**Pituitary Surgery for Cushing’s Disease**

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**Key Words**

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

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**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.

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**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, 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.
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 hypercortisolism is established, one assumes that an ACTH-secreting pituitary adenoma is the source of hypercortisolism. 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 midline orientation, 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 [7].

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 supra
eral tumor that has no or only a minor intrasellar compo
nent is still being operated upon using transcranial sur
gery. 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 vi
sual pathways and the major arteries of the anterior cere
bral circulation are dissected and the tumor is then re
sected stepwise through corridors either medially be
 tween 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 periope
rative measurements of ACTH, equating an impressive
drop in levels with successful tumor resection. This re
quires a laboratory within reach of the operating theater
or means a prolongation of the operating time. Different
regimens of corticosteroid substitution have been pro
posed [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 post
operative day [8]. Depending on these cortisol levels, sub
stitution therapy is then initiated, if needed. If early re
operations are considered in the patients without initial
remission, an early documentation of remission or per
sistent disease is required.

Results
Meticulous sella exploration by an expert surgeon re
sults in the identification of an intrasellar microadenoma
in approximately 85–90% of the patients, even if an un
selected series of patients undergoes the operation, irre
spective of imaging findings [8, 9]. In virtually all pa
tients, 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 histologi
cally. 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 asser
vation 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 out
come following hemihypophysectomy according to the
ACTH gradient found during petrosal sinus sampling in
patients in whom no microadenoma was identified intra
operatively an almost perfect remission rate was reported
[5], subsequently other centers had a much worse correla
tion between adenoma localization and ACTH gradient
which ranged from 58 to 65% [6, 13]. Patients with per
sistent 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 of
fers the possibility to compare later images with the ini
tial situation (fig. 1).

Complications
Patients with Cushing’s disease are more prone to suf
fer 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, pulmo
nary 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.

References