Pituitary Surgery for Cushing’s Disease

Michael Buchfelder  Sven Schlaffer
Department of Neurosurgery, University of Erlangen-Nürnberg, Erlangen, Germany

Key Words
Hemihypophysectomy · Hypophysectomy · Transsphenoidal surgery · Petrosal sinus sampling · Selective adenomectomy · Sella exploration

Abstract
In this article, the present status of neurosurgical operations for Cushing’s disease is briefly reviewed. Transsphenoidal surgery is considered the treatment of choice in most patients with Cushing’s disease once the diagnosis has been established. In a considerable proportion of patients, even sophisticated imaging does not directly depict the tiny microadenoma. The search for the tumor is technically difficult, particularly when the sella turcica is small, the dura vascularized and the sphenoid sinus poorly pneumatized. Thus, even in expert hands, microadenomas cannot always be identified intraoperatively. Usually, a selective adenomectomy is attempted, preserving pituitary functions. There is a huge variation of surgical outcomes reported. As an estimate, a remission rate of some 75% can be expected 5 years after surgery. Almost all data available to date derive from microsurgical operations. Unfortunately, even in patients who initially remit, recurrences may occur. Low postoperative serum cortisol levels and a long-lasting adrenocortical insufficiency seem to be factors associated with a favorable long-term outcome. When no distinct microadenoma can be identified intraoperatively, partial or even total hypophysectomy has been suggested. However, the outcome of these procedures is less favorable than with selective resections of distinct adenomas. Less than 10% of pituitary adenomas associated with Cushing’s disease are macroadenomas. These also bear a less favorable outcome than microadenomas. Only for selected patients with mainly extrasellar tumor localizations are craniotomies recommended. A close cooperation with the endocrinologist is mandatory for a neurosurgeon operating on patients with Cushing’s disease, namely for the pre- and perioperative care and for long-term follow-up.

Introduction

The depiction of distinct intrasellar microadenomas in pituitary sections of Cushing’s original paper [1], in which he, as a neurosurgeon, established the relationship between clinical features of hypercortisolism and the presence of tiny pituitary tumors, suggested the possibility of adenoma resection, sparing the normal pituitary gland. However, only the introduction of the operating microscope and fluoroscopy imaging during surgery allowed precise identification of normal and abnormal tissue within the sella turcica [2]. Even before the introduction of computerized tomography (CT) and magnetic resonance (MR) imaging, neurosurgeons already reported on successful corrections of hypercortisolism following transsphenoidal microsurgical resections of small ACTH-secreting pituitary tumors [3]. Although, to date in many patients tiny tumors can be directly depicted by sophisticated MR imaging studies, still up to 50% of these...
tumors escape radiological detection because of their minute size. The aim of this article is to briefly review the present status of neurosurgical operations for Cushing’s disease. The authors used selected pertinent literature which they comment with some personal bias which results from their own experience.

**Indications for Surgery**

When the diagnosis of ACTH-dependent hypercorticism is established, one assumes that an ACTH-secreting pituitary adenoma is the source of hypercorticism. Ideally, a visible lesion in the sellar region is identified. To date, the standard imaging procedure is MR imaging and minimal requirements would be coronal and sagittal T1-weighted sections through the sella before and after contrast enhancement [4]. If endocrine tests are not perfectly conclusive, most neurosurgeons, including ourselves, feel more comfortable to attack an inconspicuous pituitary if selective catheterization of the inferior petrosal sinus has unequivocally demonstrated a central-peripheral ACTH gradient [5, 6]. Intensive care facilities should be available for these patients.

**Operative Techniques**

There are basically two types of operations available for pituitary adenomas. The most frequently used that is suitable for the majority of patients with Cushing’s disease is the transsphenoidal (transnasal) route. Only exceptionally is a craniotomy (transcranial operation) needed.

**Transsphenoidal Surgery**

There are many possible variations starting with positioning of the patient. While some surgeons, like ourselves, prefer to operate on a patient in the supine position [7, 8] with the head slightly extended, others favor a semi-sitting position [2]. Radiofluoroscopic control is still the most commonly used, but some surgeons prefer to use a navigation system. The operation can be performed with and without dissection of the septal mucosa. Either a sublabial or medial nasal incision may be used. The medial nasal mucosa is detached unilaterally from the cartilaginous and osseous nasal septae, respectively. A nasal speculum is inserted to keep the mucosal tunnel open. Alternatively, a direct endonasal approach to the sphenoid sinus can be chosen. The vomer, which serves as an excellent navigation system. The operation can be performed with and without dissection of the septal mucosa. Either a sublabial or medial nasal incision may be used. The medial nasal mucosa is detached unilaterally from the cartilaginous and osseous nasal septae, respectively. A nasal speculum is inserted to keep the mucosal tunnel open. Alternatively, a direct endonasal approach to the sphenoid sinus can be chosen. The vomer, which serves as an excellent navigation system, is exposed and opened with forceps and drill. The septations of the sphenoid sinus are resected. Usually, now the sellar floor is already visualized through the sphenoid sinus. Incomplete pneumatization of the sphenoid requires extensive drilling. Once the sellar floor is resected, the basal dura of the pituitary fossa may be incised and the gland and adenoma visualized. The content of the sella can only be visualized properly via the transsphenoidal approach and then either sectioning of the gland, adenomectomy or a variant of hypophysectomy can be performed. Both the operating microscope and the endoscope allow an adequate visualization of the intrasellar content [5].

**Selective Adenomectomy**

In microadenomas, the tumor is mostly embedded within the pituitary. It can now be selectively released from the normal gland [2]. In larger adenomas, the dural opening allows a soft tumor to protrude through this opening. Curettes and microforceps are used to loosen and resect the tumor. The normal pituitary is identified by its yellowish color, firmer consistency and vascular surface structure. As much of it as possible is preserved. The extent and radicality of tumor resection can be estimated by inspection and palpation of the tumor cavity, visualization of the cavernous sinus bilaterally and, in larger tumors with suprasellar extension, by the arachnoid that descends into the intrasellar space. In small microadenomas which escape radiological detection, the gland must be sectioned multiply in order not to miss the tiny tumor [2, 3, 7]. This is a specific surgical problem encountered in Cushing’s disease. The normal size of the gland, the vascularization of the basal dura and the proximity of the cavernous sinus and carotid arteries make it a technically demanding enterprise. Even with utmost experience and optimal technical equipment there are still large and invasive pituitary adenomas that cannot be resected completely [9]. Very rarely, microadenomas can be found entirely outside of the sella, e.g. within the cavernous sinus. Whether they should be called ‘ectopic’ is a matter of definition [3, 10].

**Hypophysectomy**

The high density of ACTH-secreting pituitary cells in the medial portion of the gland, and his observation that many of these tiny tumours lie in the midline led Hardy [2] to suggest a partial ‘central core’ hypophysectomy in patients in whom he could not identify a distinct microadenoma intraoperatively. With the availability of ACTH gradients from bilateral cavernous sinus catheterization, Oldfield et al. [5] suggested that half of the pituitary is resected at the side with the higher ACTH concentra-
tions, as determined during preoperative petrosal sinus catheterization. Hypophysectomy is an ultimate option and means that one attempts to resect the entire gland [2, 3]. Unfortunately, it is also not possible to cure all patients with Cushing’s disease [9].

Transcranial Surgery
The decision to perform transcranial surgery is made more and more restrictively. However, to date a suprasellar tumor that has no or only a minor intrasellar component is still being operated upon using transcranial surgery. Either a pterional or subfrontal approach can be used. The frontolateral or frontotemporal craniotomies are usually preferred. Essentially, brain protection is achieved by a basal bone flap and CSF drainage. The visual pathways and the major arteries of the anterior cerebral circulation are dissected and the tumor is then resected stepwise through corridors either medially between the optic nerves or laterally between the optic nerve and the carotid artery [7].

Perioperative Management
Routine prophylaxis with antibiotics is started before the operation. Flitsch et al. [11] have suggested perioperative measurements of ACTH, equating an impressive drop in levels with successful tumor resection. This requires a laboratory within reach of the operating theater or means a prolongation of the operating time. Different regimens of corticosteroid substitution have been proposed [4]. In an earlier publication, we recommended to put the patient on replacement therapy when an adenoma was found and resected intraoperatively [3]. We have now changed to wait and determine cortisol on the first postoperative day [8]. Depending on these cortisol levels, substitution therapy is then initiated, if needed. If early reoperations are considered in the patients without initial remission, an early documentation of remission or persistent disease is required.

Results
Meticulous sella exploration by an expert surgeon results in the identification of an intrasellar microadenoma in approximately 85–90% of the patients, even if an unselected series of patients undergoes the operation, irrespective of imaging findings [8, 9]. In virtually all patients, in whom a distinct intrasellar hypointense region is visible, microadenomas can be identified and resected. Many patients experience an impressive change of their phenotype following selective adenomectomy. However, the immediate postoperative success rate reported varies considerably from series to series and ranged between 65 and 90% in a recent review [9]. Different criteria applied to assess ‘normalization’ partly explain this discrepancy. Another factor could be that the patient cohorts operated upon differ in that some series do not contain patients without clear radiological depiction of the tumors. In most successfully operated patients, shortly after surgery serum and saliva cortisol levels rapidly drop to below normal values [3, 11, 12]. In approximately 85–90% of the patients, pituitary adenomas can be identified histologically. With the technical difficulties of this operation, the lacking availability of representative tissue could explain successful operations without adequate histology [3]. The surgical results with macroadenomas are less favorable. While remission rates ranging from 33 to 83% are found in the literature [9], a recent consensus conference stated that normalization rates below 65% are reported in most large series with macroadenomas [4]. Proper tissue assurance is less of a problem in macroadenomas and thus, they should all have a positive histological verification of the diagnosis. While in the early reports of surgical outcome following hemihypophysectomy according to the ACTH gradient found during petrosal sinus sampling in patients in whom no microadenoma was identified intraoperatively an almost perfect remission rate was reported [5], subsequently other centers had a much worse correlation between adenoma localization and ACTH gradient which ranged from 58 to 65% [6, 13]. Patients with persistent disease after transsphenoidal surgery need further treatment. An early reoperation is probably a good choice in those in whom enclosed ACTH secreting tumors were verified but obviously not completely resected [4]. In any case, the availability of a delayed postoperative MRI offers the possibility to compare later images with the initial situation (fig. 1).

Complications
Patients with Cushing’s disease are more prone to suffer complications from pituitary surgery than patients with other diagnoses. Mortality is from 0.9 to 1.9% [12, 14]. A higher incidence of venous thromboses, pulmonary embolism, gastrointestinal bleeding and infections such as meningitis and pneumonia must be expected as compared to other patients with pituitary adenomas.
**Recurrences**

Even in patients who initially experience a full clinical remission after a pituitary operation for Cushing’s disease, recurrent hypercortisolism may develop. Thus, a life-long follow-up is recommended with repeated testing of adrenocortical function. A few years ago, one estimated a recurrence rate of some 5–10% after 10 years [3, 12]. However, recent data suggest that the recurrence rate is much higher and may reach 25% after 5 years [15]. Some observations suggest that in children recurrences develop more often [16]. A very low cortisol level after pituitary surgery and a long-lasting adrenocortical insufficiency requiring corticosteroid substitution therapy are considered factors predicting a favorable long-term prognosis and a low recurrence rate. However, in individual patients even after a long-lasting severe adrenocortical failure and long-term substitution, hypercortisolism may relapse and a few patients who never exhibited subnormal cortisol levels and did not need corticosteroids still have normal secretion dynamics of ACTH and cortisol, respectively, many years after transsphenoidal surgery [8, 17].

When Cushing’s disease recurs, the therapeutic options include transsphenoidal reoperations, irradiation and bilateral adrenalectomy. Intraoperative findings from reoperations reveal that mostly, as biochemistry becomes pathological, a new tumor is found [18, 19]. Its localization in proximity to the previous resection site at initial surgery suggests that relapse of hypercortisolism results from regrowth of tiny residuals missed at the initial operation. However, the results of reoperations are not as good as those following primary surgery and even after combined therapeutic attempts some patients remain suffering from active hypercortisolism or from difficult to control tumors [19].

**Disclosure Statement**

The authors of this paper have no relevant financial relationship to disclose.


