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Surgical management of Cushing's disease

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Abstract
Background Transsphenoidal selective adenomectomy is the first-line treatment for Cushing's disease. At experienced centers, early remission rates after transsphenoidal surgery range from 65 to 98 %, however disease relapse frequently occurs with rates ranging from 2 to 35 % at long-term follow up.
Methods This article discusses recently reported studies on the surgical outcomes from transsphenoidal surgery for Cushing's disease.
Conclusions One of the keys to a successful long-term surgical outcome is meticulous dissection using the adenoma's pseudocapsule as a surgical plane for complete resection. MRI-negative and invasive ACTH-secreting adenomas pose particular challenges for pituitary surgeons.

Keywords Cushing's disease · ACTH · Transsphenoidal surgery · Pseudocapsule

Cushing's disease remission and relapse after transsphenoidal surgery

Consistent diagnosis and successful treatment of ACTH-secreting pituitary adenomas associated with Cushing's disease remains a challenge for neuro-endocrinologists and pituitary surgeons. Unsuccessful treatment leads to increased morbidity, a higher mortality rate, and poor quality of life among patients with Cushing's disease [1–3].

Once the diagnosis has been firmly established, selective adenomectomy via a transsphenoidal approach is the treatment of choice for a vast majority of patients with Cushing's disease. Early surgical remission rates after transsphenoidal surgery range from 65 to 98 % at experienced centers, however as many as 20–35 % of patients with Cushing's disease are not in remission after surgery, leaving these patients at risk to the detrimental effects of persistent hypercortisolemia [4–10].

Failure to achieve remission after selective adenomectomy is caused by residual adenoma. This can occur after an incomplete resection of an invasive or large tumor, incorrect removal of a secondary, incidental, lesion instead of the ACTH-secreting adenoma, extrapituitary or parasellar adenomas, or inability to find the adenoma during careful exploration of the pituitary gland [11]. In these instances, early repeat surgery may be performed to re-explore previously unexplored portions of the pituitary gland in an attempt to identify and remove the ACTH-producing adenoma [12–16]. If none is found, the surgeon may elect to perform a partial or total hypophesectomy, often with favorable outcomes.

Although transsphenoidal surgery is effective in attaining and sustaining disease remission in a majority of cases, disease relapse is reported in 2–35 % of patients [6–10, 17, 18]. The variation of reported remission and relapse rates is clearly a result of the varying definitions used to define remission and length of follow up. For instance, Patil et al. [18] describe recurrences in 26 % of patients with 2 year follow up, 33 % at 3 years, and 46 % at 5 years. Over the past two years several large series have been published with long durations of follow up, some of which have

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Table 1 Recent retrospective studies on Cushing's Disease

Authors	Evaluable patients, N	Remission, N (%)			Mean followup	Recurrence (%)
		Overall	Hypocortisolism	Eucortisolism		
Aranda et al. [21]	32	32 (78)	12 (38)	20 (62)	14 (1–37) years	66
Berker et al. [22]	90	81 (90)	76 (94)	5 (6)	32 (5–75) months	5.6
Costenaro et al. [23]	103	84 (76)	34 (40)	–	6 (2.6–8.8) years	8
Alahmadi et al. [19]	42	28 (67)	22 (79)	6 (21)	33(3–102) months	7
Starke et al. [27]	61	58 (95)	35 (57)	23 (38)	28 (12–72) months	11
Wagenmakers et al. [28]	86	62 (72)	–	–	71 (5–164) months	16
Alexandraki et al. [20]	124[a]	84 (68)	56 (45)	28 (23)	15.9 (6–37) years	24
Hameed et al. [25]	52	43 (83)	13 (30)[b]	30 (70)	17 (2–143) months	14
Dimopoulou et al. [24]	120	85 (71)	65 (76)	20 (24)	79 months	34
Lambert et al. [26]	257	230 (89)	195 (76)	–	6.3 years (1 month–30 years)	21
Lonser et al. [29][c]	200	195 (98)	189 (95)	6 (3)	6.8 (0.3–21.3) years	7

–, not indicated in report

[a] Patients with transsphenoidal surgery

[b] Serum cortisol <2 mcg/dl

[c] Pediatric series, 27 with prior surgery

reported much higher rates of disease relapse than prior studies (see Table 1) [19–29].

In the largest of recent case series, Lambert et al. [26] studied the long-term outcomes in 257 patients with Cushing's disease treated by transsphenoidal surgery. Follow up times ranged from 1 month to 30 years with an average time of 6.3 years. Immediate remission with hypocortisolism was noted in 76 % of patients, delayed remission (which included remission after Gamma Knife, adrenalectomy, etc.) in 13.6 %, and persistent disease in 10.5 %. Overall disease relapse occurred in 21 % of the patients, with relapses occurring in 10.8 and 57.1 % of patients with postoperative hypocortisolism and delayed remission, respectively [26]. Alexandraki et al. [20] studied the long-term outcomes of 124 patients with Cushing's disease treated with transsphenoidal surgery with a minimum of 6 years follow up (range 6–29 years). They report an overall early remission in 68 % of patients, and there was a 24 % rate of disease relapse; this included recurrence in 15 % of the patients with hypocortisolim immediately after surgery using stringent criteria (serum cortisol <50 nmol/l; 1.8 μg/dl) [20].

Dimopoulou et al. [24] studied the outcomes of 120 patients who had first-time surgery and 36 patients who had revision surgery at two institutions in Munich, Germany with a mean follow up time of 79 months. The remission rates for patients having first time surgery and repeat surgery were 71 and 42 %, respectively. Among patients with remission after initial surgery, 76 % (65/85 patients) had early postoperative hypocortisolism (serum cortisol <5 μg/dl). These patients were 0.7 times less likely to have disease recurrence compared to patients with early postoperative eucortisolism. Relapse rates were 34 and 58 % for first-time and repeat surgery, respectively with an average time to relapse of 54 months (range 5–205 months) [24]. Aranda et al. [21] reported rate of relapse at 65.6 % in a 41 patient study with an average follow up of 14 years, which is much higher than previous reports. The average time to relapse was 2.4 years (range 0.5–5 years).

Among the aforementioned studies, the authors and others have attempted to identify early postoperative predictors of sustained remission and disease relapse. The best early predictor of successful surgery is hypocortisolemia in the first few days following surgery, with serum cortisol values <5 μg/dl predicting remission and profound hypocortisolism (<1–2 μg/dl) likely being highly predictive for sustained remission, although Lindsay et al. [30] reported no statistical difference in the rate of recurrence in patients with postoperative AM cortisol nadir of <1 μg/dl, <2 ng/ml, or <5 ng/ml). Note that the summary material in Table 1 suggests that the higher relapse rates tend to occur in the series with a greater fraction of patients with eucortisolism in the early postoperative interval, as well as with longer follow up. Other studies have found that prolonged hypocortisolism without recovery of the HPA axis as a good indicator of remission, although many of these patients may also have panhypopituitarism. Moreover, although identifying early predictors of surgical success has been the focus of many studies, disease relapse also occurs in patients with undetectable plasma cortisol levels after surgery and detection and treatment of it is a significant factor in postoperative patient care. All patients with Cushing's disease need prolonged postoperative assessment by an endocrinologist.

Most disease relapses occur within the first 5 years, although relapse has been reported up to 30 years after initial surgery [21, 24, 31]. Most relapse can be attributable to microscopic residual left at the adenoma margin or unrecognized microscopic dural invasion along the wall of the cavernous sinus [11]. In a study that compared the location of adenomas in patients with relapsed Cushing's disease, all recurrent tumors were found at the same site of the adenoma at the initial operation or within the adjacent dura, usually in the wall of the cavernous sinus [11]. Furthermore, a high percentage of these recurrent adenomas had surgical evidence of dural invasion that was unrecognized during the initial surgery. Repeat transsphenoidal surgery is effective in obtaining remission in 61–73 % of patients with disease relapse, which is slightly lower than remission rates after initial surgery. Friedman et al. [32] studied the outcomes of 31 patients who had recurrent Cushing's disease after transsphenoidal surgery and found that 73 % had remission after repeat transsphenoidal surgery. Patil et al. [33] conducted a similar study in 36 patients with recurrent Cushing's disease and obtained remission in 22 (61 %) with repeat surgery. In these cases, careful patient selection is required for optimal outcomes.

The histological pseudocapsule for adenoma resection

Careful pituitary exploration, adenoma dissection and complete removal are essential for optimal short and long-term outcomes. Over the last 20 years there has been an emphasis on the method for surgical approach to the sella in the pituitary surgery literature with the development of endoscopic techniques. However, few studies describe and report outcomes of pituitary surgery that focus on the method for adenoma removal, the critical portion of the operation [34–36].

The anterior pituitary gland is covered by a thin, durable capsule, which separates the gland from the adjacent dura of the sella and cavernous sinuses. The parenchyma of the anterior gland is composed of cells arranged in cords or acini. The intervening stromal tissue contains a rich network of blood vessels and supporting structural elements including collagen and reticulin. This structural arrangement gives the anterior pituitary gland a firm texture, compared to the adjacent posterior pituitary gland, which does not contain a dense collagen matrix for support.

Pituitary adenomas originate from the proliferation of a single abnormal cell without the formation of normal intervening structural support. Thus, pituitary adenomas tend to have a soft consistency. During adenoma growth, the normal pituitary tissue is compressed and displaced, leading to an interface between the adenoma and normal gland that is comprised of compressed normal gland that contains collagen and reticulin [36]. This results in the formation of an envelope around the adenoma termed the histological pseudocapsule.

An important surgical advance for Cushing's disease came with the recognition that the adenoma's pseudocapsule could be identified during careful dissection and used as a surgical plane to remove adenomas [36]. This surgical method has several advantages. First, it allows complete adenoma resection and avoids possible incomplete resection using a piecemeal approach. Second it allows the surgeon to carefully inspect the adenoma borders and appreciate areas of invasion into the pituitary capsule and adjacent dura. Finally, this method affords maximal preservation of the remaining normal pituitary gland. The use of the pseudocapsule as a surgical plane can be applied to adenomas of all sizes except for very small tumors. In adenomas <1 mm in size, there appears to be little compression of the surrounding gland, however with adenomas as small as 2–3 mm in size there is sufficient compression of adjacent normal pituitary gland to form a histological pseudocapsule [36].

One of us (EHO) has focused on the use of the histological pseudocapsule as a surgical capsule for selective adenomectomy since the early 1980s, and has previously reported the long-term results using the histological pseudocapsule as a surgical plane to remove intrasellar adenomas in Cushing's disease. In this study, all 261 patients with adenomas identified at surgery and in whom the adenoma was contained within the pituitary gland had reversal of hypercortisolism [256 (98 %) with hypocortisolism, 5 with eucortisolism] at hospital discharge, which included a large number of patients with MRI negative imaging (48 %) [8]. During the hospitalization 9 of these patients underwent early re-operation for persistent hyercortisolemia. There were only 6 patients (2 %) with disease relapse at an average interval of 56 months during a mean overall follow up of 84 months.

Following complete resection of an adenoma using this method, patients become hypocortisolemic 19.4 h after surgery on average. This rate of decline in serum cortisol level is significantly faster than the rate occurring in patients who received incomplete resections or resections using a piecemeal method [37]. This supports the idea that dissection and adenoma removal using the pseudocapsular method enables complete adenoma removal, including microscopic disease in the tumor envelope that could otherwise be potentially left behind and contribute to disease relapse.

Challenges in pituitary surgery for Cushing's disease

Negative preoperative MRI

Among patients with microadenomas that are detected on preoperative imaging and are contained within the pituitary

gland, the remission rate following surgery is high [8, 10]. However, Cushing's disease can be caused by very small adenomas that can be undetectable on even the most sensitive preoperative MRIs [38, 39]. Reported remission rates are lower for MRI-negative microadenomas [27, 28, 40]. One step that can be taken to enhance the likelihood of identifying the site of the adenoma before surgery is the use of high resolution, thin cut MRI, which demonstrates the adenoma in some patients despite negative conventional MRI [39, 41]. These cases present a unique challenge for pituitary surgeons, since there is no clear surgical target to guide dissection [35]. Inferior petrosal sinus sampling for ACTH gradients are commonly used in patients with suspected Cushing's disease and negative pituitary MR imaging to establish the diagnosis [42], although this technique is not reliable for predicting the location of the adenoma within the sella [38, 43]. This circumstance requires a careful exploration of the pituitary gland until an adenoma is found, the entire gland if necessary. Furthermore, some small ACTH-secreting pituitary adenomas can present in unusual locations outside the sella, including the sphenoid sinus mucosa, within the cavernous sinus, or within the posterior pituitary gland [44–46].

In cases where an adenoma is not found after careful exploration of the entire anterior pituitary gland, surgeons must decide whether to proceed with total or partial hypophysecotomy. Disease remission occurs in 60–75 % of patients who receive total or partial hypophysectomies, although essentially all these patients have panhypopituitarism after surgery. Since hemihypophysectomy (favoring the size of highest IPSS gradient) or subtotal hypophysectomy (where 30 % of the gland is removed from either side and 20 % is removed from the inferior aspect, leaving 20–30 % attached to the pituitary stalk), sparing a remnant of normal pituitary gland attached to the stalk, the rate of postoperative pituitary insufficiency is only 15–20 % (personal experience), which is much lower than total hypophesectomy.

Invasion

Invasive macradenomas that cause Cushing's disease are also a challenge for pituitary surgeons [47]. Several studies have reported adenoma size as a factor in achieving surgical remission, and remission rates are lower invasive macroadenomas [9, 48]. Dural invasion is higher with larger tumors; the challenge with larger tumors may be a product of the invasion, rather than tumor size. Dural invasion of ACTH-secreting adenomas is likely underappreciated. In a prospective study, Lonser et al. [49] studied a consecutive series of eighty-seven patients with Cushing's disease who underwent surgery. Among this group, 34 % of patients had histologically confirmed dural invasion [49]. In this study, there was a correlation between adenoma size and dural invasion with larger tumors more frequently invading adjacent dura [49].

Among adenomas whose invasion is limited to the dura of the medial wall of the cavernous sinus, a complete resection of all microscopic adenoma is feasible by excision of the involved dura, and there is a high rate of remission [29, 47, 49]. However, if an adenoma invades beyond the medial wall to involve structures within the cavernous sinus, a complete resection of all microscopic disease with cure is unlikely [47]. A thorough debulking of the adenoma within the cavernous sinus may lead to early disease remission, but long-term surgical remission seems unlikely without further treatment with radiosurgery.

Conclusions

Transsphenoidal surgery is an effective, definitive treatment for Cushing's disease. However, not all patients are in remission after surgery and others experience disease relapse after some time of remission. Careful pituitary exploration in a bloodless operative field, identification of the tumor, and complete removal, often by taking advantage of the tissue envelope surrounding the tumor provided by the histological pseudocapsule, are essential for optimal surgical outcomes. Patients with negative MRI and invasive adenomas remain challenging patients for surgical success.

Conflict of interest None.

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