Selective excision of adenomas originating in or extending into the pituitary stalk with preservation of pituitary function

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Most pituitary adenomas arise in the anterior lobe of the pituitary gland and can be excised selectively via transsphenoidal adenomectomy with elimination of tumor and preservation of pituitary function. However, some adenomas arise within, and remain localized to, the pituitary stalk. Other pituitary adenomas arise in the superior portion of the anterior lobe and extend superiorly into the stalk. In the past, suprasellar ectopic pituitary adenomas that involve the stalk have been removed by transcranial surgery. We report 10 cases of patients with adrenocorticotropic hormone (ACTH)-secreting pituitary adenomas that originated in the infundibulum or extended into the infundibulum through the opening of the diaphragma sella. All patients underwent transsphenoidal selective adenomectomy and showed laboratory and clinical remission of their hypercortisolism. Seven patients with normal pituitary function before surgery retained normal function after surgery, one patient with abnormal pituitary function before surgery regained normal function, and two patients with impaired pituitary function preoperatively lost additional pituitary function as a result of the surgery.

Clinical Material and Methods

Patient Population

Ten patients with adenomas that arose in the pituitary stalk above the diaphragma sella or extended superiorly into the stalk and above the diaphragma sella from the anterior lobe were identified from among 516 consecutively admitted patients who underwent transsphenoidal exploration for Cushing's disease at the National Institutes of Health between 1982 and 1995. Six patients (two women and four men, aged 26–60 years) had adenomas that extended superiorly from the anterior pituitary into the
stalk. One of these tumors was a macroadenoma (≥ 10-
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mM maximum diameter). Four patients (two male and two
female patients, aged 14–34 years) had microadenomas
that originated within, and remained confined to, the pitu-
itary stalk.

All 10 patients underwent a standard magnetic reso-

nance (MR) imaging protocol performed using a 1.5-
tesla imaging system (Signa; General Electric, Minne-
apolis, MN). Studies included T-weighed coronal and
sagittal images of the pituitary fossa in 3-mm sections.
Gadolinium-diethylenetriamine pentaacetic acid (DTPA)
(0.1 mmol/kg body weight [Magnevist; Berlex Lab,
Wayne, NJ]) was administered intravenously over 2 min-
utes. The T-weighed coronal images were then repeated.
All surgical procedures were performed by the same sur-
ger (E.H.O.).

Laboratory Evaluation

Preoperative determination of hypercortisolism and di-
agnosis of Cushing’s disease were established using cur-
rent conventional endocrinological and radiological
evaluation. The biochemical response to surgery was mea-
sured according to a standardized protocol. Each patient
received 0.5 mg of dexamethasone intravenously every 6
hours for 36 hours beginning immediately after surgery.
On the 3rd postoperative day (≥ 24 hours after the last 0.5-
mg dose of dexamethasone), morning serum cortisol lev-
eels were drawn between 7 a.m. and 8 a.m., and urine
was collected for a 24-hour urinary free cortisol (UFC) test.
These determinants were repeated for several consecutive
days. A response to surgery demonstrating remission of
hypercortisolism was classified as hypocortisolism (morn-
ing cortisol level < 7 µg/dl; UFC < 20 µg/day) or eucor-
tisolism (UFC 20–90 µg/day).

Pituitary hypothyroidism was defined as subnormal
levels of free thyroxin (< 0.9 mg/dl) with low or subnor-
mal thyroid-stimulating hormone values. Hypogonadism
was defined as the absence of menses in a woman of
reproductive age, inappropriately low follicle-stimulating
hormone (< 25 ng/ml) in an amenorrheic woman older
than 50 years of age, or subnormal plasma testosterone (<
200 ng/ml) in a man. Partial hypopituitarism was defined
as a deficiency in one or more, but not all, pituitary hor-
mones. Panhypopituitarism was defined as a deficiency in
all anterior pituitary hormones. Hypopituitarism was con-
sidered a result of surgery if hormonal replacement that
was not needed preoperatively became necessary postop-
eratively. The immediate postoperative period was desig-
nated as the time from surgery to 3 months afterward,
when the late postoperative period began.27

Surgical Technique

In all patients a transsphenoidal approach was used to
resept the adenoma selectively (Fig. 1). Adenomas in
the stalk always reached the pituitary capsule or the pia-
arachnoid and, thus, lacked the type of capsule seen in
adenomas of the pituitary gland. In contrast to intrasellar
adenomas, which generally are quite easy to separate from
surrounding normal tissue, the margin of adenomas with-
in the stalk was more adherent to the stalk than is charac-
teristic of the interface of the pseudocapsule of an adeno-
ma and the anterior lobe. To develop a clear delineation of
the pseudocapsule surrounding the adenoma and to sepa-
rating the margins of the tumor from the stalk, an incision along
the interface between the pseudocapsule and the stalk
was made and developed with a No. 11 or No. 15 scalpel on
a long bayonet handle. Blunt dissection using fine bipolar
tips, microdiscs, and small ring curettes was performed to
define the margins of the adenoma from the pituitary gland
and to remove the remaining tumor.

Results

Magnetic Resonance Imaging and Surgery

In three of the six patients with tumor arising in the
anterior lobe and extending into the stalk (Fig. 2), MR
imaging delineated the locust of the adenoma within the
sella and demonstrated the supradiaphragmatic extension
(Cases 2, 3, and 4; Table 1). In the patient in Case 5, in
whom the tumor arose between the anterior and posterior
lobes and extended through the diaphragma sella, the MR
image was normal. In Case 1 the MR image did not cor-
respond to the operative findings (the MR image showed
an enhancing area on the right side of the gland but did not
demonstrate the adenoma or the existing tumor invasion
of the diaphragma sella). In the sixth patient (Case 6) there
was a small area of extension above the diaphragma sella
on the MR image that was not appreciated prospective-
ly but was apparent when the operative findings were
known.

In three of the four patients with tumor confined to the
stalk (Figs. 3 and 4), the MR image accurately demon-
strated the tumor and its relationship with the stalk (Cases
7, 9, and 10). In one patient, the MR image revealed a sig-
nal void in the left half of the gland, but no tumor was
found there at surgery and the tumor was entirely supra-
diaphragmatic. Thus, in six of the 10 patients the results of
preoperative MR imaging corresponded with the intraop-
erative findings.

In two patients with adenomas arising from the intrasel-
lar portion of the anterior lobe, the arachnoid was pres-
served during dissection of the supradiaphragmatic por-
tion of the tumor. The arachnoid of the suprasellar cistern
was intentionally entered in the other eight patients. To
remove cerebrospinal fluid (CSF) for exposure of the tu-
mor and the contiguous infundibulum, positive pressure
ventilation was used to deliver CSF into the field, where
it was aspirated. After tumor removal, the opening in
the arachnoid and diaphragma sella was occluded by an
abdominal fat graft in the eight patients who underwent
arachnoid exploration. A lumbar CSF drain was placed at
surgery in five patients while general anesthesia was still
in effect. These patients remained at flat bedrest for 3 to 5
days of continuous CSF drainage. The five patients in
whom CSF was not drained were kept flat in bed for 2 to
3 days. None of the patients had a persistent CSF leak
after surgery.

Endocrinological Function

All patients had diagnostic central-to-peripheral ACTH
concentration gradients between the inferior petrosal
sinuses and the peripheral blood during the inferior pe-
trosal sinus sampling (IPSS) test. All patients exhibited
ACTH-staining tumors on immunohistochemical analysis. With the exception of the hypercortisolism associated with Cushing’s disease, four patients, including one of the four patients in whom the adenoma was confined to the stalk, had normal pituitary function before surgery. One patient with tumor originating in the anterior lobe and extending into the stalk suffered from hypothyroidism (Case 1), and one patient had amenorrhea (Case 3). Another patient who had a macroadenoma that originated in the anterior lobe had hypothyroidism and hypogonadism (Case 2). Three of the four patients whose tumor originated in the stalk had impaired pituitary function before surgery. One had amenorrhea, one had amenorrhea and hypothyroidism, and one had hypogonadism before surgery.
surgery. No patient exhibited posterior pituitary dysfunction before surgery. The patient who had undergone previous transphenoidal surgery (Case 4) had normal pituitary function.

All patients became hypocortisolemic in the early postoperative period. Nine patients became hypocortisolemic immediately after surgery and required cortisol supplementation at discharge (Table 1). One patient was eu- cortisolemic immediately after surgery but developed symptomatic profound hypocortisolism 1 month after surgery and required glucocorticoid supplementation for 10 months (Case 7).

The pituitary stalk was preserved intact in all patients, although in two it was somewhat attenuated. Three of the four patients with tumor confined to the pituitary stalk and five of the six patients with tumor originating in the gland and extending into the stalk had normal anterior pituitary function after surgery (Table 1). The patient with a macroadenoma and preoperative hypothyroidism and hypogonadism (Case 2) had laboratory evidence of recovery of pituitary function at 3- and 6-month reassessment and required no further medical therapy. Two patients with preoperative hypothyroidism (Case 1) and hypogonadism (Case 10) required replacement of all anterior pituitary hormones (except growth hormone and prolactin) after surgery. Six of the 10 patients had normal posterior pitu-

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**TABLE 1**

*Preoperative assessment, operative findings, and postoperative results in 10 patients with pituitary adenomas*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>MR Findings</th>
<th>Preop UFC† (µg/dl)</th>
<th>Surgical Findings</th>
<th>Pituitary Function</th>
<th>Hormone Replacement; Complications</th>
<th>Postop Follow Up (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15, M</td>
<td>enhancing lesion on rt did not correspond to operative site</td>
<td>476</td>
<td>7 × 5 × 3–mm adenoma, midline superiorly on ant stalk, dural invasion of diaphragma sella</td>
<td>&lt;1–3</td>
<td>hypothy, hypogon, GH deficiency</td>
<td>HC, 9 mos; synth, GH</td>
</tr>
<tr>
<td>2</td>
<td>28, M</td>
<td>macroadenoma w/ extension into stalk</td>
<td>14,000</td>
<td>18 × 20-mm macroadenoma</td>
<td>&lt;1</td>
<td>hypothy &amp; hypogon</td>
<td>normal</td>
</tr>
<tr>
<td>3</td>
<td>14, F</td>
<td>enhancing tumor on superior surface of gland abnormal areas 1) adjacent to rt cavernous sinus &amp; 2) lt of stalk</td>
<td>317, 98, 72</td>
<td>6-mm adenoma on superior surface of gland at junction w/ stalk</td>
<td>&lt;1</td>
<td>amenon</td>
<td>normal</td>
</tr>
<tr>
<td>4</td>
<td>60, M</td>
<td>5-mm adenoma on ant surface just lt of midline, partially attached to stalk</td>
<td>287–1080</td>
<td>5-mm adenoma extending up stalk through diaphragma sella</td>
<td>&lt;1</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>5</td>
<td>44, F</td>
<td>normal MR image</td>
<td>17–328</td>
<td>5-mm adenoma on rt between ant &amp; post lobe, extending up stalk through diaphragma sella</td>
<td>1–1.5</td>
<td>normal</td>
<td>transient DI</td>
</tr>
<tr>
<td>6</td>
<td>34, F</td>
<td>tumor on rt side of gland, small portion above sella adjacent to stalk</td>
<td>518, 351</td>
<td>adenoma on rt w/ extension up stalk &amp; adjacent to stalk above diaphragma sella</td>
<td>&lt;1</td>
<td>normal</td>
<td>transient DI, borderline hypothy</td>
</tr>
<tr>
<td>7</td>
<td>29, F</td>
<td>thick stalk, enhancing lesion, 3 × 2 mm, midstalk</td>
<td>284–473</td>
<td>5-mm adenoma post &amp; to rt in stalk, minimum disturbance of stalk</td>
<td>6–21§</td>
<td>amenon</td>
<td>transient DI</td>
</tr>
<tr>
<td>8</td>
<td>41, M</td>
<td>signal void lt half of gland; did not correspond to tumor site</td>
<td>182–488</td>
<td>7-mm adenoma arising from stalk in midline &amp; just lt of midline; stalk intact but frayed</td>
<td>&lt;1</td>
<td>NA</td>
<td>normal</td>
</tr>
<tr>
<td>9</td>
<td>26, F</td>
<td>5-mm nodule on stalk on lt</td>
<td>500–2995</td>
<td>5-mm adenoma arising from midpoint of stalk; gland &amp; stalk intact</td>
<td>&lt;1</td>
<td>amenon &amp; hypothy</td>
<td>normal</td>
</tr>
<tr>
<td>10</td>
<td>34, M</td>
<td>enhancing midline lesion in stalk contiguous w/ optic chiasm w/ post displacement</td>
<td>4330–4550</td>
<td>7-mm adenoma wedged between uppermost portion of stalk &amp; inf &amp; post surface of optic chiasm; ASHA coursing through tumor capsule; stalk deviated to lt by tumor; stalk intact but frayed</td>
<td>&lt;1</td>
<td>hypogon</td>
<td>hypothy, hypogon, DI</td>
</tr>
</tbody>
</table>

* Amenor = amenorrhea; ant = anterior; ASHA = anterior superior hypophyseal artery; DI = diabetes insipidus; GH = growth hormone; HC = hydrocortisone; hypercort = hypercortisolism; hypogon = hypogonadism; hypothy = hypothyroidism; inf = inferior; NA = not available; normal = normal ant pituitary function; post = posterior; postsurg = postsurgery; synth = synthroid; testos = testosterone.
† Normal range of 24-hour UFC is 20 to 90 µg/day.
‡ Normal range of morning (AM) cortisol is 7 to 25 µg/dl.
§ Patient developed profound hypocortisolism requiring treatment 1 month after surgery.
itary function at discharge from the hospital. Three pa-
tients had transient postsurgical diabetes insipidus (two
patients with tumor extending into the stalk from the pi-
tuitary required 1-desamino-8-D-arginine vasopressin
(DDAVP) for 3 and 7 months and one patient with adeno-
ma exclusively in the stalk had diabetes insipidus for 20
months). Postoperative delayed endocrinological assess-
ment has not been completed in the remaining patient
(Case 10), who underwent surgery only recently.
Assessment in the late postoperative period included
measurement of 24-hour UFC, diurnal cortisol levels, and
the ACTH stimulation test to evaluate return of function
to the hypothalamic-pituitary-adrenal axis. During a fol-
low-up period lasting up to 42 months, eight patients con-
tinued to show clinical and laboratory evidence of re-
mission. One patient (Case 7), who had eucortisolism
immediately after surgery but became symptomatic from
profound hypocortisolism 1 month later, developed clini-
cal and laboratory evidence of recurrent Cushing’s disease
31 months after surgery. The other patient (Case 10), who
had undergone surgery recently, was hypocortisolemic in
the immediate postoperative period. All patients required
supplemental glucocorticoid therapy for a variable inter-
val (Table 1). Seven patients have had recovery of the
hypothalamic-pituitary-adrenal axis. This recovery was
demonstrated by results of the ACTH stimulation test and
by successful discontinuation of the replacement gluco-
corticoid medications. Two patients were surgically treat-
ed within the past 10 months and the other patient has pan-
hypopituitarism.
In Case 10, MR imaging revealed a 7-mm enhanc-
ing mass abutting the inferior and posterior surface of the
optic chiasm (Fig. 4), and neuroophthalmological assess-
ment revealed diminished acuity in the left eye and a
slight visual field deficit in the inferior and lateral quad-
rant of that eye. At surgery a 6- to 8-mm gray–white ade-
noma was identified contiguous with the inferior surface of the optic chiasm, lying in front of the stalk, which had been displaced posteriorly and to the left by the microadenoma. Two small vessels, which appeared to be branches of the superior hypophyseal artery and which were embedded in the anterolateral edge of the tumor on each side, continued to extend beyond the tumor to reach the inferi- or and anterior surfaces of the optic chiasm. These vessels were interrupted to achieve complete removal of the tumor. After surgery the patient awoke with a bitemporal hemianopsia that affected the inferior quadrants with the greatest severity. There was no change in his visual fields as of his 3-week postoperative assessment, the last examination for which complete results are available.

Fig. 3. Case 9. Upper: Magnetic resonance T₁-weighted images showing an adenoma arising from the pituitary stalk. The images in the top row were obtained before contrast enhancement with gadolinium-DTPA. Lower: Intraoperative photograph of a pituitary adenoma confined exclusively to the stalk. The vertical incisions in the anterior lobe were used to explore the gland. Note the relationship of the superior portion of the tumor to the optic chiasm and the narrow remnant of the diaphragma sella between the superior surface of the pituitary and the adenoma.
Selective excision of pituitary stalk adenomas

Discussion

The transsphenoidal approach and craniotomy are the surgical approaches to the suprasellar region. One criterion that has been used to indicate safe and successful use of the transsphenoidal approach to remove tumors that arise or extend above the diaphragma sella is the presence of an enlarged sella. We have demonstrated the efficacy of the transsphenoidal approach for adenomas involving the pituitary stalk in 10 patients with a normal size sella.

Five of the eight previously reported patients with pituitary adenomas involving the pituitary stalk had Cushing’s disease. The other three had a chromophobic adenoma, a prolactin-secreting adenoma, and an adenoma of unspecified type. Three of the five patients with Cushing’s disease initially underwent unsuccessful transsphenoidal surgery. In those three cases, no tumor was identified in the gland, and the supradiaphragmatic area was not explored. One of those patients underwent a subsequent craniotomy with sectioning of the stalk and removal of the tumor. Although cured of Cushing’s disease, that patient required total hormone replacement. One other patient underwent gamma knife radiation therapy and had persistent disease at the time of the report. The third patient had no further surgery and suffered from persistent disease. Two patients underwent craniotomy only: one was cured, but the stalk was sectioned and hormone replacement therapy was required, and the other one died of postoperative complications. In a more favorable report, a patient with a nonsecreting adenoma involving the stalk underwent a craniotomy with tumor removal and preservation of pituitary function. Thus, because none of the five patients with Cushing’s disease had curative transsphenoidal surgery with preservation of pituitary function,

Fig. 4. Case 10. Upper and Lower Left: Magnetic resonance T₁-weighted images revealing a 7-mm adenoma arising high in the pituitary stalk, just beneath the optic chiasm (sagittal view before [upper left] and after [lower left] contrast enhancement with gadolinium DTPA. Note enhancement of the anterior lobe and stalk, but not the tumor. Upper and Lower Right: Intraoperative photographs of a pituitary adenoma confined to the pituitary stalk with its superior margin contiguous with the optic chiasm. Initial exposure of the tumor (upper right) revealed a gray–white mass that was not contained by the capsule of the stalk, resulting in a papillary, irregular surface of the anterior aspect of the tumor. Note the course of the small branches of the superior hypophyseal arteries through the anterolateral margin of the tumor to reach the inferior and anterior surface of the chiasm (upper and lower left), and the interface between the edge of the adenoma and the stalk (lower right), which was displaced posteriorly and to the left by the microadenoma (lower right; view after removal of a portion of the adenoma outside the capsule of the infundibulum).
Dyer, et al.,6 concluded: “The cranial approach remains the only operative approach to lesions in the supradiaphragmatic region.” Although two of the three patients with craniotomy were cured of Cushing’s disease, they both lost pituitary function; the third patient did not survive.

The success of transsphenoidal surgery is enhanced by accurate preoperative localization of the tumor. When the MR image is equivocal or normal, as was the case in four of our patients, the IPSS test may confirm the presence of sellar or ectopic pituitary tumor. With supradiaphragmatic tumors, it was not established previously whether the venous drainage reached the cavernous sinus and the inferior petrosal sinuses. In all four of these patients the results met the diagnostic criteria20 for Cushing’s disease during the IPSS test. If no tumor is identified preoperatively by MR imaging (as occurred in four of our 10 patients) and no adenoma is evident at pituitary exploration, despite endocrinological results that meet stringent criteria for a diagnosis of Cushing’s disease,9,20 the physician should consider the possibility of an ectopic ACTH-secreting pituitary adenoma that arises in the cavernous sinus28 or in the suprasellar cistern and should reassess the imaging studies specifically for the possibility of the presence of an ectopic ACTH-secreting pituitary adenoma that may not have been obvious on initial inspection.

Removal of a pituitary adenoma with preservation of pituitary function requires identification of the pseudocapsule of the tumor and selective separation of the tumor from the surrounding normal tissue. This pseudocapsule is formed from the compressed contiguous normal pituitary gland (specifically, the reticulin fibers) surrounding the expanding adenoma. In contrast, with tumors in the stalk, the delineation of the tumor edge is not as obvious as it is with tumors that arise from within the anterior lobe. In addition, the pial layer at the interface of the pseudocapsule of the tumor and the stalk is often quite tough, and sharp dissection is required to avoid excessive manipulation and preserve the anatomical integrity of the stalk. This goal was accomplished in all 10 patients in this study.

Transient hypocortisolism usually occurs after successful surgery for Cushing’s disease.16,27 Immediate postoperative hypocortisolism occurred in nine of the 10 patients, and hypocortisolism occurred during the early postoperative interval in all patients. All patients required supplemental glucocorticoid therapy for a variable period (5–21 months). This variability of return of function to the hypothalamic-pituitary-adrenal axis is well known.8,10 The patient in Case 7, whose adenoma originated in the stalk and who had eucortisolism immediately postoperatively and hypocortisolism 1 month after surgery, suffered recurrent Cushing’s disease 31 months after surgery. Because most of the other patients have not been followed for as long as the patient in Case 7, Cushing’s disease in other patients may also recur, although the incidence of recurrent Cushing’s disease in patients with postoperative hypocortisolism is low.

The most frequent complication associated with transsphenoidal surgery is persistent CSF drainage.1,13 Other potential complications include oculomotor palsy, visual loss, diabetes insipidus, hypopituitarism, the empty sella syndrome with resulting prolapse of the optic chiasm, and death. Eight of our 10 patients had normal anterior pituitary function within 3 months. Three of our patients had preoperative hypocortisolism, which commonly occurs with Cushing’s syndrome1 and which usually disappears after resolution of hypercortisolism.3,15 Hypothyroidism resolved in two of these patients; the other patient had panhypopituitarism after surgery, which also occurred in the patient with preoperative hypogonadism and a tumor high in the pituitary stalk next to the optic chiasm. Three female patients with preoperative amenorrhea resumed normal menses after surgery. No patient had permanent diabetes insipidus (the patient in Case 10 is still following a course of DDAVP 5 months after surgery). One patient with preoperative hypogonadism underwent surgery only recently, and the initial follow-up endocrinological assessment has not been performed.

One patient had bitemporal hemianopsia, primarily affecting the inferior temporal quadrants, immediately after surgery and has had no improvement during the early postoperative period. The loss of function of the portion of the optic chiasm distal from the tumor and the absence of recovery suggest that the bitemporal hemianopsia may have had a vascular cause, perhaps as a result of interruption of two small vessels that passed through the edge of the tumor to reach the chiasm. Although the chiasm receives its blood supply from multiple branches arising from the anterior cerebral and anterior communicating arteries superiorly and from branches of the internal carotid, superior hypophyseal, and posterior communicating arteries inferiorly,14,22,23,25 most of the supply is from the superior surface, via branches of the anterior cerebral and anterior communicating arteries.4,14,22,23,25 There is usually free intercommunication between the intrinsic capillary vessels of the optic chiasm and those of the hypothalamus,4,14,25 permitting excision of most tumors that arise from the stalk, such as craniopharyngiomas, without producing visual impairment. On the other hand, the largest, most numerous, and most extensive vessels in the plexus on the inferior surface of the optic chiasm are regularly supplied by the anterior superior hypophyseal arteries,4,14,25 which are distal branches of the superior hypophyseal arteries and which arise from the internal carotid artery and pass rostrally in the subarachnoid space to reach the pars tuberalis of the pituitary and inferior surface of the optic chiasm. The intrinsic capillary plexus of the chiasm, in turn, is connected to the vessels in the overlying pial network. Thus, occasionally postoperative loss of function in the optic chiasm may occur because of interruption of the superior hypophyseal arteries or their branches, which may have visual and endocrine consequences, as occurred in one of our patients.

Conclusions

Ten patients underwent transsphenoidal surgery for resection of ACTH-producing adenomas located in the pituitary stalk or extending into the stalk from the superior aspect of the anterior lobe. Previously, similar cases have been approached transcranially and most patients have lost pituitary function. Transsphenoidal exposure and selective adenomectomy permit clinical and laboratory remission of Cushing’s disease with preservation of pituitary function in most patients.
Selective excision of pituitary stalk adenomas

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References


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