Long-term results after microsurgery for Cushing disease: experience with 426 primary operations over 35 years

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Object. The aim of this paper was to demonstrate the long-term results following microsurgery in a single surgeon’s continuous series of patients with Cushing disease (CD), to assess the influence of changes in surgical procedures, and to compare the results with those of other treatment modalities. In particular, preoperative diagnosis, tumor size, results of histological examination, and complications were considered.

Methods. Between 1971 and 2004, 426 patients suffering from newly diagnosed CD underwent primary surgery. Preoperative measures included clinical examination, endocrinological workup (testing of the hypothalamic-pituitary-adrenal axis, and 2- and 8-mg dexamethasone overnight suppression tests), sellar imaging (polymography, computed tomography, and magnetic resonance [MR] imaging), and in patients with negative results on imaging studies, inferior petrosal sinus sampling. Follow-up examinations consisting of endocrinological workup, and imaging took place 1 week and 3 months after surgery and then at yearly intervals.

Results. During microsurgery as first treatment, the adenoma finding rate was 86.6%. After selective adenomectomy, the remission rate was 75.9%, and this rate showed no improvement over the years. The best results were achieved in microadenomas confirmed on MR imaging or histopathological investigation. The recurrence rate (15%) and the complication rate (5.9%) declined over the years. If no adenoma was found, exploration of the sella turcica was performed in 45.6%, hypophysectomy in 3.5%, and hemihypophysectomy in 50.9% of these patients, leading to an early remission in 37.9%. In case of persistence or recurrence, further treatment (repeated operation, adrenalectomy, radiotherapy, or medical treatment) was used to control the disease.

Conclusions. Microsurgery remains the treatment of first choice in CD, even though no improvement in remission rate was observed over the years, because complication or remission rates for other treatment options are comparable or worse. (DOI: 10.3171/JNS/2008/108/01/0009)

KEY WORDS • Cushing disease • disease recurrence • disease remission • persistent disease • transsphenoidal surgery

Cushing disease is one of the most severe and difficult to treat endocrine diseases, challenging the endocrine neurosurgeon. Microsurgical selective adenomectomy remains the first-line treatment, although other treatment options promise similar results. Because this disease is very significant for patients’ life expectancy and welfare, many studies have been published. Nevertheless, because CD is rare, most of these studies include only a small number of patients or represent the results of several centers. The number of patients in whom a single surgeon operated ranges from 9 to 310. In a multicenter study, 668 cases were presented. Because imaging methods have changed dramatically, from polymography in the beginning and CT scanning in the 1970s to the current standard of MR imaging, the patient populations within these studies vary considerably as well. Due to this inhomogeneity, complication rates as well as remission and recurrence rates, all based on different criteria, show a wide variability. Remission rates vary between 42 and 100%, recurrence rates between 0 and 63%. The mortality rate ranges from 0 to 3.6%; the rate of endocrine deficits varies between 2 and 88%; and the morbidity rate between 0 and 27%.

The first aim of this study was to demonstrate the results...
obtained by a single surgeon with an experience of 426 primary and a total of 531 surgical procedures for pituitary-dependent CD over a period of 35 years. The question arises whether increased experience gained over many years leads to better surgical results. For this reason, the changes in remission, recurrence, and morbidity and mortality rates are analyzed and compared with results detailed in the literature. Another aim was to compare the value of different surgical treatment strategies (selective adenomectomy or partial and total hypophysectomy) with other treatment options such as radiotherapy, medical treatment, and adrenalectomy. Finally, we wanted to ascertain if there was a relationship between different variables and the surgical results. In this paper, special attention is paid to factors that previously have not been taken into consideration, such as diagnostic procedures (IPS sampling and MR imaging) and histological findings, as well as tumor size and the sex and age of patients.

Clinical Material and Methods

Patient Population

Between January 1971 and October 2004, a total of 531 operations in 471 patients suffering from pituitary-dependent CD were performed by 1 surgeon (R.F.). These procedures consisted of 426 primary and 105 repeated operations. The 426 patients who underwent primary surgery are included in this study. Two operations were performed via the transcranial approach, whereas in the remaining 424 patients surgery was performed via a transsphenoidal route. All patients who were included underwent at least 1 follow-up evaluation (3 months postsurgery) at the study hospital. The study population consisted of 325 female and 101 male patients (female/male ratio 3.2:1). The patients’ age at surgery ranged between 5 and 77 years (mean 39.4 years). Follow-up time ranged from 3 to 300 months (mean 72.3 months, median 66.8 months). In 87 patients, the follow-up period was < 2 years. In 23 of them, however, surgery had been performed > 2 years earlier. In the meantime, 64 patients have been lost to follow-up, 23 of them after the first follow-up examination.

Clinical Examination

During clinical examination, typical signs of CD such as traction atrophy, diabetes mellitus, hypertension, osteoporosis, moon face, or hypokalemia were recorded. Furthermore, an ophthalmological workup was performed prior to and 1 week after the operation to rule out glaucoma, visual field defects, or a loss of visual acuity due to a macroadenoma.

Preoperative and Postoperative Endocrinological Evaluation

Basal serum or plasma levels of ACTH, prolactin, human growth hormone, luteinizing hormone, follicle-stimulating hormone, estradiol or testosterone, thyroid-stimulating hormone, thyronine, and thyroxine were determined in a standard fashion prior to and 1 week after operation. Serum concentrations of cortisol were determined as basal values and following stimulation with ACTH. Furthermore, a 2-mg DEXA was performed in all patients. When the latter test is used, CD is ruled out if the serum cortisol at 9:00 a.m. is < 2 μg/dl after the administration of 2 mg dexamethasone at 10 p.m. the night before.

Preoperative evaluation was completed with an 8-mg DEXA in all patients to confirm the pituitary-dependent origin of the disease and to rule out an adrenal or paraneoplastic Cushing syndrome.74 If necessary, a 16-, 32-, or 64-mg DEXA and in some cases a CRH test was performed, sometimes combined with IPS sampling (197 patients). In the latter test, a central-to-peripheral gradient > 2- to 3-fold before or after stimulation performed using CRH indicates the central origin of CD, and an interpetrosal gradient of more than 1.2-fold points to the localization of the suspected adenoma.54 In some cases that were difficult to diagnose, elevated free urinary cortisol (> 300 μg/24 hours)75 or an abolished diurnal rhythm of cortisol secretion was considered to be an indication of the disease. During the day, the cortisol level in the afternoon is less than half of the value measured in the morning, and furthermore, a minimum level is found between 12 p.m. and 3 a.m. in a healthy patient.

Follow-up examinations were performed 3 months after surgery and then at yearly intervals. They consisted of laboratory studies to determine baseline levels of anterior pituitary lobe hormones and a stimulation test, in which ACTH was used to rule out a pituitary insufficiency. Furthermore, a 2-mg DEXA was performed to document long-term remission of the disease.

The inclusion criteria for this study were a pathological finding on 2-mg DEXA and suppression below 50% of the basal cortisol level following 8- or 16-mg DEXA, which confirms the central origin of the disease. Patients were considered to be cured if the basal cortisol level following a 2-mg DEXA was < 2 μg/dl and the patient exhibited clinical remission of the disease.

Neuroimaging Results

At the beginning of the era of endocrine neurosurgery, imaging of the sellar region consisted of x-ray polytomography, which was replaced by CT scanning in 1975. Thin-slice CT scans of the sellar region (obtained using a Siemens Somatom DR3 or Siemens Somatom plus4) in coronal and sagittal reconstruction were used at that time. Since the beginning of the 1980s, thin-layer MR imaging studies in 1- to 2-mm slices (at first obtained using a Siemens Magnetom GBS2, and later a Siemens Somatom Sonata [1.5 tesla]) have been performed using different T1- and T2-weighted protocols. The standard imaging protocol included T1-weighted images (TR 600 msec, TE 20 msec, 256 × 512 pixels, field of view 22 × 22 cm) with and without contrast enhancement and T2-weighted images (TR 3850 msec, TE 111 msec, 256 × 512 pixels, field of view 22 × 22 cm) in coronal and sagittal planes. In most patients, preoperative imaging was performed at the study hospital. Furthermore, coronal and sagittal x-ray films of the skull were obtained for intraoperative orientation.

Perioperative Management

In case of severe metabolic changes, medical pretreatment with ketoconazole (600–800 mg/day) was at least temporarily used to decrease the cortisol level by blocking its biosynthesis and to improve the patients’ clinical condi-
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Operative Treatment

The transphenoidal approach (424 patients) to the sella turcica was performed either sublabially, pernasal parasagittally, or directly pernasally. After opening the sphenoid sinus and removing the mucosa, the sellar floor was opened with a diamond drill. The basal dura mater was incised with microscissors and the visible adenoma was removed using curettes and suction, either directly or after incision of the normal pituitary gland. In some cases a histological specimen could not be obtained due to the small size of the tumor. If no adenoma was visible on MR imaging, a meticulous sectioning of the pituitary gland and a bilateral periglandular inspection with visualization of the medial wall of the CS and of the diaphragm were performed to detect a microadenoma. If no adenoma was found by this procedure, a hemihypophysectomy according to the interpetrosal gradient (> 1.2) of ACTH and prolactin concentrations, as determined by the results of IPS sampling, was performed (29 patients). If cerebrospinal fluid leakage was recognized during surgery, fascia lata from the thigh was used to close the sella turcica at the end of the operation and a lumbar drain was placed. We generally did not perform packing of the sella by using abdominal fat during primary surgery. If a focal tumor invasion into the CS was found, an attempt was made to remove the invasive part after placing a small incision in the wall of the sinus. If there was a larger invasion, total tumor removal was impossible due to the risk of major bleeding. In that case, only an incomplete resection could be performed.

A transcranial approach to the sella turcica (used in 2 patients) was usually performed via a right temporal or frontotemporal trepanation, depending on the side of worse vision. After slightly retracting the frontal lobe, the optic nerve and the chiasm were visualized and the tumor removed. During this procedure, care was taken to stay within the intracapsular space and not to damage any vessels supplying the optic system or the brainstem. Furthermore, care was taken to preserve the pituitary stalk.

Results

Primary surgery was performed in 426 patients. In these individuals, the adenoma finding rate according to the impression of the surgeon was 369 (86.6%) of 426, resulting in a selective adenomectomy. A microadenoma was resected in 330 (89.4%) and a macroadenoma in 39 (10.6%) of these 369 cases. In 13.4% of the patients (57 of 426) no adenoma was found (Fig. 1).

With respect to selective adenomectomy (Fig. 2), hypercortisolism persisted in 89 (24.1%) of the 369 patients. In 15 of these a second operation was performed, which led to a remission in 3 of them. The remaining 86 patients required additional treatment.

By performing a selective adenomectomy, a remission of hypercortisolism was achieved in 280 (75.9%) of 369 patients. In the latter group of patients, long-term remission of hypercortisolism was observed in 238 (85%) of 280 and a recurrence of the disease was found in 42 (15%) of 280. In the patients with > 6 years of follow-up (range 74–278 months, mean 122.3 months), the recurrence rate was 5.6%. The time between the first and the second operation ranged from 13 to 207 months (mean 73.2 ± 43.2 months [± standard deviation]). In the recurrent cases, a bilateral adrenalectomy was performed in 1 patient (of 42 [2.4%]), who was cured thereby. In 2 other patients radiotherapy was performed and in 2 more patients successful repeated surgery took place at another institution. One patient has not been further treated so far, and another showed only a biochemical recurrence. A repeated operation, with the goal of a second adenomectomy, was performed in 35 patients (83.3%), and this operation led to a remission in 13 of them (37.1%). The tumor localization during recurrent surgery has been analyzed in another paper. In 2 patients a second recurrence was observed; 1 of them underwent a successful reoperation and the other underwent radiotherapy. In the remaining 22 patients, improvement or normalization of hypercortisolism was achieved by bilateral adrenalectomy in 8 (36.4%), by radiotherapy alone in 9 (40.9%), and by a combined therapy consisting of radiotherapy and adrenalectomy in 2 of them (9.1%). In 3 patients (13.6%) no further treatment was applied because the symptoms were only mild or the age of the patients was too advanced.

In the patients who underwent successful primary selective adenomectomy according to the impression of the surgeon at the study hospital, long-term control of the disease could be achieved in 250 (89.5%) of 280 patients after 1 or more surgical procedures.
In the 57 patients in whom no adenoma was found (Fig. 1) during primary operation, 3 therapeutic options were possible. The first option, an exploration of the sella turcica, was performed in 26 (45.6%) of 57 patients because there was no clear interpetrosal gradient in ACTH concentrations found during IPS sampling or because the pituitary was small, making a hemihypophysectomy impossible. In all of these patients, even though a repeated operation was performed in 1 of them, hypercortisolism persisted. In the early days of pituitary surgery, a hypophysectomy was performed with the intent of producing a normalization of the pathological ACTH-secreting pattern. In our series, this was done in 2 (3.5%) of the 57 patients. A long-term remission resulting in a cure was observed in 1 of them, whereas hypercortisolism persisted in the other. Finally, a partial hypophysectomy (hemihypophysectomy) on the side of suspected tumor growth was performed in 29 (50.9%) of 57 patients (tumor growth was suspected based on an interpetrosal gradient in ACTH concentrations determined using IPS sampling). This led to an early remission in 11 of the patients (37.9%). Hypercortisolism persisted in 18 (62.1%) of 29 patients, necessitating further treatment such as adrenalectomy or radiotherapy. However, a repeated operation led to a remission in 1 patient. The long-term remission rate following a partial hypophysectomy was 41.4% (12 of 29 cases).

In summary, primary neurosurgical treatment alone (including hypophysectomy or hemihypophysectomy) on the side of suspected tumor growth was performed in 29 (50.9%) of 57 patients (tumor growth was suspected based on an interpetrosal gradient in ACTH concentrations determined using IPS sampling). This led to an early remission in 11 of the patients (37.9%). Hypercortisolism persisted in 18 (62.1%) of 29 patients, necessitating further treatment such as adrenalectomy or radiotherapy. However, a repeated operation led to a remission in 1 patient. The long-term remission rate following a partial hypophysectomy was 41.4% (12 of 29 cases).

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In summary, primary neurosurgical treatment alone (including hypophysectomy or hemihypophysectomy) led to an early postoperative remission of CD in 292 (68.5%) of 426 cases. Including repeated surgery, a long-term treatment success was achieved in 266 (62.4%) of 426 cases.

The overall complication rate for a first operation was 25 (5.9%) of 426 cases. The mortality rate was 0.7% (3 of 426), with causes reported as follows: 1 overweight patient died of an acute respiratory distress syndrome, 1 patient died of meningitis, and a third died due to hypovolemic shock following massive, stress-induced gastrointestinal bleeding. Since 1998 no surgery-related deaths after the first operation have been reported, and no patient has died within the first 3 months postoperatively. In the remaining 22 patients minor complications were observed as follows: 1 mesenteric infarction (0.2%), 2 cases of rhinorrhea (0.5%) requiring repeated operation, 3 cases of meningitis (0.7%), 1 transient oculomotor nerve palsy (0.2%), 4 additional insufficiencies of ≥ 1 anterior pituitary lobe hormones (0.9%), and 4 newly diagnosed cases of diabetes insipidus (0.9%). As described earlier, implantation of fascia lata and placement of a lumbar drain in case of suspected cerebrospinal fluid leakage during surgery resulted in the low rate of repeated operation to treat rhinorrhea. Because the tumors were located mostly in the infrasellar region, however, sealing of the diaphragm seldom became necessary. Although low-dose heparin was administered for anticoagulation therapy, a deep venous thrombosis occurred in 7 cases (1.6%). Within the last 7 years there have only been 2 complications: 1 deep venous thrombosis and 1 mesenteric infarction, both of which resolved after administration of heparin. There was no deterioration of vision or any postoperative rebleeding that would have required a repeated operation.

With regard to imaging, the MR modality is the gold standard. In the patients included in this series, 270 MR images were performed. A tumor or at least a suspected lesion was found in 137 patients (50.7%), whereas no tumor was found in 133 patients (49.3%). Among these 137 patients with either an apparent or suspected tumor on the MR im-
aging study, an early remission was observed in 99 (72.3%) and persistence in 38 (27.7%). In cases in which there was no evidence of a tumor, an early remission was achieved in 86 (64.7%) of 133 and persistence was observed in 47 (35.3%) of 133 (Fig. 3). There is no significant difference regarding remission whether an adenoma is found on MR imaging or not (p = 0.18, chi-square test).

Since 1997, prior to the primary operation a total of 49 IPS sampling procedures were performed, and a central-to-peripheral gradient of ACTH concentrations was found in 46 of them (93.9%). Because the pituitary origin of the disease was excluded in the remaining 3 patients, they were excluded from this study. During the subsequent examination, a peripheral source for the ACTH hypersecretion was found. Catheterization of both IPSs was technically possible in 44 (95.7%) of 46 cases. Due to anatomical variations, catheterization of only 1 IPS was performed in the other 2 cases (4.3%), making the determination of an interpetrosal gradient impossible. Of the 44 cases in which catheterization of both IPSs was possible, there was an interpetrosal gradient to the right side in 19 (43.2%), to the left side in 20 (45.4%), and no interpetrosal gradient was found in 5 (11.4%). The latter was assumed to indicate a midline tumor. Agreement between the intraoperative findings and the results of IPS sampling was found in 24 (61.6%) of the 39 cases in which an intersinus gradient was found. In none of the patients without a gradient was the tumor found in the midline. As a result, in a total of 24 (54.5%) of 44 cases the IPS sampling revealed a correct prediction of tumor position.

In regard to histological results in primary selective adenomectomy, a pituitary adenoma (including micro- and macroadenomas) was confirmed in 281 (76.2%) of 369 cases. According to Saeger and Lüdecke,60 a follicular hyperplasia of ACTH-producing cells was found in the histopathological workup in 24 specimens (6.5%), whereas both pituitary adenoma and follicular hyperplasia were found in 6 patients (1.6%). No clear histological results were obtained in 58 patients (15.7%); in these patients either normal pituitary tissue was found or the specimen was too small to obtain a detailed histological result. In 1 patient, an additional Rathke cleft cyst was found incidentally. Remission according to the histological results was as follows: a remission was achieved in 219 (77.9%) of 281 patients with an ACTH-producing tumor, whereas persistence was observed in 62 patients (22.1%). In the 24 patients exhibiting an ACTH cell hyperplasia, the remission rate was 13 (54.2%) of 24 and the persistence rate was 45.8% (Fig. 4). There is a very highly significant difference in remission after surgery when pituitary adenomas and follicular hyperplasia are compared (p = 0.009, chi-square test).

In our series, 39 macroadenomas were found in 426 patients, resulting in the high share of 9.2% of the total study group. Examination of the results based on tumor size shows a remission in 23 (59%) of 39 macroadenomas, and in 257 (77.9%) of 330 microadenomas. The recurrence rate was 3 (13%) of 23 macroadenomas and 39 (15.2%) of 257 microadenomas, which led to a long-term control of the disease in 20 (51.3%) of 39 patients with macroadenomas and in 218 (66.1%) of 330 with microadenomas. Persistence was observed in 16 (41%) of 39 macroadenomas and
in 73 (22.1%) of 330 microadenomas. There is a highly significant difference (p = 0.009, chi-square test) in remission when micro- and macroadenomas are compared.

When patients were divided according to sex, a remission was achieved in 229 (70.5%) of the 325 females and in 62 (61.4%) of the 101 males, exhibiting no significant difference between the sexes (p = 0.08, chi-square test).

Taking into account the age of the patients, a total of 38 children (≤ 18 years of age) underwent surgery. A selective adenomectomy could be performed in 36 of them (94.7%). In 1 of the remaining patients an exploration of the sella turcica was performed, and, in the other, suspect tissue was found. In the latter patient, normalization of the hypercortisolism could be achieved as well. A remission of the disease was found in 31 (86.1%) of 36 patients following selective adenomectomy. Nevertheless, there was no significant difference when the results in children were compared with the results in adults (p = 0.586, chi-square test).

In terms of newer techniques, intraoperative MR imaging and neuronavigation were applied only in a few cases in which the tumor was large or in cases of narrowed intercarotid space. Because of the small number of cases in which these techniques were used, a detailed evaluation of their efficacy could not be performed at the present time.

Discussion

In general, in a single neurosurgeon’s series, a continuous improvement in normalization of the hypersecretory status for prolactin and human growth hormone–producing adenomas as well as a decrease of pituitary insufficiency following surgical treatment of nonfunctioning tumors could be experienced and has been documented. On the contrary, during surgical treatment of pituitary-dependent CD, we did not observe this phenomenon. Although in an early series published in 1986 the adenoma finding rate was 95% and the remission rate was 74%, the rates were comparable in the latest series of 100 patients (84 and 75%, respectively).

In general, these results are comparable to those reported in the literature; in unselected series the remission rates are similar to the results in the present series, whereas a preselection or combined treatment leads to better results. The remission rates reported in series that included a small number of patients were comparable to our series or even better, whereas in a series including a larger number of patients similar results were obtained.

Due to a meticulous systematic sectioning of the pituitary gland and a consequent periglandular inspection, including the medial wall of the CS, good results regarding remission and finding rates were achieved. The latter especially is achieved more easily if the tumor can be localized. In the beginning of this series, however, this inspection was not possible and one had to rely on indirect signs such as the results of sellar excavation or the less sensitive CT scanning. Based on these experiences, the endocrine results do not differ significantly, whether or not an adenoma was visible on MR imaging (remission rate 72.3% compared with 64.7%). This opinion, however, represents experiences from the last decade and is not shared by all investigators, especially if they do not have a comparable long-term experience.

In the mid-1980s, increasing knowledge about the relations among structures inside and around the CS gained by either MR imaging and/or a direct view induced the senior author (R.F.) to start to incise the medial wall of the CS in focally invasive adenomas. This was supported by the fact that the CS was not displaced laterally and the sella turcica was of normal diameter (10–12 mm) and anatomical shape. Nevertheless, it is an impediment to some surgeons that in ACTH-producing microadenomas there is always venous bleeding around the more or less anatomically preserved pattern of the pituitary and its venous structures (the CS) in the duplicated sellar dura mater. This is in contrast to surgery in larger tumors. For that reason, the pioneer of pituitary microsurgery, Dr. Hardy, had originally abandoned an opening of those structures in earlier times (J Hardy, personal communication, 1982). With further improvement of surgical technique, the thin wall of the CS could be incised
Long-term results after primary microsurgery for CD in 426 cases

![Chart showing correlation of surgical results and histopathological findings in 369 patients with CD.](image)

FIG. 4. Chart showing correlation of surgical results and histopathological findings in 369 patients with CD.

and the focally invasive tumor could be followed in the area medial to the carotid artery. One reason for the worse results (a 33–66.7% normalization rate of hypercortisolism) during surgery for macroadenomas might be the fact that the tumor is extended beyond that area. In contrast to other functioning microadenomas, the tumors in CD are not round and well circumscribed; they are frequently binodular with small connections, sometimes of a diffuse growing pattern, and they are not always enclosed. Even if most adenomas are deliquescent, some of them present with a firm consistency and therefore can easily be misinterpreted as normal pituitary tissue.

One reason for the lack of improvement in findings and remission rates might be a preselection of the patients. Whereas the 100 patients included in the first series were referred by 1 endocrine specialist (O.A.M.) practicing in the vicinity of our hospital who supervised the nonlocal patients elsewhere, other endocrinologists later began to refer more patients, and this physician has become less continuously involved in the evaluation of CD. Meanwhile, from time to time the neurosurgeons in our group accepted patients from other hospitals and completed the diagnosis of some nonpituitary-dependent CD, resulting in contraindication for transsphenoidal surgery. Nevertheless, we also decided to perform exploration of the sella turcica in nontypical ACTH-secreting tumors in doubtful diagnostic situations rather than to abandon it. Furthermore, we always accepted patients independent of the severity of the disease. Another reason for the failure of the remission rate to increase might be the fact that we performed hypophysectomy only in exceptional cases. This was to avoid an extensive pituitary insufficiency. Moreover, the remission and finding rates might be influenced negatively in case of a cyclic course of the disease. Although the diagnosis of hypercortisolism is confirmed by the endocrinologist during the disease’s active state, after the waiting period for the operation the excess in ACTH secretion may already be inactive. This influences the success and finding rates in a negative way.

Regarding the recurrence rate, 3 observations were made. In series[13,28,63,64,66,70] with a short follow-up period (mean ~ 3 years), recurrence rates between 0 and 9.5% are reported, which is comparable to the experience of the senior author. After a follow-up duration of > 5 years, the recurrence rates were > 12%, which is comparable to the findings in this series. Rates from 22%[3] up to 63.2% are found, however, in cases of repeated surgery. If patients are followed > 7 years, recurrence rates of 25%,[14] 26.9%,[14] or 41%[18] have been reported. Contrary to the latest experience, in this series the recurrence rate was lower in the subgroup of patients with a follow-up period of > 6 years. This indicates that recurrences may happen early, presumably in the first 5 years postsurgery, whereas late recurrences remain rare.

In the beginning of the surgical era, IPS sampling was found to be helpful in localizing the tumor. Due to our negative experience (wrong prediction of tumor localization by interpetrosal gradient, difficult or impossible bilateral catheterization, or different draining pattern from each side),[37,42] this diagnostic tool has been used very infrequently in recent times, especially in children, due to the increased rate of complications. Nevertheless, it is still useful in cases of difficult differential diagnosis to evaluate a central-to-peripheral gradient or to determine the source of ectopic ACTH production. Even if the results obtained following stimulation with CRH seemed to be superior,[63] our attitude is justified by the literature[3,42] with 1 exception.[32]

Even if the endocrinological results did not improve over the years despite an obvious increase of the surgeon’s experience in treating other pituitary entities, it is highly recommended that surgery for CD be performed by an experienced endocrine neurosurgeon. First of all, the surgeon takes a high personal responsibility in surgical decision making. Second, surgical preparation of the normal pituitary gland and its vicinity requires the maximum amount of surgical skills, precision, and patience, because there is a higher risk of bleeding from the CS and some sinuses in the oblique direction of the sella turcica. In case of a hemorrhage, it is stopped by the use of Gelfoam whenever necessary. Very often, coagulation of the double endosteal layer (endost) is not helpful and the sella has to be opened at 2 to 4 other spots while coagulation is supported at the remaining ones. Third, the perioperative course has to be monitored carefully because rapid normalization of the hypercortisolism or complications require some specific therapy. Because of the rapid occurrence of normo- or hypocortisolism, optimum adjustment of the medical therapy becomes necessary, especially in circumstances of a resolving diabetes mellitus and the changeover from hyper- to hypotension, but also due to the high rate of infections and pulmonary embolism. In this field, the gain of experience over the years is reflected in the fact that only a few experienced surgeons report similar results regarding the complication rate.[36,66] The mortality rate and the rate of pituitary insufficiency are exceptional.[32]

Finally, evaluation of surgical success and decision mak-
ing about the next steps of treatment, especially regarding indications for repeated operation or introduction of additional interdisciplinary treatment, has to be done by the neurosurgeon and requires comprehensive experience with the endocrine system. In our opinion, a repeated operation should not be performed in the first 2 weeks of the postoperative course because we observed a delayed remission (Days 8–10) in approximately 10% of cases. This is especially important given that hospital stays lasting 10–12 days were no problem in Europe in earlier times. However, this is in contrast to reports in the literature.\textsuperscript{35,39} Moreover, in our opinion intraoperative imaging using the MR modality or intraoperative or early postoperative endocrine testing\textsuperscript{20,21} is not suitable to conclude whether total tumor removal was accomplished or if an early repeated operation should be performed.

A fact not presented in the literature so far, concerns follicular hyperplasia of ACTH-producing cells. Even though the clinical findings are comparable to CD caused by an adenoma, the remission rates are worse. This might be due to the fact that hyperplasia is not circumscribed and is found at different locations. Nevertheless, this assumption has yet to be clarified.

Even if some authors state that microsurgery of CD has to be replaced by alternative treatment, in the hands of an experienced neurosurgeon the remission rate is comparable to radiation therapy (50–80%),\textsuperscript{18,26,31,59,69,73} and the complication rates are even lower, especially in terms of endocrine deficiencies (7–86%),\textsuperscript{18,69,75} but also in terms of neurological deficits.\textsuperscript{41} In only 1 exceptional series\textsuperscript{60} has a better remission rate (92%) been reported following radiotherapy. After Gamma Knife surgery, remission rates vary between 16.7 and 100%, and an improvement of the endocrine status is reported to appear in approximately 50% of the cases,\textsuperscript{27,30,57,76} if this modality is used alone. After a combination with microsurgery, the remission rates vary between 35 and 100%, whereas an improvement of the endocrine status was observed in 25–75%,\textsuperscript{29,34,40,44,46,55,56,65} Nevertheless, the rate of endocrine (16%) and neurological complications (\textlesssim 33%) is higher as well. Visual deficits were found in 2.3% of the cases.\textsuperscript{44} Linear accelerator radiosurgery was found to be helpful after unsuccessful microsurgery in pituitary adenomas, but patients treated with this modality also experienced higher rates of complications.\textsuperscript{79}

Even when adrenalectomy is performed successfully,\textsuperscript{7} lifelong hormone replacement therapy is needed to treat chronic fatigue.\textsuperscript{55} Moreover, the overall complication rate is high (\textlesssim 25%),\textsuperscript{37,77} and there is a risk of developing Nelson syndrome, which requires radiation therapy.\textsuperscript{22,24} The latter treatment again presents the risk of developing a pituitary insufficiency.

Medical treatment has not yet shown its long-term efficacy, but it might be of use temporarily. At the moment, there is hope that SOM230 has potential as a drug that could cure the disease without surgery.\textsuperscript{2}

Conclusions

We found that a continuous improvement of endocrine results after surgical treatment for CD could not be achieved by increasing one’s experience in pituitary surgery. We believe, however, that microsurgery remains the first choice for treatment. This point of view is supported by the fact that the number of patients included in this series who were suitable for surgery and the severity of their disease increased, but the complication rate remained low. To achieve these results, the surgical techniques and strategy were adapted to the challenges of the disease, which consisted mainly of the small tumor size and the anatomical facts stated earlier in this paper, especially invasiveness into the CS and periglandular growth. For that reason, surgical treatment belongs in the hands of an experienced endocrine neurosurgeon. Moreover, MR imaging and IPS sampling were not found to be helpful in localizing the tumor, and managing the postoperative course in these patients requires a considerable endocrine and surgical knowledge. Compared with radiotherapy, radiosurgery, medical treatment, and adrenalectomy, microsurgery yields comparable endocrine results but a lower complication rate. Furthermore, with microsurgery there is no need for lifelong hormone replacement. Everything in the preceding list except microsurgery, however, is a second-line treatment option.

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