REVIEW ARTICLE

Management of Cushing's Disease After Failed Surgery - A Review

Nancy McLaughlin, Amin B. Kassam, Daniel M. Prevedello, Daniel F. Kelly

ABSTRACT: Selective transsphenoidal adenomectomy is generally recommended for initial treatment of Cushing's disease (CD) because it achieves a high (70-85%) rate of remission. However, if initial surgery is not successful, the approach to persistent or recurrent CD is more complex. Because residual or recurrent adenoma is typically found at the site of the original adenoma, repeat transsphenoidal surgery is recommended including selective adenomectomy, hemihypophysectomy or total hypophysectomy. If repeat pituitary surgery does not achieve remission, then possible adjuvant therapies include radiosurgery or stereotactic radiotherapy, bilateral adrenalectomy, and/or medical therapy. In all cases of persistent or recurrent CD, successful treatment requires close collaboration of endocrinologists, radiation oncologists and neurosurgeons.

RÉSUMÉ: Revue du traitement de la maladie de Cushing suite à l'échec de la chirurgie. L'adénomectomie transsphénoïdale est généralement recommandée comme traitement initial de la maladie de Cushing (MC) parce que le taux de rémission obtenu est élevé, de l'ordre de 70% à 85%. Cependant, si la chirurgie initiale est un échec, la conduite à tenir en cas de persistance ou de récidive de la MC est plus complexe. Étant donné que, de façon typique, l'adénome résiduel ou récidivant est situé à l'endroit où était situé l'adénome initial, une nouvelle chirurgie transsphénoïdale est recommandée, avec adénomectomie sélective, hémihypophysectomie ou hypophysectomie totale. Si une réintervention à l'hypophyse n'entraîne pas de rémission, des traitements adjuvants dont la radiochirurgie ou la radiothérapie stéréotaxique, la surrénalectomie bilatérale et/ou le traitement médical sont des options à considérer. Chez tous les cas de MC persistante ou récidivante, le succès du traitement dépend d'une collaboration étroite entre endocrinologues, radio-oncologues et neurochirurgiens.

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Cushing's disease (CD) is the most common cause of Adrenocorticotropic Hormone (ACTH)-dependent Cushing's syndrome[1]. It is defined as hypercortisolism caused by an ACTH-secreting pituitary adenoma, most often located within the anterior pituitary gland[1]. If left untreated, chronically elevated cortisol levels are associated with a fourfold increase in mortality[2-3], largely related to abnormal glucose metabolism and cardiovascular complications including coronary heart disease, congestive heart disease and cerebrovascular events[4-6]. Transsphenoidal adenomectomy can normalize cortisol levels in approximately 70-85% of cases[2,7-14]. In these patients, remission is characterized by 4 to 18 months of sustained hypocortisolemia that requires steroid replacement before intrinsic cortisol function recovers[15]. After successful treatment of CD, age- and sex-adjusted survival rates approximate those of the general population.

Unfortunately, CD may persist in 7-31%[12,16] and recur in 3-27%[2,4,12,13,15,17-20] of patients who have undergone initial transsphenoidal surgery. When initial surgery fails, repeat surgery with selective adenomectomy, hemi-hypophysectomy or total hypophysectomy should be considered. If repeat surgery does not produce remission, adjuvant treatment options include radiation therapy, adrenolytic medical treatment, bilateral adrenalectomy, or a combination of adjuvant treatments. This review outlines the overall management of persistent or recurrent CD after failed initial transphenoidal surgery, with special emphasis on the indications for repeat surgery and the specific techniques for re-operation (Figure 1).

Assessment following initial surgery and surveillance of patients in remission

Early postoperative management

Following initial transsphenoidal surgery, patients require close biochemical and clinical monitoring to determine whether remission has been achieved. Blood specimens for serum

From the Neuroscience Institute & Brain Tumor Center, John Wayne Cancer Institute at Saint John's Health Center, Santa Monica, California, USA.

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Correspondence to: Daniel Kelly, Brain Tumor Center, John Wayne Cancer Institute at Saint John's Health Center, 2200 Santa Monica Blvd., Santa Monica, California, 90404, USA.

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cortisol and ACTH testing should be obtained twice daily (6 a.m. and 6 p.m.) on post-operative Days 1 and 2. Post-operative glucocorticoids should be withheld until hypocortisolemia (serum cortisol ≤ 5 μg/dl or ≤ 140 nmol/liter) is documented, typically within 24-48 hours of successful surgery[10]. Corticotroph function then is assessed at least every three months as glucocorticoid replacement therapy is slowly tapered. Sustained remission corresponds to at least six months of glucocorticoid replacement, followed by clinical and biochemical evidence of eucortisolemia (serum cortisol level and normal 24-hour urinary free cortisol). To ensure early detection of recurrence, patients should be followed up with 24-hour urinary free cortisol levels every six months for the first five years and at least annually thereafter[1].

Early prediction of long-term remission

Several methods have been used to predict long-term remission from CD. Provocative tests include the overnight low-dose dexamethasone suppression test and the corticotrophin-releasing hormone (CRH) stimulation test. Non-provocative tests include the measurement of morning serum cortisol and ACTH levels, and 24-hour urinary free cortisol concentrations within the early post-operative period. Recent studies indicate that both provocative and non-provocative tests are accurate for predicting remission[7]. Most studies have measured early post-operative serum cortisol level[12], but the timing of its measurement and the cut-off level for remission are variable. In a recently published series, a morning cortisol level of 5 μg/dl (~ 140 nmol/liter) or less on post-operative Day 1 or 2 was predictive of sustained remission in 97% of patients[10]. However, up to 4.5% of patients who achieve remission will not have a drop in cortisol levels during the first three days after surgery[10,21-22]. Also, undetectable cortisol values in the immediate post-operative period are not invariably associated with long-term remission[23]. In a large European multicenter study of CD, 4.3% of patients with undetectable serum cortisol levels in the immediate post-operative period developed relapse during follow-up[19]. Unmeasurable postoperative cortisol values predict a better outcome[4,24-26] but does not eliminate the possibility of recurrence. Furthermore, Bochicchio and colleagues showed that 24.4% of patients with normal serum cortisol levels immediately after surgery eventually relapse[19]. In the early post-operative period a low-dose dexamethasone suppression test may help distinguish patients with durable remission from those who have residual tumor and will need early re-operation.

Factors associated with a lower probability of remission

Factors associated with a poorer surgical outcome include ACTH-producing macroadenomas that extend above the floor of the sella[12], invade the cavernous sinus[2,27,28], or infiltrate the dura (infiltration may be present without visible evidence of invasion during surgery[2,28-30]). In a recent series, initial remission rate was 86% for microadenomas, 83% for macroadenomas contained within the sella, 63% if macroadenomas extended above the floor of the sella, and 65% if tumor extended to the cavernous sinus[2]. Not surprisingly, overall remission rates are lower and recurrence rates are higher (12-45%) in patients with macroadenomas versus microadenomas[27,29,31]. Similarly, time to recurrence is shorter with macroadenomas versus micro-adenomas (mean 16 months vs 49 months)[27,29,31]. In Dickerman and Oldfield's series, dural invasion was identified in 42 (62%) of 68 patients with recurrent CD, including all patients with macroadenomas and more than half of patients with microadenomas[28]. Most (93%) of these invasive adenomas involved the cavernous sinus[28].

In addition, clinicopathological studies have begun correlating the behavioral characteristics of pituitary tumors with histopathological and immunohistochemical features[32]. Specifically for CD, it has been found that the absence of peritumoral Crooke's change may be a predictor of recurrence after successful surgical treatment[33]. Normally, Crooke changes represent corticotroph cells' response to elevated glucocorticoid excess and is believed to functionally suppress these cells[34]. Therefore the absence of Crooke's changes indicates a lack of suppression, indicating that corticotroph cells may have some intrinsic abnormality predisposing to adenomatous islands and recurrence[33]. Interestingly, corticotroph adenomas composed mostly of Crooke's cells are aggressive when compared to typical corticotroph adenomas and have a higher recurrence rate[35]. Overall, invasive pituitary adenomas tend to have a higher proliferative rate and immunopositivity for p53[32]. Further assessment is required to characterize the histological features that may help predict long-term outcome and recurrence.

Basis of persistent and recurrent Cushing disease

The causes of failure after a first transsphenoidal surgery for CD may be due to the presence of residual tumor remaining hidden in the gland, in the cavernous sinus or less commonly in an ectopic parasellar region[28]. In most cases, residual tumor responsible for persistent or recurrent CD is found at or immediately contiguous to the site of the initial surgery[28,36]. Failure is often due to residual invasive tumor within the dura of the sella or in the cavernous sinus[28,37]. Dickerman found that unappreciated dural invasion within the cavernous sinus, even without evidence of invasion on MRI, is the basis of failure in many CD patients.[28] Failed surgery may also result from the fact that the diagnosis of CD is incorrect. Other causes may include ectopic ACTH hypersecretion, corticotroph hyperplasia, pseudo-Cushing syndrome, and facticious Cushing syndrome[9,13,27]. Therefore, before repeat transsphenoidal surgery is performed on patients whose CD diagnosis is not confirmed by ACTH-staining adenoma in the first surgical specimen, the results of all pre-operative endocrine and imaging evaluations must be carefully reviewed preferably in a multi-disciplinary fashion.

Persistent Cushing's disease

As stated above, 7-31% of CD patients do not achieve remission after a first transsphenoidal surgery[12,16]. Persistent CD corresponds to a sustained elevation in post-operative cortisol levels and/or a need for therapy of CD within six months of initial surgery[2]. Its cause may be residual tumor hidden in the gland or less commonly in an ectopic site in the intrasellar or perisellar region[28]. Persistent CD may also be due to residual invasive tumor within the dura of the sella or the cavernous sinus[28,37]. Rarely, nodular corticotroph hyperplasia of the pituitary gland may be responsible for a persistently elevated serum cortisol level[9,13]. Finally, postoperative hypercortisolism

occasionally reflects a false diagnosis of CD; if the surgical specimen did not stain positive for ACTH, all pre-operative endocrine and radiologic evaluations should be re-reviewed.

Recurrent Cushing's Disease

Recurrent CD is identified by clinical and biochemical characteristics of CD appearing more than six months after initial remission[15]. Large studies with prolonged follow-up have reported overall recurrence rates of 3-27%; median post-operative time to recurrence is 2.3 to 7.2 years, or in rare cases as late as ten years[2,4,12,13,15-17,19,20,38]. Because most recurrences are due to regrowth of adenoma cells left in the peritumoral tissue during the first surgery[28,36,39,40], repeat surgery should not be planned until the site of the initial tumor has been determined, often by reviewing the original operative note and the original pre-operative MRI.

Imaging and inferior petrosal sinus sampling prior to repeat surgery

A high quality pre-operative sellar MRI should be obtained before repeat surgery for persistent or recurrent CD. In Dickerman's series 53% of ACTH-secreting adenomas were detected on MRI performed prior to repeat surgery[28]. In this study, 52% of the tumors removed during repeat surgery measured less than 5 mm[28]. It must be noted however that pre-operative MRI may not reveal a definitive adenoma; scar tissue and repair materials placed at the original surgery may also be misleading[40]. Dynamic MRIs which acquire images within seconds after the injection have shown improved sensitivity but decreased specificity compared to conventional static MRIs[41]. Recent studies have found that 3 Tesla MRI of the pituitary gland are also more sensitive to pituitary adenomas than 1.5 Tesla images of the sella region[42]. It has been proposed that dynamic post-gadolinium 3 Tesla MRIs should be included in the investigation of patients with CD when 1.5 Tesla imaging is negative or equivocal[42,43]. However the utility of 3 Tesla MRI in patients with recurrent CD is unproven.

For patients with a negative or ambiguous MRI, inferior petrosal sinus sampling (IPSS) may help establish the etiology of ACTH hypersecretion and can help localize the side of the microadenoma[16,40]. If not performed prior to the initial surgery and there is some doubt as to whether the patient actually has CD, IPSS using CRH stimulation may be useful to confirm a pituitary origin of ACTH secretion and potentially localize the side of the adenoma[1,15,29,44,45]. However, in patients with proven CD who have a recurrence, there is relatively little utility to IPSS given that the test is only 50% accurate in predicting tumor laterality[40], and this invasive procedure carries some risk of potential complications.

Timing of repeat intervention

If hypercortisolism persists more than three days following transsphenoidal surgery, a repeat operation should be considered in the immediate post-operative period, especially if the pre-operative imaging was positive, if a tumor was visualized during first surgery and if the pathology showed ACTH-positive staining tumor[8].

Repeat surgery within the first post-operative week has several advantages. First, it allows re-exploration of the sella with minimal additional trauma, because it is undertaken before the formation of scar tissue and modification of surgical anatomy[45,46]. Second, the surgeon often is able to recall particular anatomical details from the earlier operation, which may be essential to the re-exploration[46]. Third, immediate repeat surgery avoids the deleterious effects of continued hypercortisolism, and prevents the potential problems associated with the alternative adjuvant treatments. Finally, as compared with delayed repeat surgery, early repeat surgery for persistent CD has a relatively low morbidity[46].

In patients with recurrent CD, repeat surgery should be performed as soon as the diagnosis of recurrence is clearly established.

Surgical strategy for the management of failed trans-sphenoidal procedure

Once the diagnosis of persistent/recurrent CD is established, selective removal of the persistent/recurrent adenoma by transsphenoidal surgery is the preferred first treatment option, as it is for newly diagnosed CD. As described below, some patients may require more aggressive removal of the gland by hemi-hypophysectomy or even total hypophysectomy[11,14,40,47].

Because of significant scar tissue and altered normal anatomy, repeat surgery for recurrent pituitary adenomas is in general more challenging than an initial operation or an immediate re-operation for persistent disease. Adhesions of soft tissues may complicate access to the sphenoid sinus and sella. If bony closure of the operated sella is encountered, careful reopening of the sellar face is required. The extent of bony removal can be adapted to the presumed location of the persistent/recurrent adenoma but in general a wide exposure is essential. A wide and tall sphenoidotomy will allow access to the entire sella; bone removal over the sellar face should extend laterally beyond the medial portions of the cavernous sinus, superiorly to the planum – tuberculum junction, and inferiorly to the sellar floor. This exposure over the cavernous sinus is particularly important if the original tumor was in the lateral aspect of the gland or sella. Altered anatomic conditions in revision surgery require particular precautions to identify key neurovascular structures, especially the cavernous carotid arteries. Surgical navigation and the Doppler probe are highly recommended for localizing the portion of the internal carotid artery within the cavernous sinus and for confirming regional anatomy[48,49].

For persistent and recurrent CD, once the sella is reached, the first step of repeat surgery should be a thorough re-exploration of the original resection site. Several studies indicate that most cases are due to adenoma cells that persist/recur locally and that a selective adenomectomy is typically possible[28,36,39,40]. The Table 1 summarizes the reported series of persistent/recurrent CD treated by repeat surgery. In a series of eight patients undergoing repeat surgery for recurrent CD, Nakane et al reported that all recurrent adenomas were at the site of the original tumor[36]. Patil et al reported 36 cases of recurrent CD: 67% underwent selective adenomectomy and only 14% required a total hypo-physectomy[47]. In a study by Hofmann et al, 13 of the 16 patients undergoing repeat surgery for recurrent CD had

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recurrent adenoma in the original tumor bed[40]. In Dickerman and Oldfield's series of 68 patients with recurrent CD, all 43 patients in whom tumor was found at the first surgery had recurrent tumor at the same site or an immediately contiguous site[28].

Given these observations, it appears the origin of recurrent tumor is typically in the original tumor bed within the pituitary gland or in the adjacent cavernous sinus, presumably resulting from growth of microscopic tumor rests left behind during the original surgery[40]. If the original tumor site was in the lateral sella, even in instances with an initial negative MRI, wide exploration of the lateral sellar area and clear visualization of the medial cavernous sinus wall are essential. Once the tumor is encountered, a selective extracapsular dissection should be attempted but may not be feasible because of scarring related to the prior surgery[11,50]. Adhesions between the tumor wall and the cavernous sinus are not uncommon in patients with recurrent/persistent CD. If the tumor-gland interface is ill-defined, it is usually prudent and safe to include a margin of normal-appearing gland, working medially from the tumor. This thin rim of normal gland increases the likelihood of remission and carries only a low risk of new hypopituitarism[51].

Regarding possible cavernous sinus invasion by adenoma, adhesions may be present between the tumor wall and the cavernous sinus. Given the high frequency of dural invasion in recurrent tumors, adequate exposure of the medial cavernous sinus and sellar floor dura is essential in repeat surgeries for CD[28]. Enhanced anatomical knowledge of the parasellar area, surgical navigation systems and high-definition endoscopy have improved the safe and effective surgical access to this region[52-54]. After sellar tumor removal, zero-degree and angled endoscopes should be used to visualize the lateral sella and medial cavernous sinus. Although the medial cavernous sinus can often be visualized with the purely microscopic view, the endoscope's more panoramic view may allow more complete removal of cavernous sinus tumor. If tumor extends into the cavernous sinus through a defect of the medial cavernous sinus wall, this dura can be incised under direct endoscopic or microscopic visualization. Tumor within the medial cavernous sinus can be removed using gentle suction and ring currettes. Abnormal-appearing dura in the medial wall of the cavernous sinus should also be removed and dural edges should be lightly cauterized. However, great care must be taken to avoid injuring the cavernous carotid artery. In experienced hands, surgical management of pituitary adenomas invading the cavernous sinus does not result in permanent cranial nerve palsy or internal carotid artery injury[28,55].

If no tumor is visualized on pre-operative MRI, sequential vertical incisions in the gland are performed[50]. A bilateral periglandular inspection with visualization of the medial wall of both cavernous sinuses and of the diaphragm is also performed in order to identify tumoral tissue. Hemihypophysectomy or total hypophysectomy are performed more frequently in repeat surgery than at initial surgery[7]. However, the role of total hypophysectomy for patients with new or recurrent CD remains controversial, in part because the remission rate following total hypophysectomy ranges from 0-100%[47,56]. Also, total hypophysectomy increases the risk of post-operative hypopituitarism[8]. If complete removal of invasive tumor is not possible or if no definitive tumor is identified, the residual gland can be mobilized and separated from the invasive site by an intervening fat graft; this graft protects the gland during postoperative radiotherapy and thereby reduces the risk of hypopituitarism.

If no tumor is found in the anterior lobe, the interface between anterior and posterior lobes should be carefully explored. A small subset of patients may have residual tumor in this region of the sella or within the posterior lobe itself[57]. In order to gain access to the posterior lobe, a 2-mm vertical crevice is created in the anterior gland, exposing the gelatinous contents of the intermediate lobe and afterwards the anterior surface of the posterior lobe[57]. According to Weil and colleagues, ACTH-secreting adenomas within the posterior lobe generally have a pale gray-blue or gray-brown color visible on inspection of the neurohypophysis[57]. However, if the entire posterior lobe must be removed to treat an invasive adenoma, insertion of the infundibulum into the hypophysis should be sharply cut, avoiding traction on the stalk and minimizing the risks of permanent diabetes insipidus (Edward Laws, personal communication, February 2010).

Potential complications of repeat surgery

The higher rate of post-operative hypopituitarism after repeat surgery is related in part to the extent of pituitary tissue removed[14]. Overall, the risk of new hormonal deficiencies after a repeat transsphenoidal operation varies between 2-50% and is usually around 20%[8,14,46,47,58]. Importantly, the risk of hypopituitarism after repeat surgery appears to be lower than reported rates of hypopituitarism occurring several years after radiotherapy[8]. Post-operative CSF leaks have been reported more frequently after repeat transsphenoidal surgery than first-time surgery[45,46,59]. Chee et al found that rates were 46% after repeat transsphenoidal surgery versus 13% after initial transsphenoidal surgery[60]. However, in experienced hands the risk of CSF leak following repeat endonasal transsphenoidal surgery may be minimal[47]. In our experience, only one patient with repeat surgery for failed CD developed a CSF leak post-operatively[10].

Remission after repeat surgery

Repeat surgery using a microsurgical, endoscopic-assisted or purely endoscopic approach can produce remission in most patients with persistent/recurrent CD. The remission rate following repeat surgery using specifically the conventional microscope technique varies from 37-87.5% (Table 1) (simple [unweighted] average 66%). However, relapse after repeated surgery ranges from 0 to 35% at a mean follow-up of 31 months[61]. More recently, Wagenmakers et al has reported the first series of data on repeated transsphenoidal surgery using a purely endoscopic technique for patients with persistent or recurrent CD[14]. Remission was obtained in 71% of patients (50% of persistent CD and 87.5% of recurrent CD[14]. None of these cases relapsed during a mean follow-up of 34 months[14]. These results suggest that purely endoscopic surgery is at least as good as the microscopic technique for repeat surgery. Additional prospective collection of data using the purely endoscopic technique in experienced centers is necessary to confirm these preliminary favorable results.

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Table: Studies of repeat transsphenoidal surgery for persistent or recurrent Cushing's disease

	N	Criteria for Remission	Remission Rate	Relapse Rate	Mean Follow-up
Nakane et al (1987)[36]	8R	N/R	87.5%	N/R	N/R
Friedman et al (1989)[58]	31P&R	Morning C≤6 μg/dl; UFC<90 μg/day	71%	13.6%	11 months
Ram et al (1994)[46]	17P	Morning C≤5μg/dl; UFC<90 μg/day	71%	25%	34 months (range, 4-84)
Knappe el al (1996)[39]	16P 24R	N/R	P:70.8% R:56.3%	P:24% R:22%	N/R
Shimon et al (2002)[13]	13 P&R	Clinical resolution of hypercortisolism; Normalization of UFC; Suppression of C levels by 48-h low-dose Dexa	62%	N/R	N/R
Locatelli et al (2005)[45]	12P	Clinical symptoms of hypocortisolism; Morning C≤2 μg/dl	67%	0	27 months (range, 3-84)
Benveniste el al (2005)[61]	12P/30R	N/R	57%	35%	31 months
Hofmann et al (2006)[40]	16R	Morning C 10-21μg/dl; C<2 μg/dl after 2 mg Dexa	37%	0	N/R
Hofmann et al (2008)[11]	35P&R	Clinical remission; C<2 μg/dl after 2 mg Dexa	37.1%	N/R	N/R
Aghi et al (2008)[18]	10P 13R	Morning C≤5μg/dl; UFC<20μg/day	P: 70% R: 77%	N/R	N/R
Patil et al (2008)[47]	36R	Elevated 24-hr UFC	61%	9.1%	36 months
Wagenmakers et al (2009)[14]	6P 8R	Clinical remission; C≤50 nmol/l after glucocorticoid withdrawal for 24-48h; C≤50 nmol/l after overnight 1 mg Dexa within first 3 months	71%	0	34 months

Dexa, Dexamethasone. N, number of patients undergoing repeat surgery. N/R, not reported. P, persistent Cushing's disease. R, recurrent Cushing's disease. C, serum cortisol. UFC, urinary free cortisol

Adjuvant radiotherapy for persistent or recurrent Cushing's disease

If repeat transsphenoidal surgery does not produce biochemical remission of persistent/recurrent CD, adjuvant treatment should begin immediately[1,16,62]. Adjuvant treatment options include radiation therapy, medical therapy, bilateral adrenalectomy, or a combination of multiple treatments. In the 36 patients described by Patil et al, 61% achieved remission of recurrent CD with surgery alone, and 22% achieved remission after surgery plus adjuvant therapy, for a total success rate of 83%[47]. Adjuvant treatments used in this study were radiosurgery, adrenalectomy and/or Ketoconazole therapy.

Although radiation was widely used for first-line treatment of CD from the 1940s to the early 1980s, it is now more likely to be a secondary treatment after failed transsphenoidal surgery[7,8,15,27,62]. Conventional fractionated radiation therapy has historically been the primary radiation regimen used to treat CD. Reported remission rates vary from 56-83%, with an average time to remission of two years[14,63]. The incidence of hypopituitarism after fractionated radiation therapy ranges from 50 to 100% several years after treatment[64,65]. Other less common

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complications related to fractionated radiotherapy include radiation necrosis, cerebral vasculopathy, damage to surrounding sellar and parasellar structures, and development of radiation neoplasm[28,66-69].

Few studies have specifically assessed the efficacy of fractionated stereotactic radiotherapy (SRT) for CD[70,71]. In a study reported by Colin at al, SRT produced remission in 9 (75%) of 12 patients at a mean of 29 months[70]. In this series, the toxicity was significantly lower for ACTH-secreting pituitary adenomas, with no radio-induced pituitary deficiency and no neurological or optic injury[70]. Theoretically, SRT focused to the target volume may be more suitable than conventional external radiotherapy. However, series with larger populations and longer follow-ups are required to evaluate radiation-induced delayed complications and determine the incidence of biochemical recurrence.

Single-treatment stereotactic radiosurgery (SRS) using photon beams has replaced conventional fractionated radiation therapy as the primary radiation modality for persistent or recurrent CD[8,72], because one high dose has a larger radiobiological effect than multiple lower doses when the target is a slow-growing lesion. In the three largest series of patients who underwent adjuvant radiosurgery using the gamma knife (single fraction therapy), cortisol production normalized in 63% at an average of 12.1 months[73], in 54% at an average of 13 months[74], and in 43% at an average of 22 months[75]. Despite initial enthusiasm for SRS with gamma knife, the relapse rate is high (up to 20%)[73-76]. Also, the incidence of new-onset hypopituitarism requiring replacement therapy after SRS is 16-55%, with a median time to onset of 50-60 months[74-77]. However, SRS seems to lead to faster normalization of hormone levels with lower risk of hypopituitarism and visual deterioration in comparison to fractionated radiotherapy[73,74]. Since recurrences of CD and hormonal deficiencies may arise during long-term follow-up, biochemical surveillance is indicated.

Recently, two groups have reported their results with proton-beam radiosurgery[18,78]. Proton-beam radiosurgery offers improved dose distributions as compared with photon beams[18,79]. These studies obtained remission rates of 52% and 58%, similar to those obtained with gamma knife SRS[18,78]. The toxic effects to the cranial nerve and the disease recurrence rates are slightly lower than those with the gamma knife[18]. However, the incidence of hypopituitarism is 42%-52% in recent studies[18,78]. Larger series with longer follow-up are required to assess the advantages of proton beam radiosurgery over gamma knife SRS, as well as the occurrence of late radiation-related sequelae.

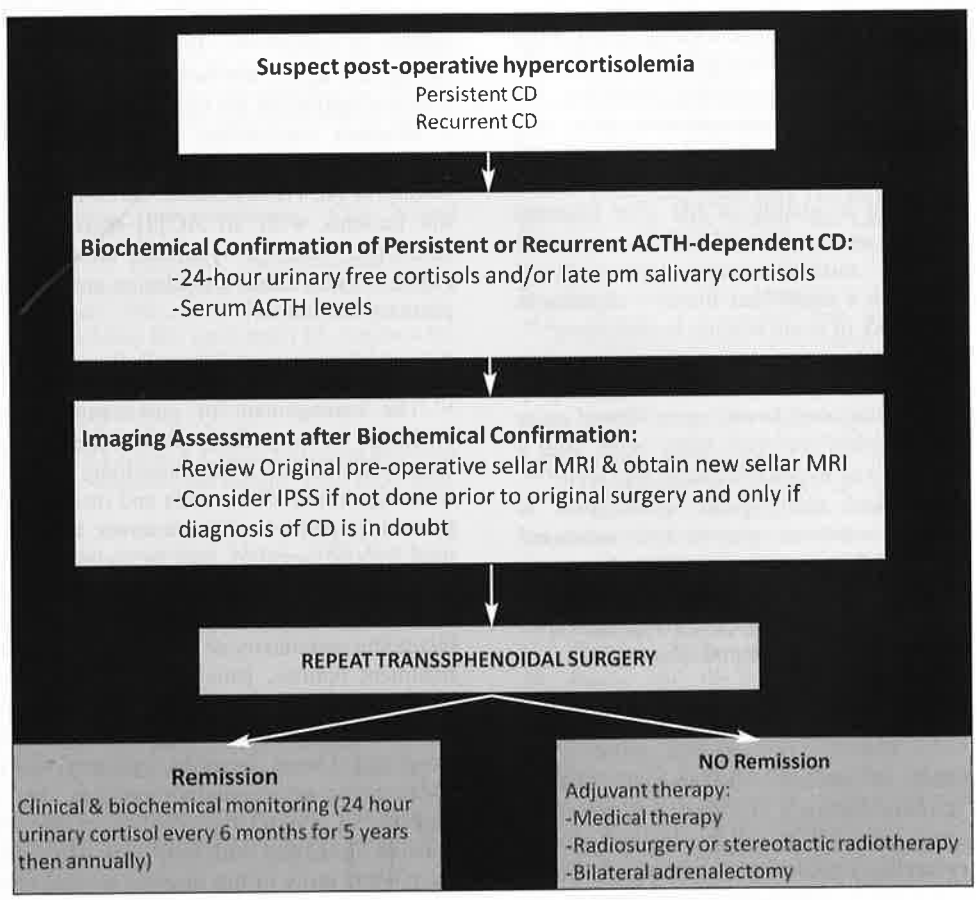

Figure 1: *Schematic summary of the management of Cushing's disease after failed surgery*

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Adjuvant medical treatment

Medical treatment is used to improve a patient's clinical condition before transsphenoidal surgery or before radiation treatment produces its effect. It may also be used when curative resection was prevented by the tumor's size or extent, and for patients who refuse surgery. Overall, medical treatment may be useful in up to one-third of CD patients[80]. Medical treatment for CD includes drugs inhibiting steroidogenesis such as Ketoconazole, cortisol-receptor antagonists such as mifepristone, drugs modulating ACTH release such as somatostatin analogues (Octreotide), and dopamine agonists (Bromocriptine)[8,16,81]. Medical treatment requires lifelong administration and cortisol monitoring to keep cortisol levels in normal ranges. If it is used to bridge the interval before radiation treatment takes effect, it may be discontinued once remission has been documented.

Bilateral adrenalectomy

Bilateral adrenalectomy immediately reverses hypercortisolism in 88-100% of cases[7] but should only be considered when pituitary-directed treatments of persistent/recurrent CD have failed or are contraindicated. Typically, candidates for bilateral adrenalectomy have already undergone multiple surgeries and/or radiosurgeries, or may be unable to obtain medical control of their hypercortisolism without adverse effects.

Open adrenalectomy has been associated with 23% perioperative morbidity and 4% operative mortality[82]. More recently, laparoscopic adrenalectomy has become accepted as the standard approach for resection of most benign adrenal lesions[83]. Recent series have reported 10% peri-operative morbidity, 1% peri-operative mortality, decreased post-operative pain, and shorter hospital stay[83,84]. Although there are persistent quality of life deficits after biochemical remission of CD, numerous studies have found an improvement in quality of life after bilateral adrenalectomy for persistent or recurrent CD[83,85]. However, the requirement for lifelong mineralo- and glucocorticoid replacement therapy requires a significant lifestyle adjustment and does not eliminate the risk of acute adrenal insufficiency[1,15]. Moreover, residual adrenal rests and accessory glands located in various sites can regrow under the chronic stimulation of highly elevated ACTH levels. This may explain why up to 10% of cases may resume endogenous cortisol secretion many years after a bilateral adrenalectomy, and why hypercortisolism may recur[1,62].

Clinical, biochemical and radiological surveillance is necessary to monitor for adenoma growth and increased ACTH plasma levels following bilateral adrenalectomy[1]. Adrenocorticotropic Hormone plasma levels should be measured and a pituitary MRI should be obtained three to six months after bilateral adrenalectomy and at regular intervals thereafter[62].

Onset and management of Nelson's syndrome after bilateral adrenalectomy

Approximately 8-46% of patients who undergo bilateral adrenalectomy will develop Nelson's syndrome[86-90], which is characterized by elevated serum ACTH, skin hyperpigmentation, and progressively enlarging corticotropic adenomas. These adenomas are often invasive[7,91]. Most cases occur five to ten years after surgery, but this interval may be as short as six months or as long as 24 years[88-89,92].

There is no proven medical treatment for corticotroph tumor progression after bilateral adrenalectomy[62]. Early repeat transsphenoidal surgery and/or radiotherapy should be conducted as soon as significant tumor growth occurs[93]. However, neurosurgical management of Nelson syndrome is challenging due to the aggressive and often invasive nature of these ACTH-producing adenomas. In five patient series published from 1982 to 2002, surgery was effective in improving or restoring vision and reducing the degree of hyperpigmentation[93-97]. However, the ACTH levels normalized in fewer than 50% of patients and additional radiation therapy was required in 20-30% patients to help control tumor growth[93-97].

Fractionated external beam radiotherapy or stereotactic radiosurgery has been used in patients with Nelson syndrome after bilateral adrenalectomy to complement or replace repeat transsphenoidal surgery[62,72,77,78,98]. Although remission rate was only 0-36%, tumor growth was controlled in 82-100% of cases[77,98]. One study investigated prophylactic radiation after bilateral adrenalectomy. Although prior radiation therapy reduced the risk and delayed the onset of Nelson's syndrome[99] further studies are required before preventive radiotherapy can be recommended[15,62].

Currently, there is no proven efficacious medical treatment for corticotroph tumor progression after bilateral adrenalectomy[62]. Dopamine agonists such, as cabergoline, have been used with variable success[100]. Multireceptor ligand somatostatin analogue, such as pasireotide, has shown favorable results *in vitro*[101,102]. Temozolomide, an alkylating chemotherapeutic agent, has been reported in two case reports as an effective option for the treatment of Nelson's syndrome[103].

Pituitary carcinomas occur in 0.1-0.2% of all pituitary adenomas[104]. Of all the reported cases, 42% occurred in the setting of ACTH-dependent adenomas. Approximately half of the patients with an ACTH-secreting pituitary carcinoma developed Nelson's syndrome throughout their follow-up[105]. Patients with Nelson's syndrome are also at risk of developing pituitary carcinoma[7,91].

Conclusion

The management of persistent/recurrent CD remains a challenge for the pituitary neurosurgeon. Repeat transsphenoidal surgery for selective adenomectomy is the treatment of choice, with exploration of the sella and medial walls of the cavernous sinuses for possible invasive tumor. In some instances, hemi- or total hypophysectomy may be indicated. When repeat surgery fails, other treatment options include SRS or SRT, medical treatment with ketoconazole and/or bilateral adrenalectomy. Given the complexity of this disorder and the wide spectrum of treatment options, patients with failed initial transsphenoidal surgery are best cared for by a multidisciplinary team comprising neurosurgeons specializing in pituitary lesions, Ear, Nose and Throat surgeons, pituitary endocrinologists, radio-oncologists, neuro-ophthalmologists, and general surgeons. Because of the relative challenges of altered anatomy and scarring associated with both persistent and recurrent CD, and the relative rarity of this disease, we and others recommend that patients be treated at specialized pituitary centers[8,14].

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