Pituitary (2022) 25:713–717
https://doi.org/10.1007/s11102-022-01254-8

Pituitary surgery in Cushing's disease: first line treatment and role of reoperation

Pamela S. Jones[1] · **Brooke Swearingen**[1]

Accepted: 4 July 2022 / Published online: 20 July 2022

Abstract
Cushing's disease is the most common cause of endogenous hypercortisolemia, and transsphenoidal surgery remains the first line therapy for removal of the ACTH-secreting adenoma. While post-operative remission rates are high in experienced hands, there remains a 2% risk of recurrence per year. Patients with the highest chance for cure are those with small, non-invasive tumors that are visible on pre-operative MRI and identified during surgery and are performed by high-volume pituitary neurosurgeons. Surgery for persistent or recurrent disease is frequently indicated and is most successful in the hands of experienced surgeons and in cases where tumor is visible on MRI.

Keywords Transsphenoidal · Cushing's disease · Cushing's remission · Cushing's recurrence

Introduction

Transsphenoidal surgery is recommended as first-line therapy for patients with Cushing's disease (CD) [1]. The goal of surgery is selective adenomectomy to remove the ACTH-secreting tumor. Surgical options include the microscopic transsphenoidal approach, either through sublabial or endonasal exposure, as well as the endoscopic endonasal transsphenoidal approach. Post-operative remission rates range from 65% to greater than 90%, with higher rates of remission achieved by more experienced neurosurgeons and in cases of non-invasive microadenomas visible on pre-operative MRI [2]. Early reoperation for cases of persistent disease is recommended when patients' plateaued cortisol levels do not meet remission criteria [3]. Reoperation for cases of recurrence is recommended particularly if the tumor is visible and/or the neurosurgeon is experienced and operates at a high-volume pituitary center [4].

✉ Pamela S. Jones
psjones@mgh.harvard.edu

Brooke Swearingen
bswearingen@mgh.harvard.edu

[1] Department of Neurosurgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Transsphenoidal surgery

Transsphenoidal surgery has been the mainstay approach for pituitary and CD surgery since the 1960s and is performed either by microscopic or endoscopic endonasal technique. Craniotomy is rarely necessary. In recent decades, the use of the endoscopic approach has significantly increased while the microscopic method has decreased, although outcomes and complication rates for CD remain largely equivalent between the two techniques [5]. This shift may in part be because endoscopes offer the advantage of a wider field of view and the capacity to inspect regions of the sella for residual tumor [6]. The endoscopic endonasal transsphenoidal surgery is typically performed by both a neurosurgeon and an otolaryngologist (ENT) with specialization in rhinology. The ENT surgeon obtains endoscopic access into the sphenoid sinus, at which point the neurosurgeon opens the sella and works to find and remove the tumor. Intraoperative navigation is provided by either fluoroscopy or CT- and/or MRI-guided stereotaxy. Endoscope technology has allowed for crisp, high-definition visualization, including 4 K resolution and some surgeons also utilize and prefer 3-D endoscopes [7].

Post-operative remission

Remission criteria

There is no single absolute determinant of post-operative remission; an ideal criterion would correlate with both clinical improvement and minimal risk of recurrence. Early predictors of remission include general indicators of hypoadrenalism, including low fasting serum cortisol (< 2 µg/dL), low 24 h urine free cortisol levels (below 20 µg/24 h), low serum ACTH (less than 5 pg/mL), or low midnight salivary cortisol within the first week after surgery [8]. Some data suggests that morning serum cortisol level less than 1 µg/dL predicts remission with a positive predictive value (PPV) of 96% [8], although other studies have shown that undetectable levels can still be seen in cases which later recur [9].

Remission rates

Remission is seen in approximately 80% of patients with microadenomas and 60% with macroadenomas, with overall remission rates of 68–91% [2]. Patients in remission require glucocorticoid replacement until a cortisol stimulation test demonstrates hypothalamic–pituitary–adrenal (HPA) axis recovery [10]. In some cases, especially in patients with mild hypercortisolism or cyclic Cushing's disease, remission can be difficult to determine and, occasionally, patients will achieve remission without marked postoperative hypocortisolism or in a delayed fashion up to 4–6 weeks after surgery [3]. Continued outpatient monitoring until postoperative cortisol nadir occurs can usually identify such cases. Nevertheless, patients with persistent serum cortisol levels greater than 5 µg/dL typically warrant early reevaluation by the neuro-endocrinologist and neurosurgeon for possible additional treatment, and patients with cortisol levels between 2 and 5 µg/dL warrant close observation as well [11]. The optimal approach for postoperative testing varies between centers; some withhold glucocorticoid replacement until testing is complete, while others discharge the patient on replacement doses of glucocorticoids and complete testing as an outpatient [12].

Determinants of remission

Several factors have been linked to the likelihood of successful surgical outcome, including small size of tumor (< 10 mm), lack of tumor invasiveness, and ability to identify tumor on preoperative MRI as well as intraoperatively (Table 1). Most studies show an improved rate of remission with microadenomas, with a recent meta-analysis indicating a remission rate of 83% for microadenomas, 68% for macroadenomas, and overall remission rate of 80% [13, 14]. Patients with non-encapsulated macroadenomas may have worse outcomes as these tumors are more likely to be invasive and invasion of the cavernous sinus and dura or suprasellar tumor extension results consistently in a higher incidence of persistent disease [15]. Identification of the adenoma on preoperative MRI has also been linked to improved chance of remission [16, 17] data indicates that remission can be as high as 81% when a lesion is visible on preoperative MRI, as compared to 69% remission rates in MRI negative cases [14]. Intraoperative confirmation

Table 1 Predictors of post-operative remission in CD

Tumor features	Remission rates
Size	< 10 mm: ~ 80%
	> 10 mm: ~ 60%
Invasion	CS absent: ~ 80%
	CS present: ~ 30%
MRI features	MRI-positive: 81–88%
	MRI-negative: ~ 69%
Surgery	
Pathologic confirmation	Tumor found: 87%
	Tumor not found: 45%
Microscopic vs. Endoscopic	NS difference overall in remission (~ 80%)/ recurrence (~ 10%)
Surgeon experience	Trend towards increased remission with high-volume surgeon

CS cavernous sinus, *NS* non-significant

of adenoma histopathology has also been linked to improved chance of surgical cure as studies indicate that, on systematic exploration of the gland for small or invisible tumors, the use of intraoperative cytologic smears and/or frozen sections may be useful in achieving remission [18, 19]. Meta-analysis of the effect of microscopic versus endoscopic surgical technique on outcomes for CD shows no major difference in remission or recurrence rates, although there may be a benefit of endoscopic technique for achieving improved remission in cases of macroadenomas [20].

Correlation with surgical experience and technique

Treatment at a high-volume center by an experienced surgeon has been correlated with improved remission rates [21, 22]. While database studies indicate a volume-outcome effect, where surgeons that perform a higher volume of pituitary surgery have reduced morbidity and mortality rates, the exact contribution of surgical experience to surgical success in CD is difficult to document [23, 24]. While some studies show no change in remission rates over a surgeon's career, several others report improvement with experience over time [9, 16, 22].

Surgical morbidity

Overall, rates of surgical morbidity and mortality remain low, with more experienced surgeons having lower complication rates than less experienced surgeons [25, 26] Surgeon experience has also been associated with shorter postoperative length of stay, and lower costs. The most common complications still occur at relatively low frequency, with new-onset hypopituitarism occurring in approximately 10% of patients, cerebrospinal fluid (CSF) leak in 4–13%, permanent diabetes insipidus (DI) in ~ 2–4%, and venous thromboembolism (VTE) in 1–2%. Data suggests that electrolyte complications, such as DI and post-operative hyponatremia, occur more frequently with surgery for CD as compared to surgery for non-functioning adenomas [27]. Overall, perioperative mortality remains low at < 1% [21]. In systematic review, rates of complication in CD based on microscopic versus endoscopic surgical technique are largely equivalent, with a higher rate of CSF leak with the endoscopic method (12.9% vs 4%) but similar low rates of meningitis (0.1% vs 0.6%) [20].

The role of re-operation

Re-operation for persistent disease

For patients who do not meet criteria for immediate or delayed remission following initial surgery, early reoperation for persistent disease is often recommended, especially for patients with pathologic confirmation of adenoma on initial surgery [28]. Remission rates in reoperation for persistent CD range from 40–70%, with a recent meta-analysis indicating remission rate of 54% in persistent disease [14, 29]. Although early re-operation (within a few weeks) is technically less difficult given minimal early post-operative scarring, data supports waiting until cortisol levels have plateaued before proceeding with a second surgery [3], as delayed remission may occur as late as one month after surgery and patients with mild hypercortisolism or cyclic Cushing's disease may not have marked postoperative hypocortisolism. Due to increased gland sampling or even partial or total removal of the pituitary gland in a second surgery, reoperation leads to higher rates of hypopituitarism, DI, and CSF leak [30].

Re-operation for recurrence

Recurrent disease at 5 years occurs at a rate of approximately 10–15%, increasing to 20–25% at 10 years, or approximately 2% per year [13, 31]. Patients who did not have postoperative hypocortisolemia (nadir AM cortisol > 2ug/dL) or experienced delayed biochemical remission following initial surgery have a significantly increased risk for recurrence as compared to patients with immediate remission after surgery [3, 14, 32]. Additional predictors of recurrence include history of revision surgery and tumor size > 10 mm [14]. There are multiple diagnostic techniques for surveillance of recurrence; late-night salivary cortisol (LNSC) levels and 24-h urine free cortisol (UFC) levels are commonly assessed, with data indicating that LNSC may be the most sensitive for recurrence [33]. With the advent of new pharmacologic agents, there are now a number of treatment modalities for the management of recurrent disease, but repeat transsphenoidal surgery remains a viable treatment option, especially in patients with visible tumor on MRI [34–36]. At high-volume centers, reoperation performed in the absence of detectable adenoma on MRI is more successful when there has been proven ACTH-staining adenoma on pathology or a central ACTH gradient on IPSS at the initial operation [34, 35]. Tumor features such as size, invasiveness, and extrasellar extension should be considered when weighing the role and benefit of surgery over other treatment options like radiation therapy [16]. Remission rates after reoperation vary widely in the literature, ranging from 40 to 80%, at least in part because of different indications for re-operation, remission criteria, and follow-up duration [30]. A recent meta-analysis found overall remission rates for recurrence to be 80% [14]. As with initial surgery, findings of tumor and positive histopathology have correlated with increased remission rates in some studies of reoperation [37]. Although the literature reports higher rates of both

surgical (i.e., CSF leak, meningitis) and endocrinological complications (i.e., DI and hypopituitarism) with repeat versus initial surgery, serious morbidity remains low and is less likely in experienced hands [16].

Clinical considerations and recommendations for pituitary surgery for CD

In summary, we recommend patients with CD undergo surgery as primary therapy in specialized pituitary tumor centers of excellence [38]. Surgery should be performed by an experienced pituitary neurosurgeon and follow-up done by a multidisciplinary team including a pituitary endocrinologist. If the original procedure is unsuccessful, re-operation can be considered. In cases of recurrence, we suggest repeat transsphenoidal surgery in patients with biochemical evidence of recurrent CD especially if tumor is visible on MRI and particularly if the first surgery was not performed by a high-volume pituitary neurosurgeon. If MRI does not show tumor presence, reoperation might be appropriate if an experienced surgeon at a high-volume center considers it feasible and positive pathology or a central gradient on IPSS was seen before the initial operation.

Author contributions Authors PSJ and BS were both involved in the drafting, writing, and editing of this manuscript.

Funding None applicable.

Declarations

Competing interests The authors have no competing interests to declare with regards to this manuscript.

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