTH secreting adenomas. Can J Neurol Sci 17:74–77
125. Prevedello DM, Pouratian N, Sherman J, Jane JA Jr, Vance ML, Lopes MB, Laws ER Jr (2008) Management of Cushing's disease: outcome in patients with microadenoma detected on pituitary magnetic resonance imaging. J Neurosurg 109:751–759
126. Ram Z, Nieman LK, Cutler GB Jr, Chrousos GP, Doppman JL, Oldfield EH (1994) Early repeat surgery for persistent Cushing's disease. J Neurosurg 80:37–45
127. Rees DA, Hanna FW, Davies JS, Mills RG, Vafidis J, Scanlon MF (2002) Long-term follow-up results of transsphenoidal surgery for Cushing's disease in a single centre using strict criteria for remission. Clin Endocrinol (Oxf) 56:541–551
128. Robert F, Hardy J (1991) Cushing's disease: a correlation of radiological, surgical and pathological findings with therapeutic results. Pathol Res Pract 187:617–621
129. Rollin G, Ferreira NP, Czepielewski MA (2007) Prospective evaluation of transsphenoidal pituitary surgery in 108 patients with Cushing's disease. Arq Bras Endocrinol Metabol 51:1355–1361
130. Salenave S, Gatta B, Pecheur S, San Galli F, Visot A, Lasjaunias P, Roger P, Berge J, Young J, Tabarin A, Chanson P (2004) Pituitary magnetic resonance imaging findings do not influence surgical outcome in adrenocorticotropin-secreting microadenomas. J Clin Endocrinol Metab 89:3371–3376
131. Shimon I, Ram Z, Cohen ZR, Hadani M (2002) Transsphenoidal surgery for Cushing's disease: endocrinological follow-up monitoring of 82 patients. Neurosurgery 51:57–61
132. Swearingen B, Biller BM, Barker FG, Katznelson L, Grinspoon S, Klibanski A, Zervas NT (1999) Long-term mortality after transsphenoidal surgery for Cushing disease. Ann Intern Med 130:821–824
133. Tagliaferri M, Berselli ME, Loli P (1986) Transsphenoidal microsurgery for Cushing's disease. Acta Endocrinol (Copenh) 113:5–11
134. Tahir AH, Sheeler LR (1992) Recurrent Cushing's disease after transsphenoidal surgery. Arch Intern Med 152:977–981
135. Tindall GT, Herring CJ, Clark RV, Adams DA, Watts NB (1990) Cushing's disease: results of transsphenoidal microsurgery with emphasis on surgical failures. J Neurosurg 72:363–369
136. Trainer PJ, Lawrie HS, Verhelst J, Howlett TA, Lowe DG, Grossman AB, Savage MO, Afshar F, Besser GM (1993) Transsphenoidal resection in Cushing's disease: undetectable serum cortisol as the definition of successful treatment. Clin Endocrinol (Oxf) 38:73–78
137. Valassi E, Biller BM, Swearingen B, Pecori GF, Losa M, Mortini P, Hayden D, Cavagnini F, Klibanski A (2010) Delayed remission after transsphenoidal surgery in patients with Cushing's disease. J Clin Endocrinol Metab 95:601–610
138. Yap LB, Turner HE, Adams CB, Wass JA (2002) Undetectable postoperative cortisol does not always predict long-term remission in Cushing's disease: a single centre audit. Clin Endocrinol (Oxf) 56:25–31
139. Dekkers OM, Lagro J, Burman P, Jorgensen JO, Romijn JA, Pereira AM (2010) Recurrence of hyperprolactinemia after withdrawal of dopamine agonists: systematic review and meta-analysis. J Clin Endocrinol Metab 95:43–51
140. Losa M, Giovanelli M, Persani L, Mortini P, Faglia G, Beck-Peccoz P (1996) Criteria of cure and follow-up of central hyperthyroidism due to thyrotropin-secreting pituitary adenomas. J Clin Endocrinol Metab 81:3084–3090
141. Ronchi CL, Varca V, Giavoli C, Epaminonda P, Beck-Peccoz P, Spada A, Arosio M (2005) Long-term evaluation of postoperative acromegalic patients in remission with previous and newly proposed criteria. J Clin Endocrinol Metab 90:1377–1382
142. Arafah BM, Rosenzweig JL, Fenstermaker R, Salazar R, McBride CE, Selman W (1987) Value of growth hormone dynamics and somatomedin C (insulin-like growth factor I) levels in predicting the long-term benefit after transsphenoidal surgery for acromegaly. J Lab Clin Med 109:346–354
143. Chang EF, Sughrue ME, Zada G, Wilson CB, Blevins LS Jr, Kunwar S (2010) Long term outcome following repeat transsphenoidal surgery for recurrent endocrine-inactive pituitary adenomas. Pituitary 13:223–229
144. Serri O, Rasio E, Beauregard H, Hardy J, Somma M (1983) Recurrence of hyperprolactinemia after selective transsphenoidal adenomectomy in women with prolactinoma. N Engl J Med 309:280–283
145. Ahmed S, Elsheikh M, Stratton IM, Page RC, Adams CB, Wass JA (1999) Outcome of transphenoidal surgery for acromegaly and its relationship to surgical experience. Clin Endocrinol (Oxf) 50:561–567

146. Swearingen B, Barker FG, Katznelson L, Biller BM, Grinspoon S, Klibanski A, Moayeri N, Black PM, Zervas NT (1998) Long-term mortality after transsphenoidal surgery and adjunctive therapy for acromegaly. J Clin Endocrinol Metab 83:3419–3426
147. Freda PU, Wardlaw SL, Post KD (1998) Long-term endocrinological follow-up evaluation in 115 patients who underwent transsphenoidal surgery for acromegaly. J Neurosurg 89:353–358
148. Freda PU, Nuruzzaman AT, Reyes CM, Sundeen RE, Post KD (2004) Significance of "abnormal" nadir growth hormone levels after oral glucose in postoperative patients with acromegaly in remission with normal insulin-like growth factor-I levels. J Clin Endocrinol Metab 89:495–500
149. Biermasz NR, Smit JW, van Dulken H, Roelfsema F (2002) Postoperative persistent thyrotrophin releasing hormone-induced growth hormone release predicts recurrence in patients with acromegaly. Clin Endocrinol (Oxf) 56:313–319
150. Sonino N, Zielezny M, Fava GA, Fallo F, Boscaro M (1996) Risk factors and long-term outcome in pituitary-dependent Cushing's disease. J Clin Endocrinol Metab 81:2647–2652
151. Lindsay JR, Oldfield EH, Stratakis CA, Nieman LK (2011) The postoperative basal cortisol and CRH tests for prediction of long-term remission from cushing's disease after transsphenoidal surgery. J Clin Endocrinol Metab 96:2057–2064
152. Kreutzer J, Buslei R, Wallaschofski H, Hofmann B, Nimsky C, Fahlbusch R, Buchfelder M (2008) Operative treatment of prolactinomas: indications and results in a current consecutive series of 212 patients. Eur J Endocrinol 158:11–18
153. Ludecke DK, Abe T (2006) Transsphenoidal microsurgery for newly diagnosed acromegaly: a personal view after more than 1, 000 operations. Neuroendocrinology 83:230–239
154. Karavitaki N, Ansorge O, Wass JA (2007) Silent corticotroph adenomas. Arq Bras Endocrinol Metabol 51:1314–1318
155. Popovic V (2005) Are there alternative tests for diagnosis of acromegaly? J Endocrinol Invest 28:73–74
156. Igarashi-Migitaka J, Yamada S, Hara M, Sano T, Ozawa Y, Ohtani-Kaneko R, Hirata K (2003) Gene expression study of thyrotropin releasing hormone (TRH) receptor using RT-PCR: relationship to clinical and immunohistochemical phenotypes in a series of human pituitary adenomas. Endocr J 50:459–467
157. Arosio M, Giovanelli MA, Riva E, Nava C, Ambrosi B, Faglia G (1983) Clinical use of pre- and postsurgical evaluation of abnormal GH responses in acromegaly. J Neurosurg 59:402–408
158. Brockmeier SJ, Buchfelder M, Fahlbusch R (1993) TRH/GnRH test in acromegaly. Long-term follow-up experience with successfully treated patients. Horm Metab Res 25:275–277
159. Valdemarsson S, Bramnert M, Cronquist S, Elner A, Eneroth CM, Hedner P, Lindvall-Axelsson M, Nordstrom CH, Stromblad LG (1991) Early postoperative basal serum GH level and the GH response to TRH in relation to the long-term outcome of surgical treatment for acromegaly: a report on 39 patients. J Intern Med 230:49–54
160. Biermasz NR, van Dulken H, Roelfsema F (2000) Ten-year follow-up results of transsphenoidal microsurgery in acromegaly. J Clin Endocrinol Metab 85:4596–4602
161. Dorward NL (2010) Endocrine outcomes in endoscopic pituitary surgery: a literature review. Acta Neurochir (Wien) 152:1275–1279
162. Rotenberg B, Tam S, Ryu WH, Duggal N (2010) Microscopic versus endoscopic pituitary surgery: a systematic review. Laryngoscope 120:1292–1297
163. Strychowsky J, Nayan S, Reddy K, Farrokhyar F, Sommer D (2011) Purely endoscopic transsphenoidal surgery versus traditional microsurgery for resection of pituitary adenomas: systematic review. J Otolaryngol Head Neck Surg 40:175–185