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## Treatment of Cushing's Disease: A Retrospective Clinical Study of the Latest 100 Cases

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### Abstract

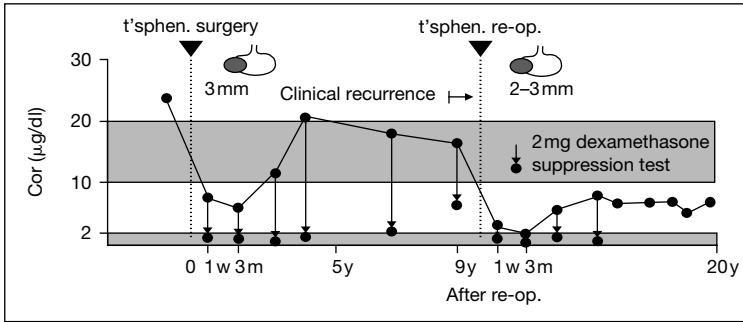
We evaluate the current role of microsurgery for Cushing's disease (CD) and the efficacy of adjuvant treatment modalities. The standard treatment for primary CD remains transsphenoidal surgery followed by adjuvant therapy in cases with persisting hypercortisolism. Moderately severe cases are treated with radiotherapy, while in the very severe adrenalectomy is performed. In our series of primary CD (March 1997 to September 2004, mean observation period 18.8 months) adenomas were confirmed intraoperatively in 84.0% of the cases. Remission was achieved in 75.0% and recurrence was observed in 4.8% of the patients. Complications occurred in 2.0% of the cases and all resolved without resulting in permanent morbidity. In the literature, the rates of intraoperative confirmation of an adenoma vary between 59.1 and 100%, remission rates between 42 and 100%, and recurrence rates between 3.0 and 63.2% depending on the experience of the surgeon and on the definition of remission. These rates have not improved significantly over the years. In experienced hands selective adenomectomy remains the least damaging and most effective treatment modality since it results in rapid clinical improvement if performed successfully. Therefore, it remains the treatment of choice. Patients not cured by surgery alone benefited from a combination of adjuvant treatment tailored to their specific needs using medications, radiation and/or adrenalectomy. In this fashion, we achieved normalization of cortisol levels in 79% and improvement in another 18% of the patients. We expect these rates to increase further once patients treated with radiotherapy begin to experience its full effect within the next few years.

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### Introduction

Within pituitary surgery Cushing's disease (CD) takes a special place. The differential diagnosis of central CD is based on sophisticated dynamic



**Fig. 1.** Long-term follow-up after successful (repeated) microneurosurgery in Cushing's disease.

endocrinological tests on which the indication for surgery is based. Selective microsurgical adenomectomy is considered the first treatment option but recently some authors have propagated extensive resection of the anterior lobe, although this results in more endocrine deficits and more complications. Since the first selective adenomectomy for CD was introduced by us 35 years ago [1], we have developed the impression that even in the hand of experienced endocrine surgeons no convincing improvement in remission rates has been achieved. Nevertheless, long intervals of endocrine and clinical remission have been observed following (even repeated) microneurosurgery (fig. 1). The inhomogeneous definition of remission of hypercortisolism and its still not fully understood pathophysiology might be reasons for this. It remains unclear if technical progress (e.g. endoscopy, neuronavigation, intraoperative MRI) is helpful in the treatment of this particular disease. Following the increasing importance of focused radiotherapy this treatment option is again being discussed as an alternative.

In several microsurgical studies [2–30] the rates of confirmation of an adenoma during surgery vary between 59.1 and 100%, remission rates between 42 and 100% and recurrence rates between 3.0 and 63.2%. Complications are reported in up to 27% of the cases with a maximum mortality rate of 3.6%. New endocrine deficits are observed in up to 88% of the patients.

The aim of this paper is to demonstrate the current role of microsurgery in primary CD and to compare its results with the effects of other treatment modalities. This leads to the definition of new (combined) treatment strategies. For this purpose we will first demonstrate the modern diagnostic procedures and the results of multimodal treatment strategies on the basis of a consecutive series of the latest 100 patients we have treated. Our results will be compared with the literature, and the efforts to improve the operative results will be discussed based on our many years of experience.

## Current Diagnosis of Cushing's Disease

The classical phenotypical symptoms can be impressive or even absent. Often the disease is only suspected after diabetes mellitus or hypertension is observed and is difficult to treat successfully.

Dynamic endocrine function tests lead to the diagnosis of the disease: a fasting morning basal cortisol level of  $>2 \mu\text{g}/\text{dl}$  after administering 2 mg dexamethasone (DEXA; 2-mg DEXA suppression test) at 10.00 p.m. the previous day leads to the diagnosis of Cushing's syndrome. The pituitary origin of the disease is proven by suppression of the cortisol level to  $<50\%$  of the original value after administration of 8–32 mg DEXA [31, 32]. Furthermore, the function of the anterior pituitary lobe is assessed by determining serum levels of prolactin, TSH, thyronine, thyroxine, LH, FSH, estradiol or testosterone, and ACTH plasma levels as well as cortisol serum levels before and after ACTH stimulation following an overnight fast.

A thin-layer MRI scan (2–3 mm) of the sellar region including T<sub>1</sub> and T<sub>2</sub> coronal and sagittal planes is performed to confirm a sellar tumor. When no adenoma is visible on MRI and the pituitary origin of the disease is in doubt, an inferior petrosal sinus sampling (IPSS) combined with a selective catheterization of the abdominal and thoracic veins is performed and ACTH and cortisol plasma levels are determined. By using these tests, an adrenal origin of the hypercortisolism or ectopic or paraneoplastic ACTH production can be ruled out. Furthermore they yield indirect evidence of the precise intrasellar location of the tumor. This is important for choosing the side on which to perform hemihypophysectomy in case no adenoma is found during sella exploration. In this test a larger than twofold central to peripheral gradient of ACTH levels (larger than threefold after CRH stimulation) is highly sensitive for the diagnosis of a pituitary adenoma and a more than 1.4-fold interpetrosal gradient is indicative of the lateral tumor localization [33]. Recently, its value in predicting the exact intrasellar tumor location has been discussed controversially [33–36]. In about 15% of the patients, technical problems with catheterization occur (e.g. the presence of a unilateral sinus only), and in about one third the prediction of a pituitary adenoma is false (i.e. a false-positive result).

An elevated free urinary cortisol ( $>300 \mu\text{g}/24 \text{ h}$ ) [37] or an abolished diurnal rhythm of cortisol secretion (normally exhibiting a maximum in the morning and at 8.00 p.m. the value is  $<50\%$  of the morning value) are indicative of CD as well, and might be of use in uncertain cases.

A single CRH test (0–60 min) is used less often but is still of diagnostic value. Patients suffering from ectopic Cushing's syndrome may show no increase in cortisol and ACTH after administering CRH and, in the case of an adrenal tumor, ACTH levels may be within the lower normal range [38].

## Preoperative and Operative Treatment

Since the advent of modern anesthesiology methods preoperative treatment to improve the patients' clinical status prior to surgery is necessary only if exceptionally severe metabolic changes caused by their hypercortisolism, such as hypokalemia or diabetes mellitus, hypertension or severely symptomatic osteoporosis are present. Ketoconazol is still the drug of choice; it exerts its effect by blocking corticosteroid synthesis in the liver at the level of cytochrome P-450 enzyme. By administering 600–800 mg/day at least a temporary decrease in cortisol plasma levels can be achieved until the development of adverse hepatic side effects preclude further use of the drug [39].

The transsphenoidal approach to the sella turcica, either by a sublabial paraseptal, a pernasal paraseptal or a direct pernasal route, has become the surgical standard. After opening the sphenoid sinus and removing the mucosa the sellar floor is opened using a diamond drill and the endosteum is opened with a pair of scissors. In case an adenoma is visible on MRI, a selective adenomec-tomy is performed by incising the pituitary body near the suspected tumor pole and removing the adenoma with ring curettes or suction. Furthermore, a small rim of the surrounding tissue is removed to ensure complete resection.

In case there is focally invasive tumor growth into the cavernous sinus and especially when a pseudocapsule is visible, tumor resection can be continued by carefully opening the medial wall of the cavernous sinus and then total tumor removal from the sinus can be attempted. Bleeding from smaller injuries to the cavernous sinus can be handled by an experienced surgeon. Larger scale tumor invasion of the cavernous sinus reaching the passing carotid arteries precludes further resection in this area. Tumor remnants have to be left within the cavernous sinus, leading to subtotal tumor resection.

If no tumor is found on MRI, sellar exploration is performed. Meticulously, systematic incisions into the pituitary body are carried out approximately 1–2 mm apart while the surgeon is looking for tissue suspicious for an adenoma. Once all adenomatous tissue has been removed, the whole pituitary body as well as the extraglandular space is explored in order to not miss any tumor. In the case of a negative exploration in the presence of an interpetrosal ACTH concentration gradient confirmed by preoperative sampling, a hemihypophysectomy of the putative side harboring the adenoma is performed [33]. Complete hypophysectomy is considered as an obsolete operation today. Five to 7 days perioperatively, antibiotics (usually clindamycin) and low-dose heparin (5,000 IU three times/day) are given. Postoperatively the patient may be kept in the intensive care unit overnight in order to treat the expected effects of hypocortisolism (e.g. hypotension) following successful tumor removal.

Histopathological work-up consists of normal HE staining of the specimen as well as immunohistochemical staining for pituitary hormones. Furthermore, a cell explant culture can be performed to document ACTH expression.

### **Definition of Outcome and Cure**

Postoperatively, an early basal cortisol level is determined the day following surgery (if necessary also the day thereafter) and replacement of corticosteroids is started if the cortisol levels are below the normal range. This is considered one criterion of remission. One week and about 3 months postoperatively dynamic endocrine function tests are repeated to confirm remission of the disease as well as to detect possible new endocrine deficits. The patient is defined as in endocrinological remission if the fasting basal cortisol level following 2 mg DEXA is  $<2 \mu\text{g/dl}$ . This may occur immediately or in a delayed fashion (1–3 months) following surgery.

### **Current Treatment after Initial Diagnosis of Cushing's Disease: A Clinical Study of Our Latest 100 Cases**

To illustrate our current treatment regimen the latest 100 consecutive patients suffering from CD who underwent pituitary microsurgery at the Neurosurgical Department of the University of Erlangen–Nuremberg, Germany, will be analyzed. The results will be compared to the literature and to those reported for alternative treatment regimens.

#### *Patients*

From March 1, 1997 until September 30, 2004, a total of 100 patients suffering from primary CD underwent initial surgical treatment.

In 98 patients the primary diagnosis of CD was made prior to admission to our hospital and confirmed by us prior to surgery (table 1). In 1 of these patients, the preoperative work-up was incomplete. In another patient, the biochemical data obtained preoperatively were inconsistent. Subsequently, surgical exploration of the sella was performed. Five patients were treated with ketoconazol, preoperatively. In the 2 remaining of the 100 cases there were no clinical signs for hypercortisolism but later histological work-up revealed an ACTH-producing pituitary adenoma.

There was a female preponderance of 77:23 (3.3:1) and an age range at the time of surgery of 5–77 (mean 40.7) years. The age range of the female patients was 5–77 (mean 42.5) years and that of the male patients 9–60 (mean 33.4) years.

#### *Endocrinological Work-Up*

Preoperatively basal cortisol levels ranged between 2.9 and 100.2 (mean 25.5)  $\mu\text{g/dl}$ . Excluding 5 patients (2 harbored silent ACTH-secreting tumors, 2 were diagnosed at an external hospital by high-dose DEXA or SPS, and 1 patient with an incomplete preoperative work-up), the

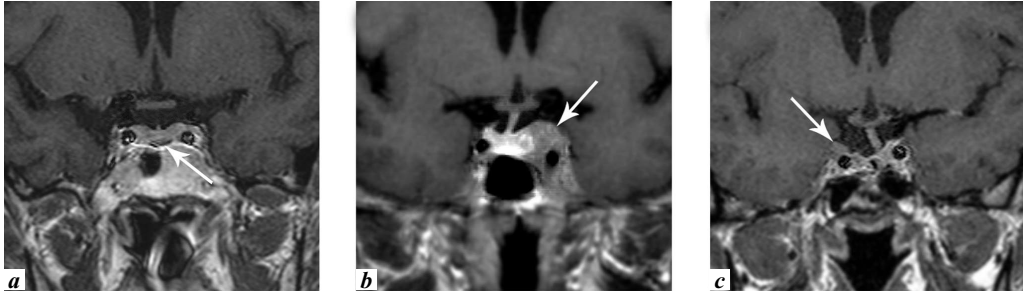
**Table 1.** Pre- and postoperative findings in 100 patients

Patient collective	100	
Female/male	77/23	3.3/1
Age	5–77 years	
Preoperative endocrine function		
Basal cortisol	2.9–100.2 µg/dl	mean 25.5 µg/dl
ACTH		
Cortisol follow-up, 2 mg DEXA	2.3–61.2 µg/dl	mean 19.2 µg/dl
Petrosal sinus sample	50	
Unilateral catheterization only	3	
Gradient right	21 (44.7%)	
Gradient left	21 (44.7%)	
No gradient	5 (10.6%)	
Imaging	100	
Adenoma visibile	15 macro, 35 micro	
Indirect sign of adenoma	8	
No adenoma found	42	
Operation		
Ketoconazol pretreatment	5	
Transsphenoidal	99	
Transcranial	1	
Macroadenoma	15	
Microadenoma	69	
Histological work-up		
Adenoma	76 (90.5%)	
Hyperplasia	2 (2.4%)	
None/normal pituitary	5 (5.9%)	
Crooke cells	1 (1.2%)	
Postoperative endocrine function		
Cortisol <5 µg/dl	47	
Cortisol <9 µg/dl	7	
Cortisol ≤21 µg/dl	24	
Cortisol >21 µg/dl	22	
Cortisol follow-up, 2 mg DEXA		
Normal	65	
Pathological	34	

preoperative cortisol levels following 2 mg DEXA, ranged between 2.3 and 61.2 (mean 19.2) µg/dl. Except for 1 case in which the central origin of Cushing's syndrome was not certain, all patients met the criteria for the diagnosis of CD following high-dose DEXA suppression testing. The postoperative observation period was between 3 and 86 (mean 18.8) months.

### *Radiological Results*

An MRI scan (Siemens Somatom Sonata<sup>®</sup>, 1.5 T) was performed in all 100 patients at the study hospital. In these MRI scans, there was clear evidence



**Fig. 2.** Radiological findings in Cushing's disease. **a** Intrasellar microadenoma. **b** Invasion into the cavernous sinus. **c** Invasive tumor remnant in the cavernous sinus, scheduled for radiosurgery.

of a macroadenoma in 15 and a microadenoma in 35 cases who, taken together, represent 50% of the patients. Assuming that a microadenoma was also present in all patients with negative MRI scans, there was a prevalence of 15% for macro- and 85% for microadenoma (fig. 2a). These findings correspond to those in the literature which report macroadenomas in 9–20% of the cases [3, 4, 7].

Indirect evidence of an adenoma, such as a deviated pituitary stalk, an increase in intrasellar volume or erosion of a subjacent part of the sellar floor, was found in 8 patients. In 42 patients no evidence of a tumor was visible on the MRI scan.

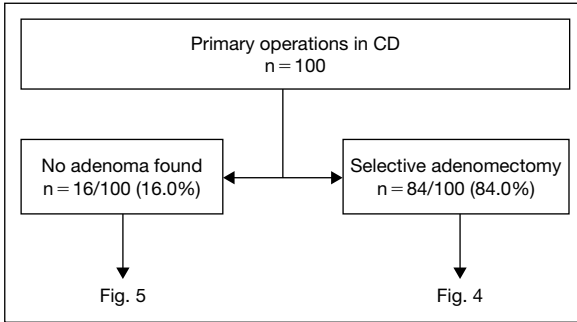
An IPSS was performed in 53 patients. A significant gradient between central and peripheral ACTH levels were found in 50 of these cases (94.3%). Furthermore in 2 patients a gradient was found but was not significant. Catheterization of both inferior petrosal sinuses was possible in 47 cases. An interpetrosal gradient towards the right sinus was found in 21 (44.7%), towards the left sinus in 21 (44.7%), and no gradient was found in 5 cases (10.6%).

### *Operative Results*

In 84 of 100 patients who underwent primary surgery a tumor was found and (selective) adenectomy was attempted. No tumor was found in 16 of 100 patients, and sella exploration (n = 9) or hemihypophysectomy (n = 7) were carried out (fig. 3).

### *Analysis of the Postoperative Outcome*

In the following, the surgical results are presented and analyzed on the basis of the various pre- and intraoperative findings.



**Fig. 3.** Findings during primary operation.

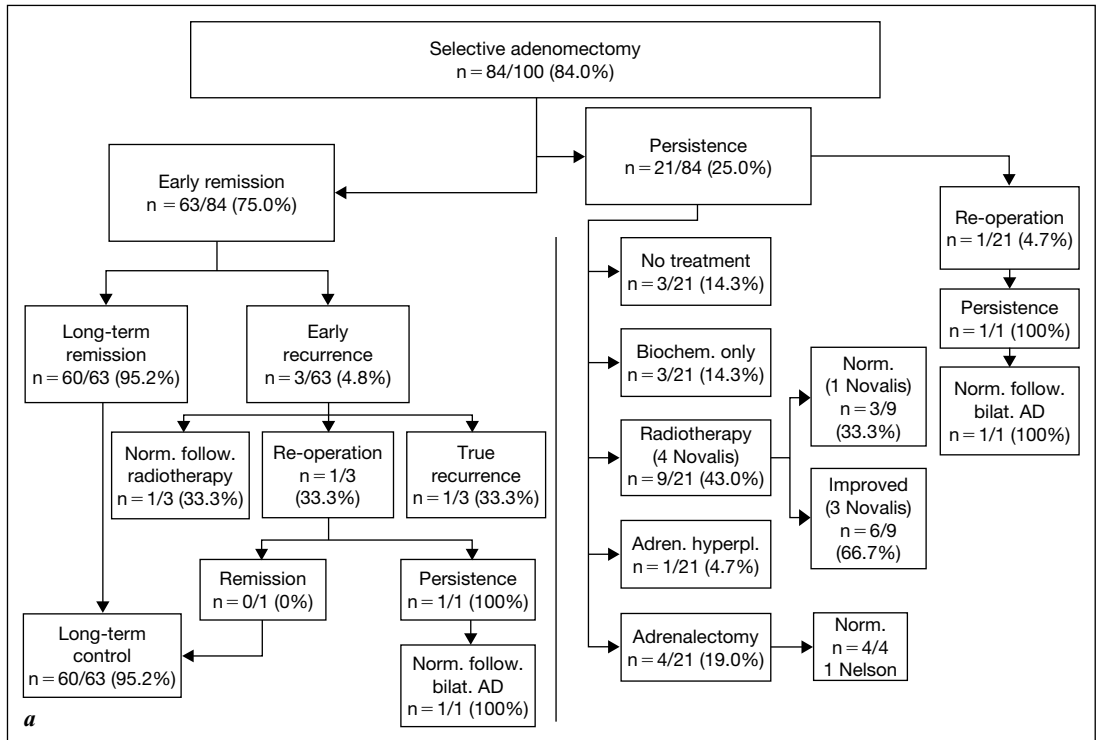
In 84 of 100 patients an adenoma was found during transsphenoidal surgery leading to a selective adenomectomy (fig. 4a). Tumor size ranged from 1.2 to 26.0 (mean 6.7) mm according to the surgeon's impression. Invasive tumor growth was found in 11 patients. In 2 of these, the tumor was only focally invasive allowing its removal from the cavernous sinus.

63 of 84 patients (75.0%) showed early remission following transsphenoidal adenomectomy and recurrence was observed in only 3 of them (4.8%). The mean observation period of these 3 patients was 18.8 (range 3–86) months. For them, remission was either achieved by radiotherapy alone, successful re-operation at another center, and unsuccessful re-operation succeeded by radiotherapy, respectively. In summary, long-term remission was observed in 60 of 63 cases (95.2%) following selective adenomectomy alone and in 100% following surgery succeeded by augmentative treatment.

The persistence rate of the disease was 25.0% (21/84) requiring further treatment as described below.

Histological work-up (table 1) confirmed a pituitary adenoma in 76 of 84 cases (90.5%). Expression of ACTH was proven by immunohistochemistry in all except one of the specimens which was too small for precise examination. Follicular hyperplasia was found in 2 cases (2.4%). No tumor or only normal pituitary tissue (at the tumor margin) was found in 5 cases (5.9%). In 1 case (1.2%) Crooke cells were found within the normal pituitary tissue, which is an indirect sign for the presence of an ACTH-producing adenoma [40].

As invasiveness into the cavernous sinus (fig. 2b) can be regarded as a negative predictor of total tumor removal as well as the elimination of hypercortisolism, the results after selective adenomectomy of noninvasive tumors are better (fig. 4b). Their tumor size was between 1.7 and 25.0 (mean 6.0) mm and showed no significant difference compared to the total patient collective. The

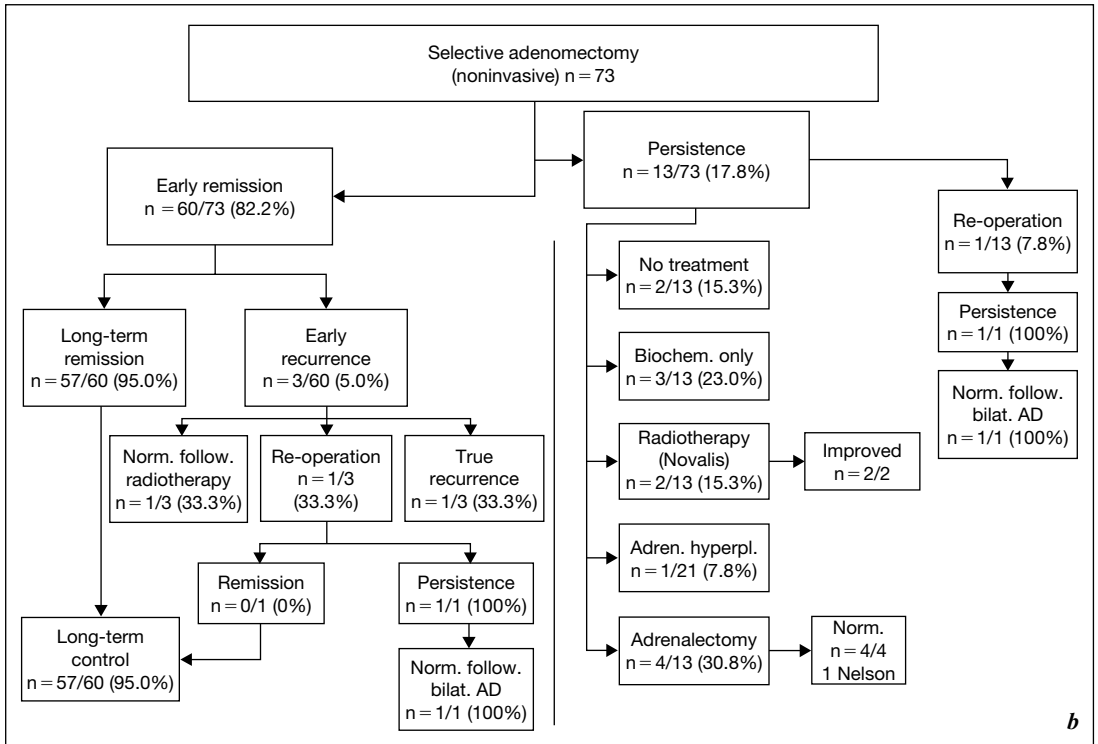


**Fig. 4. a** Outcome after selective adenomectomy in Cushing's disease. **b** Outcome after selective adenomectomy in Cushing's disease in patients with noninvasive tumors.

remission rate in these patients was 82.2% (60/73) while the recurrence rate was 5.0% (3/60) resulting in a long-term remission rate of 95.0% (57/60). Persistence of the disease occurred in 17.8% (13/73).

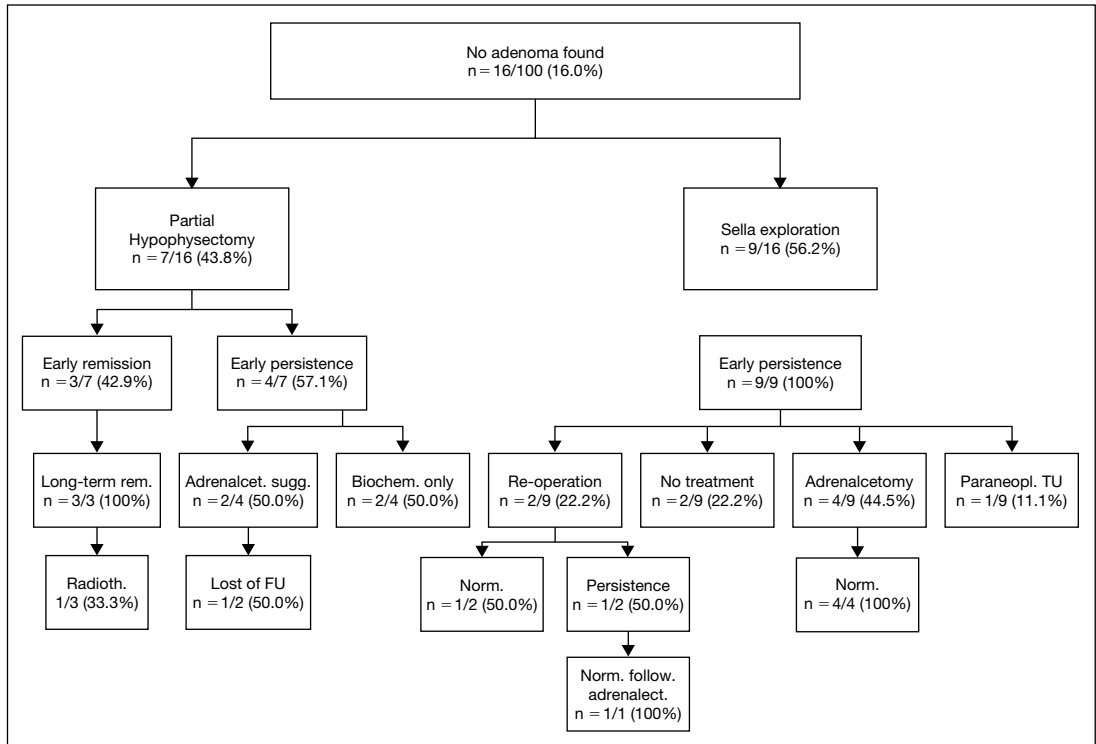
The remission rate is correlated to the tumor size after selective adenomectomy. It is substantially higher after surgery for microadenoma compared to macroadenoma. 56 of 69 patients (81.2%) suffering from a microadenoma were in remission following transsphenoidal surgery whereas only 7 of 15 patients (46.7%) suffering from a macroadenoma were in remission.

During primary transsphenoidal surgery in patients suffering from CD no adenoma was found in 16 of 100 patients (fig. 5). In 9 of these 16 patients (56.2%) exploration of the sella contents was performed but no adenoma was found and hypercortisolism persisted. A hemihypophysectomy was not carried out in these patients either because no convincing gradient could be obtained during IPSS or because a small volume of the pituitary gland made it impossible



to perform the procedure. In the remaining 7 of 16 patients (43.8%) partial hypophysectomy was performed. Early and long-term remission was observed in 3 of them (42.9%). One patient underwent additional radiotherapy. Persistence of the disease after surgery was observed in 4 of 7 patients (57.1%). The mean observation period was 18.4 (3–76) months. Augmentative treatment of these patients was performed according to the guidelines as described below.

Postoperative assessment of endocrine function in the whole series, including the cases in which sella exploration was negative, revealed the following results. 44 of the 100 patients met remission criteria immediately postoperatively and 22 more met them after 3 months, leading to a total remission rate of 66%. One patient left the hospital without undergoing endocrinological testing. The mean cortisol level of all the other patients following DEXA was 6.4 (range 0.1–49.7)  $\mu\text{g}/\text{dl}$  and in those patients meeting remission criteria, it ranged between 0.1 and 2.1 (mean 1.0)  $\mu\text{g}/\text{dl}$ . One patient was believed to be cured despite a slightly elevated cortisol level (2.1  $\mu\text{g}/\text{dl}$ ) because he showed clear



**Fig. 5.** Outcome when no tumor was found during operation.

evidence of clinical remission and, on further follow-up, his cortisol level was  $<2.0 \mu\text{g/dl}$  following 2 mg DEXA (table 1).

Basal cortisol levels 1 week after surgery were between 0.2 and 64.4 (mean 12.6)  $\mu\text{g/dl}$ . In 54 patients the level ranged between 0.2 and 8.9 (mean 2.2)  $\mu\text{g/dl}$ . At least temporarily in these patients it became necessary to start substitution therapy by administering hydrocortisone, 25 mg/day (table 1). 47 of these 54 patients exhibited tertiary adrenal insufficiency with postoperative basal cortisol levels of  $<5.0$  (range 0.2–4.9, mean 1.5)  $\mu\text{g/dl}$  and were considered to be cured of CD. The insufficiency was due to the long-term suppression of normal ACTH-producing cells within the pituitary by ACTH oversecretion from tumor cells [41].

The mean observation period in all 100 patients was 18.8 (range 3–86) months.

In the present series, preoperative bilateral blood sampling from both inferior petrosal sinuses was possible in 47 patients. In 42 of these patients a

significant gradient to one side was observed, but in only 27 of these 42 cases (64.3%) was a tumor found on the corresponding side. These numbers are comparable to other series published in the literature [34, 35]. Hence, hemihypophysectomy after negative sella exploration does not guarantee a remission even if performed on the side suggested by preoperative IPSS.

In this series no mortality occurred. The morbidity includes two complications (complication rate 2%). One patient suffered from a deep vein thrombosis and another one from a mesenteric infarction which both resolved after administration of heparin. There was no new endocrine deficit other than corticotrope insufficiency; permanent hypocortisolism was found in 3 patients (3.0%), following selective adenectomy in 2 and following hemihypophysectomy in 1. In 1 of the patients it persisted for a follow-up period of more than 3 years. This probably is related more to a long history of preexisting disease and the resulting permanent suppression of anterior pituitary function rather than to surgery.

#### *Additional Treatment and Outcome in Persisting Hypercortisolism*

In 21 cases the hypercortisolism persisted following primary transsphenoidal surgery and intended selective adenectomy (fig. 4a).

In 1 of these patients (4.7%) unilateral adrenalectomy was performed because of accompanying adrenal hyperplasia and the patient improved. In 1 case (4.7%) transsphenoidal re-operation was performed after an incomplete transcranial resection to remove the remaining intrasellar parts of the tumor. When this failed to achieve normalization, bilateral adrenalectomy was carried out.

Radiotherapy was performed in 9 patients after surgery did not result in normal cortisol levels (9/21, 43.0%). In 4 cases linear accelerator (LINAC) radiosurgery using the NOVALIS® system was performed for small circumscribed generally invasive tumor remnants in the lateral cavernous sinus (fig. 2c). Before the advent of radiosurgery or because the tumor remnants were large or too close to the optic system, the 5 remaining cases were treated with conventional co-planar radiotherapy. Normalization of ACTH and cortisol levels was achieved in 3 of 9 cases (33.3%). One of these had undergone radiosurgery. In the remaining 6 patients (3 treated with radiosurgery) cortisol levels improved but the observation period to date has been very short.

Because there were neither visible pituitary tumor remnants nor any circumstantial evidence of them on the MRI scans adrenalectomy was performed in 4 of 21 patients (19.0%). In all of them, hypocortisolism was achieved. One patient developed a Nelson tumor which necessitated radiotherapy of the sella.

In another 3 patients, there were only biochemical but no clinical signs of CD. These patients are being observed closely but do not require any treatment. The last 3 patients exhibit only mild symptoms of the disease and are of

advanced age and, therefore, not subject to any treatment but rather observation at short intervals.

A negative surgical exposure of the sella took place in 9 patients whose hypercortisolism subsequently persisted (fig. 5). In 1 (11.1%) of them further diagnostic tests revealed a paraneoplastic tumor which was then removed. Despite no clear evidence of a pituitary origin of the disease, this patient demanded sella exploration. In 2 of these patients (22.2%) no further treatment was necessary as symptoms of their disease were only mild and they were of advanced age. Four patients (44.5%) were normalized following adrenalectomy and 1 patient (11.1%) underwent re-operation followed by adrenalectomy due to failure of the former procedure. Another patient (11.1%) was in remission following re-operation.

Following partial hypophysectomy in 3 patients normocortisolism was observed, but hypercortisolism persisted in 4 patients (fig. 5). In 2 of the latter, there were only biochemical but no clinical signs of persistence of CD, so that no further treatment became necessary and the patients are being observed to date. Adrenalectomy was suggested for 2 other patients, but 1 of them refuses therapy and 1 has been lost to follow-up.

Combining all treatment methods, a normalization of cortisol levels was achieved in 80 cases. Clinical remission despite biochemical persistence of the disease occurred in 5 patients. Five patients showed only mild symptoms of CD after treatment. An improvement has so far been found in a further 7 cases. In 6 of them normalization of cortisol levels is expected to occur in the near future when the radiotherapy they underwent takes full effect. No change in symptoms was observed in those 2 patients who did not undergo any treatment and the 1 who suffered from paraneoplastic tumor. Nelson syndrome was observed in 1 of 11 adrenalectomized patients but in no patient who underwent combined treatment with adrenalectomy and radiotherapy.

### **Current Value of Surgical Treatment in Cushing's Disease**

A review of the literature over the last decades yielded 31 series ranging from 9 [42] to 668 [4] patients treated. These include single-surgeon as well as multi-center studies. Some studies examined only adults or children, while others combined both groups. Some series give an overview on the treatment of Cushing's syndrome in general. Others focus on the treatment of pituitary adenomas. Their great variety makes them difficult to compare. In the following, an overview on the rates of confirmation of an adenoma, remission and recurrence rates as well as complication rates will be given and some studies of interest will be discussed. Only studies examining more than 20 patients have been considered.

The rates of confirmation of an adenoma during surgery are reported in 20 modern series published between 1985 and 2004. They range from 59.1 to 94.1% [2, 6–12, 15, 16, 18–21, 27–29, 43, 44]. Rates vary depending on whether the surgeon's impression of tumor removal only or also histological results were taken into account (90.0 vs. 66.7%) [15]. In one series, the surgeon intraoperatively had the impression that a tumor was present in 90% of the cases, albeit this was not confirmed with a pathological work-up [25]. These results were comparable to those of our series. It is obvious that there is a difference in the rates of intraoperative confirmation of an adenoma depending on whether those of microadenomas only, or those of both micro- and macroadenomas are examined (73.5 vs. 82.4%) [7]. Furthermore, technical advances have not resulted in a significant improvement. In another series with a 100% adenoma finding rate, the impression of the surgeon only was considered [2].

Remission rates are reported in 25 series and range from 42.0 to 98.2% [2–4, 6–13, 15, 16, 18–21, 25–30, 43–45], with a majority reported between 70 and 90%. There is no change in remission rates over the years but they are strongly dependent on the remission criteria used. The remission rate depends on whether an adenoma is found intraoperatively and on what kind of surgical procedure is done. There was a higher remission rate when an adenoma was found intraoperatively than when hemihypophysectomy was performed following negative exploration of the sella (69.2 vs. 62.5%) [12]. Furthermore, the remission rate is dependent on the surgeon's experience, which should correlate to the number of operations in his/her series. This relationship may be compromised when a surgeon has to deal with a selected patient collective consisting of more complicated cases. Comparing micro- and macroadenomas, there is a better remission rate found in the former group (88.0 vs. 33.3% [7], 92.6 vs. 66.7% [28]). The remission rate after surgery for recurrent tumors is lower than that after surgery of primary ones [26, 45]. The remission rate in children is about 70% [12, 18]. In a multicenter study, which might represent a good cross-section with regard to patient collective and individual surgeon abilities, the remission rate is 76.3% [4].

Recurrence rates are reported in 17 series and range from 3.4 to 50% [2, 4, 6, 8–10, 13, 16, 18, 20, 21, 25–28, 43, 44]. The rate quoted in 1 series was believed to be biased because no distinction was made between primary and recurrent disease [11]. The time between operation and recurrence ranged between 16 months and 10 years during a mean follow-up period of 3 months to 7 years. The remission rate was <5% in 2 series, <10 and 15%, respectively, in 4 series each, <20% in 1 series, <25% in 2 series, and >25% in 4 series. There was no reduction in the recurrence rates over the years. As expected, the incidence of recurrent disease increases with the length of the observation period.

The recurrence rate seems to be higher (50%) [6] and the appearance of recurrent disease takes place earlier [3] after primary resection of macroadenomas

than of microadenomas. It might be higher in children which is shown in a series [18] examining children only (41.2%), and is supported by another series examining a collective of children and adults (26.9%) [10]. In the European multicenter study the recurrence rate was 12.7% [4].

Mortality and morbidity were reported in 14 series. The mortality rate was 0% in 10 series and 1.7 up to 8.4% in the others [2–4, 9, 10, 15, 16, 20, 23, 26, 29, 30, 44]. A mortality rate of 8.4% was reported in a large series [19] reviewing early pituitary surgery. In the more recent series no mortality was reported.

Hypocortisolism after surgery is a good prognostic factor predicting a lower risk of recurrence. It may persist due to adrenal insufficiency caused by long-term suppression of normal pituitary tissue. Persistent hypocortisolism was reported in 5 series with an incidence ranging from 1.7 to 44.4%. After hemihypophysectomy the incidence was reported to be 33.3% [2, 20, 26, 29, 30]. As their CD is cured, this side effect is generally well accepted by the patients and they are subsequently placed on replacement therapy.

Other persisting endocrine deficits are reported in 0–71% of all treated cases [2–4, 7, 9, 10, 15, 16, 18, 20, 23, 26, 30, 44]. In about half of the series they are reported to occur in <1 of 5 cases but even in some newer series, their incidence exceeds 25%. The reason for this might be injury to the normal pituitary during aggressive tumor removal performed to achieve cure of the disease. On closer examination, the high incidence of rates of endocrine deficits are found either in older or in smaller series. This leads to the assumption that the experience of the surgeon plays a major role in sparing the normal pituitary tissue.

Morbidity rates ranged between 0 and 53% [2, 4, 9, 10, 15, 16, 19, 20, 23, 26, 29, 30, 44] with the exception of a 65% rate reported in a series examining macroadenomas only [3]. In a multicenter study it was 14.5% [4].

No morbidity at all was found in 3 series, the rate was <5% in 3 series, <10% in 1 and <15% in 3 series. Thus, in 10 of 14 series the morbidity rate was <15%. Among the other series there were 2 each with a morbidity rate of below and above 50%.

There seems to be no correlation between morbidity rates and the number of patients examined or the length of time that has passed since the study was performed.

Major complications reported were CSF leakage, meningitis, sinusitis, deep vein thrombosis and pulmonary embolism, visual deficits, cranial nerve palsies, wound healing problems, and perforations of the nasal septum.

#### *Intraoperative Prediction of the Operative Results*

It is of major interest to determine the outcome of an operation intraoperatively, and this was the aim of a number of studies, but so far all methods tried seem to have failed in CD. Intraoperative MRI scans using 0.2 or 1.5 T scanners

are helpful in larger and/or invasive pituitary adenomas. The extent of the resection can be determined intraoperatively and in case there is some accessible tumor left it can be removed during a second look [46, 47]. Considering a spatial resolution in MRI of 3 mm [48] and the small tumor size mostly found in CD, it is easy to understand that intraoperative control of the resection does not make sense in those cases.

Another attempt to determine the remission of endocrine hypersecretion was to measure the intraoperative decline of excess hormone levels. As shown in an unpublished series by the authors, this is possible in patients suffering from acromegaly and prolactinomas, but remains difficult in patients with ACTH hypersecretion. There might be too much interference with pituitary function resulting from stress in the immediate pre- and postoperative period and during anesthesia as the normal ACTH-producing cells may not be totally suppressed by hypercortisolism. This may lead to elevated intraoperative cortisol levels in spite of complete adenoma removal. Furthermore increased ACTH levels may result from the variability of the secretion pattern within the adenomas and from manipulation of the tumor. These findings are in accordance with the literature [49, 50].

Another attempt was made by Flitsch et al. [51] to differentiate between adenomatous tissue and normal anterior lobe during surgery in order to facilitate total tumor resection. Homogenization of biopsies was performed by ultrasound and ACTH levels were determined. An ACTH level of >300 ng/100 mg was considered evidence of adenomatous tissue. But this method, also, could not guarantee that all parts of, e.g., an invasive or dumbbell-shaped adenoma were removed.

#### *Progress in Microsurgical Treatment of Cushing's Disease*

By comparing the present study with the literature as well as the first series of 100 cases published by the senior author in 1986 [14], the rate of intraoperative confirmation of an adenoma (84.0%) is above the median of all published rates but not as good as in the senior author's previous study (96%). The remission rate remained almost unchanged (present 75%/previous 74%) and lies within range given in the literature. The recurrence rate is low (4.8%) compared to the literature and has improved slightly since 1986 (5%). The lower rate of intraoperative confirmation of an adenoma might be due to the increasing number of diagnostically challenging patients referred to our specialized center nowadays. The remission rate has not changed since 1986, similar to the other series in the literature. This may be a consequence of the relatively large number of patients in our series with very small tumors that are difficult to detect on the one hand, and with macroadenomas, which are difficult to resect completely on the other. Unfortunately, these disadvantages cannot yet be overcome by