Update on the management of recurrent Cushing's disease

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After transsphenoidal surgery, Cushing's disease (CD) shows excellent long-term remission rates, but it may recur and pose a therapeutic challenge. Findings in recent published reports on the treatment of recurrent adrenocorticotrophic hormone (ACTH)-secreting tumors suggest that repeat resection, radiation-based therapies such as Gamma Knife surgery and proton-beam radiosurgery, pharmacotherapy, and bilateral adrenalectomy all have important roles in the treatment of recurrent CD. Each of these interventions has inherent risks and benefits that should be presented to the patient during counseling on retreatment options. Radiation-based therapies increasingly appear to have efficacies similar to those of repeat resection in achieving biochemical remission and tumor control. In addition, an expanding repertoire of medication-based therapies, several of which are currently being evaluated in clinical trials, has shown some promise as tertiary adjunctive therapies. Lastly, bilateral adrenalectomy may offer durable control of refractory recurrent CD. An increasing number of published studies with long-term patient outcomes highlight the evolving treatment patterns in the management of recurrent CD.

<http://thejns.org/doi/abs/10.3171/2014.11.FOCUS14703>

KEY WORDS Cushing's disease; adenoma; adrenocorticotrophic hormone; recurrent; radiation; surgery; radiosurgery; adrenalectomy

CUSHING's disease (CD), first described by Harvey Cushing in 1932, is an uncommon disorder in which a pituitary adenoma leads to overproduction of adrenocorticotrophic hormone (ACTH). This overproduction results in hypercortisolemia, causing symptoms such as hypertension, diabetes mellitus, cardiovascular disease, osteoporosis, thromboembolism, obesity, and depression.¹ Women are disproportionately affected by CD, although men who have the disease are typically younger and display more severe symptoms.³⁹ Prompt and accurate diagnosis of CD is critical because of the high morbidity and mortality rates associated with its natural history; mortality rates of CD are estimated to be 50% at 5 years in untreated individuals.⁵⁴

Once CD is diagnosed, endonasal transsphenoidal resection provides an excellent first-line intervention that removes ACTH-producing cells while preserving native pituitary function. Remission rates of CD have been extensively studied and range from 69% to 93%, with a median or mean time to recurrence ranging from 20 to 84 months.^{1,57} Importantly, initial resection fails to achieve remission in

7%–31% of patients, and the disease will recur in 3%–22% of patients after > 3 years.^{1–3,10,11,16,21,22,24,25,37,43,44,46,47,50,51,66} a rate that can approach 20%–25% at 10 years postoperatively.⁵⁷ These observations highlight the importance of long-term surveillance for recurrence of CD. The diagnosis of recurrence involves use of similar biochemical testing as used at the time of the original diagnosis, including measurement of urinary free cortisol, of serum cortisol after a dexamethasone-suppression test, or of late-night salivary cortisol. The dexamethasone-suppressed corticotropin-releasing hormone stimulation test may be used for equivocal cases of CD.³⁰ Because cortisol levels often fluctuate, and results sometimes vary across multiple measurements even in the same patient, repeat testing is recommended.^{30,40,57} Dynamic MRI of the pituitary gland may be used to identify recurrent ACTH-secreting pituitary adenomas. Bilateral inferior petrosal sinus sampling is typically not used to evaluate recurrent CD because the venous drainage of the pituitary gland lateralizes unpredictably after initial surgery.

There is little consensus on predictors of CD recur-

ABBREVIATIONS ACTH = adrenocorticotrophic hormone; CD = Cushing's disease; GKS = Gamma Knife surgery.

SUBMITTED October 7, 2014. **ACCEPTED** November 11, 2014.

INCLUDE WHEN CITING DOI: 10.3171/2014.11.FOCUS14703.

DISCLOSURE The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

rence; tumor size, location, and surgeon experience have been posited as potential predictors, but have remained unproven in multiple studies. Here we review management strategies for recurrent CD, including repeat transsphenoidal surgery, which is often the first-line treatment for recurrence; radiation with a particular emphasis on radiosurgery; and medical management with a particular emphasis on cabergoline, mifepristone, and the novel multireceptor ligand and somatostatin analog pasireotide (SOM230), which has produced encouraging results in a recently completed Phase III clinical trial.

Methods

Literature Searches

To identify recent advances in the diagnosis and management of recurrent CD, we performed a comprehensive search of the published literature on PubMed. The following search terms were used: “Cushing,” “Cushing’s,” “recurrent,” “remission,” “persistent,” “radiosurgery,” “MRI,” “mifepristone,” “ketoconazole,” “adrenalectomy,” “pasireotide,” and “Nelson’s syndrome.” All reports identified in this search and published from the time of the senior author’s (M.K.A.’s) last publication in 2008 on recurrent CD until 2014 were included for review, including abstracts and full-length publications. All publications on repeat resection and radiation-based treatments described cases of recurrent CD rather than cases of persistent disease. Recurrent CD was defined as the presence of hypercortisolemia immediately after the primary treatment. However, the primary treatment for these patients upon initial diagnosis of CD was not uniform: some patients received primary surgery and some received primary radiation-based strategies after a biochemical diagnosis of CD.

Results and Discussion

Repeat Transsphenoidal Surgery

We identified 4 studies (Table 1) published between 2008 and 2014 that had available outcomes data for patients who had recurrent CD; the studies’ cohort sizes ranged from 8 to 40 patients.^{22,30,38,61} In the largest series, recurrent CD was diagnosed as elevated 24-hour urinary free cortisol with symptoms consistent with the disease in 40 patients; for 36 of these, patient outcomes data were available.³⁸ The patients were offered repeat surgery only when the recurrent tumor was evident on MRI scans or when a centralized ACTH gradient was identified on inferior petrosal sinus sampling and with high-dose dexamethasone suppression. The median time to recurrence after the initial transsphenoidal surgery was 3 years. After repeat resection, they defined tumor remission as normal levels of 24-hour urinary free cortisol postoperatively or as a need for continued glucocorticoid replacement. In total, 24 patients (67%) underwent selective adenectomy, and of these, 1 (2.8%) underwent hemihypophysectomy, 6 (17%) underwent subtotal hypophysectomy, and 5 (14%) underwent total hypophysectomy. In 22 patients (61%) the disease was in remission; of note, when compared with the original cohort of patients who underwent first-time resection (and in whom remission was 85%), the failure rates were 39% for repeat surgery and 15% for primary surgery.

This difference highlighted that the efficacy of repeat surgery for treating CD does not match that of primary surgery. The 14 patients who had persistent CD were treated with radiosurgery, ketoconazole, and bilateral adrenalectomy. Only the presence of a recurring tumor larger than 1 cm (macroadenoma) had a statistically significant and inverse association with remission: remission failed in all 3 patients who showed symptoms of macroadenoma recurrence.³⁸

In another large series of 35 patients,²² remission was observed in only 13 patients (37%) after repeat transsphenoidal surgery, and tumors recurred on average 73 months after the primary operation. Nineteen (86%) of 22 unsuccessfully treated patients were further treated with bilateral adrenalectomy (36%), with radiotherapy (41%), or with a combination of those 2 modalities (9%). The authors noted that similar to the findings by Patil et al.,³⁷ macroadenomas were significantly more likely to be associated with recurrence than microadenomas: 16 of 39 macroadenomas (41%) versus 73 of 330 microadenomas (22%) recurred. Similar to what has been noted in earlier studies with extended follow-up,^{1,15,29,35,37} both early (< 5 years) and late (> 5 years) recurrences were observed.²²

Finally, in 2 smaller series of 8 patients⁶¹ and 10 patients⁵ with recurrent CD, mean times to recurrence were 74 months and 35 months, respectively. In the 10-patient series, remission rates after repeat surgery were 50% for macroadenomas and 83% for microadenomas.⁵

Across the studies included here, complications were incompletely reported, but when noted they included diabetes insipidus, CSF leak, infection, cavernous sinus hemorrhage, carotid artery injury, and need for partial or total hormone replacement for panhypopituitarism. Probably because of the relatively small numbers of recorded and reported recurrences of CD, the identification of factors significantly associated with recurrence remained elusive. The 2 larger series reported higher rates of recurrence in cases of macroadenomas than in cases of microadenomas,^{38,22} but recurrence did not appear to be associated with age, sex, MRI-based tumor identification, or extent of resection. Furthermore, Wagenmakers et al. found no statistically significant differences in remission or recurrence for patients undergoing repeat resection, including MRI-based tumor identification, age, sex, and time interval between primary and repeat resections.⁶¹

Radiation-Based Therapies for Recurrent CD

An increasing number of radiation-based therapies are now used in the treatment of pituitary adenomas, including fractionated radiotherapy and stereotactic radiotherapies such as Gamma Knife surgery (GKS), CyberKnife, and proton-beam therapy. Accordingly, the recent literature reflects a greater focus on these treatment strategies as a means for achieving tumor control and disease remission in recurrent CD.^{5,19,32,58} Such strategies are important for adjuvant or salvage therapy for patients in whom repeat resection was unsuccessful or who seek noninvasive treatments. They are also relevant for treating tumors that cannot be repeatedly resected because of cavernous sinus invasion or equivocal appearance on MRI scans.

Gamma Knife surgery has largely replaced conven-

TABLE 1. Studies published between 2008 and 2014 with available data on outcomes after repeat transsphenoidal surgery for recurrent CD

Authors & Year	No. of Pts w/ Tumor Recurrence Undergoing Repeat Op	Recurrence Criteria	Remission After Repeat Op (%)	Length of FU (mos)	Remission Criteria
Patil et al., 2008 ³⁸	36	Normal 24-hr UFC for at least 3 mos before subsequent recurrence	61	36	Normal postop 24-hr UFC or continued need for glucocorticoid replacement
Hofmann et al., 2008	35	Abnormal DST results	37	—	Normal DST results
Wagenmakers et al., 2009	8	Development of clinical symptoms of hypercortisolism & inadequate suppression of plasma cortisol level after o/n 1-mg DST	88	31	Disappearance of symptoms of hypercorti- solism w/ basal plasma cortisol level ≤50 nmol/L 24–48 hrs after glucocorticoid withdrawal &/or suppression of plasma cortisol level ≤50 nmol/L after o/n 1-mg DST w/in the first 3 mos after transsphenoidal op
Liubinas et al., 2011	14	Abnormal serum &/or UFC levels	79	—	Normalization of serum &/or UFC levels

DST = dexamethasone suppression test; FU = follow-up; o/n = overnight; Pts = patients; UFC = urinary free cortisol; — = information unavailable.

tional fractionated radiation therapy after the latter failed to control initial or recurrent CD. Because radiosurgery has been shown to achieve better tumor control and biochemical remission and to have an improved safety profile, many authors have advocated for its use to treat recurrent CD.^{1,27} Used as far back as in the 1950s for pituitary tumors, GKS has proven effective in the treatment of CD since the 1970s to 1980s.¹⁴ Since 2000, the rates of remission after GKS for recurrent or persistent CD have ranged from 17% to 54%.² Studies published since 2008 suggest a trend toward improved rates of remission, with longer follow-up periods and greater patient numbers than previously reported in the literature.

In the largest series available, Sheehan et al. present their experience with 96 patients.⁴⁹ The median follow-up period was 4 years, and overall remission was 70% with a median time to remission of 16.6 months. The mean target volume was 1.8 cm³ with a mean margin dose of 22 Gy and a mean maximum dose of 47.2 Gy. Although the results were somewhat obscured by the previous use of radiotherapy in 6 patients (6%) and by an unclear primary treatment strategy of transsphenoidal surgery, open craniotomy, or initial radiosurgery, the authors reported similarly high rates of radiological response, with 70% of the tumors exhibiting a decreased size, 28% a stable size, and only 2% an increased size. Notably, patients receiving ketoconazole during GKS treatment had a significantly longer time to remission than those who did not receive the drug (21.8 vs 12.6 months, $p < 0.012$). Recurrence after radiosurgically induced remission was observed in 15.6% of the patients, partial loss of pituitary function in 36%, and cranial neuropathies in 5.2%.

In another study examining patients with CD, prolactinomas, or acromegaly,²⁶ ACTH-secreting adenomas showed the most favorable response to GKS, with 35% of 30 patients having normalization of cortisol levels. Gamma Knife surgery also normalized prolactin levels in 17.4% of 27 patients who had prolactinoma and growth hormone levels in 4.8% of 67 patients who had acromegaly. The study had a mean follow-up period of ≥ 3 years, and tumor control was 100% across all 3 groups.²⁶ In an-

other large study of 49 patients, GKS treatment achieved a 66% remission rate by 5 years postradiosurgery, with one-half of the treated patients exhibiting remission within 3–4 years.³² A comprehensive summary of recent radiosurgery studies, including those with smaller case series, is shown in Table 2.

The most recent study of GKS treatment for CD and Nelson's syndrome included 26 patients who were followed up for a mean length of 99 months.³³ Seventeen patients underwent primary resection, and 9 underwent prior radiosurgery. Of note, all patients in this series were given medication (ketoconazole combined first with metyrapone and then with cabergoline as needed) before and after radiosurgery until ACTH levels normalized. Similar to the observations by Sheehan et al.,⁴⁹ the results for patients who had CD were encouraging: in 81% of the patients, cortisol levels normalized at a median time of 30 months, and none of the patients had CD recurrence. Furthermore, radiographic follow-up between 2 and 5 years posttreatment revealed tumors that remained stable (8%), had decreased in size (62%), or had resolved completely (31%) without any evidence of regrowth. Patients who showed Nelson's syndrome had lower rates of ACTH normalization (2 [14.3%] of 14 patients), and radiographic follow-up over the same 2- to 5-year period indicated regrowth of 1 tumor (9%), an unchanged size for 3 tumors (27%), a decreased size for 5 tumors (45%), and disappearance of 2 tumors (18%). Another small series on the outcomes of radiosurgical treatment for Nelson's syndrome followed 10 patients over a mean period of 7 years and also noted abrogated tumor growth in all patients and normalization of ACTH levels in 1 patient (10%).⁶⁰ It has been suggested that radiosurgery before bilateral adrenalectomy may efficiently reduce the onset of Nelson's syndrome.³⁴ In a study by Hornyak and colleagues, including Dr. Nelson after whom the syndrome is named, the authors recommended resection as the primary therapy, reoperation for recurrent tumors, radiation for unresectable disease, and adrenalectomy as a last resort.²³

Comparing the results of studies that have used different radiation modalities is difficult because of variations in the

TABLE 2. Studies published between 2008 and 2014 with available data on outcomes after radiosurgery for CD*

Authors & Year	No. of Pts w/ Tumor Recurrence Undergoing RT	Recurrence Criteria	Treatment Modality	Remission After RT (%)	Length of FU (mos)	Remission Criteria
Petit et al., 2008	33†	—	Proton-beam SRS	52	14	Sustained (3 mos) normalization of UFC after completion of washout period during which medical therapy was withdrawn
Castinetti et al., 2009	18	Abnormal DST levels	GKS	50	28	Normalized 24-hr UFC w/ suppressible plasma cortisol level (<50 nmol/L) after low-dose DST
Swords et al., 2009	4	—	GKS	50	27	Mean serum cortisol levels obtained from 5 samples taken from 9 AM to 7 PM
Castro et al., 2010	9	—	GKS	66	—	Normal serum ACTH level
Losa et al., 2010	49	—	GKS	53	—	Normal 24-hr UFC
Wein et al., 2012	17	—	SRS	59	23	Normal UFC levels w/o cortisol-lowering medications
Sheehan et al., 2013	96	Abnormal serum cortisol, ACTH & 24-hr UFC	GKS	70	12.6‡ & 21.8	Normal 24-hr UFC & normal morning serum cortisol levels
Lee et al., 2014	64	—	GKS (whole sellar)	71	10	Normal age- & sex-appropriate UFC (<45 mg/24 hrs) & off medication for 2 mos
Marek et al., 2014	26	—	GKS	81	78	Normal 24-hr UFC, morning serum cortisol, & morning ACTH
Verma et al., 2014	5	—	RT	20	55	—
Wattson et al., 2014	74	—	Proton-beam SRS	54 at 36 mos; 67 at 60 mos	47	Biochemical complete response defined as >3 mos of normal lab values w/o medical treatment
Wilson et al., 2014	41	Elevated morning serum cortisol level >140 nmol/L or elevated 24-hr UFC >276 nmol/24 hrs	LINAC	25	—	Normal 24-hr UFC & normal morning serum cortisol levels

LINAC = linear accelerator; NS = Nelson's syndrome; RT = radiotherapy.

* In all studies, most patients underwent initial resection; in some of the studies, tumors were initially treated with radiosurgery or repeat treatments were performed for persistent disease after an initial treatment.

† The patients showed persistent CD after the primary surgery.

‡ Time to remission was 12.6 months in patients off ketoconazole and 21.8 months in patients on ketoconazole.

criteria for remission and in the comanagement of recurrence with medical therapy. Nonetheless, insight gleaned from the past 2 decades of published studies suggests that multiple radiation modalities are similarly successful in achieving tumor control and biochemical remission of CD. Remission rates of 89%–100% have been reported for patients treated with fractionated radiotherapy or radiosurgery,^{31,53} although radiosurgery appears to provide earlier remission than fractionated radiotherapy-based therapy.^{13,17,34,48} While complications arising from radiation-based modalities are inevitable, studies have shown that radiosurgery can be used safely: reduction of the margin radiation dose and avoidance of tumors with suprasellar extension may help prevent hypopituitarism,^{28,65} which can reach 32% at 5 years postradiosurgery.⁶⁵ Neurocognitive decline, stroke, and secondary neoplasms appear to be rare complications, and are more associated with fractionated radiotherapy than with radiosurgery.^{6,7,48,56}

Proton-beam radiosurgery is a promising and relatively

new modality in the treatment of pituitary adenomas including CD. It enables better dose distribution than GKS, and early findings suggested that it decreases rates of cranial neuropathy and tumor recurrence.^{41,52} The most recent and largest examination of proton-beam radiosurgery for CD treatment showed a biochemical tumor remission rate of 67% at the 5-year follow-up in 74 patients, with a median time of 32 months for demonstrated remission. Most intriguing was the observation that ACTH-secreting adenomas showed a significantly faster response to therapy in terms of time to remission than other functional adenoma subtypes. Furthermore, tumor control rates were excellent (98%), although this included all subtypes, and data specific for patients who had CD were not reported. Rates of posttreatment hypopituitarism after proton-beam radiosurgery were higher (57%) than after GKS treatment, but the limited number of studies on proton-beam radiosurgery makes accurate comparisons difficult.

Pharmacotherapy

For patients unresponsive to or intolerant of repeat resection or radiation-based treatments, 3 classes of medications are available as adjuvant therapies. Drugs such as ketoconazole, metyrapone, and aminoglutethimide represent a group of antisteroidogenesis agents that may help prevent hypercortisolemia, blocking cytochrome p450 enzymes (in the cases of ketoconazole and etomidate), 11 β -hydroxylase (metyrapone), and cholesterol side cleavage (aminoglutethimide).¹ Second, agents that indirectly block ACTH production have some utility, including pasireotide and cabergoline. Third, mifepristone provides efficacious treatment of CD because it blocks the glucocorticoid receptor directly. It also showed a significant benefit in glucose control and blood pressure in SEISMIC (Study of the Efficacy and Safety of Mifepristone in the Treatment of Endogenous Cushing's Syndrome), a multicenter study of 50 patients with Cushing's syndrome in whom multimodality treatments had failed.¹⁸ At present, treatment with medications is reserved for patients in whom surgery fails to control the tumor either at diagnosis or at recurrence or for patients who are awaiting remission after radiosurgery. The relative efficacy of pharmacotherapy for achieving tumor control and biochemical remission remains unclear.

Of note, pasireotide, cabergoline, and mifepristone have been studied in detail and show promising results for the management of recurrent CD in several studies outlined in the following. In 2012, a group of investigators published the results of a 12-month, Phase III trial of pasireotide (SOM230),¹² a somatostatin-receptor inhibitor with activity against receptor Subtypes 1–3 and particularly against Subtype 5. Pasireotide has demonstrated efficacy in lowering cortisol levels in patients who have CD. Patients included those in whom the disease was persistent after an initial round of therapy, and those who had recurrent tumors or who had a newly diagnosed disease, but were not considered candidates for surgery. The criteria for a diagnosis of CD were a mean 24-hour urinary free cortisol level 1.5 times the upper limit of normal levels, a morning corticotropin concentration of 5 ng/L, and a confirmed tumor in the pituitary gland. The patients were randomized to receive either 600 μ g or 900 μ g pasireotide twice daily. Fifty of 103 patients (48%) showed reductions in urinary free cortisol levels 6 months after these treatments such that their levels were normalized or at least 50% decreased from the pretreatment baseline.¹² The effect was more pronounced in patients who had lower baseline urinary free cortisol levels, but a beneficial effect was also noted in patients who had higher baseline cortisol levels. Importantly, signs and symptoms of CD were also improved, including weight, blood pressure, LDL (low-density lipoprotein) cholesterol levels, and quality of life scores. Gastrointestinal upset and hyperglycemic events were the most common adverse effects, and only 6% of the patients discontinued the drug because of these effects.¹² On the basis of these results, the FDA approved pasireotide for the treatment of patients who have CD and who cannot be surgically treated.

Cabergoline is used in the treatment of hyperprolactinemia; it is a D₂ receptor agonist that has recently been studied for use in the treatment of CD. In a study of the

short and long-term effectiveness of cabergoline in the treatment of CD,²⁰ 30 patients were followed up, including 3 patients treated with cabergoline primarily. The other 27 patients had unspecified recurrent or persistent CD. A complete response (defined as restoration of normal urinary free cortisol) was noted in 11 of the patients (37%) and a partial response (defined as urinary free cortisol < 125% of the upper limit of normal) in 4 of the patients (13%), together representing 50% of the 30-patient cohort. Nine of the 11 full responders (82%) maintained normal cortisol levels after a mean treatment duration of 37 months and exhibited regression of clinical signs and symptoms of the disease. Interestingly, the cabergoline treatment failed in 2 patients (7%) after 2 years of complete normalization of urinary free cortisol. Initial tumor size, ACTH levels, degree of hypercortisolemia, and timing of cabergoline initiation before or after surgery did not correlate with treatment response.²⁰

Importantly, this study represented patients from a variety of treatment approaches and disease scenarios (primary medical treatment and persistent or recurrent disease following surgical treatment), and it may be difficult to draw conclusions from this relatively small and mixed cohort. The authors' results mirror those from the study of Pivonello et al.: in that study, 8 (40%) of 20 patients who had recurrent or persistent CD after initial surgery exhibited normal urinary free cortisol after cabergoline treatment, 4 patients (20%) had tumor shrinkage, and most of the patients showed improvements in hypertension and glucose intolerance after the treatment.⁴²

The SEISMIC study¹⁸ examined the efficacy of mifepristone, a progesterone-receptor antagonist with known glucocorticoid receptor antagonist activity, in treating 43 patients who had CD. In this 24-week, open-label multicenter study of daily oral administration of mifepristone, blood glucose levels and hypertension were assessed as primary end points. Twenty-six (60%) of the patients showed at least a 25% drop in their area under the curve for glucose during 2-hour oral glucose tolerance testing at Week 24 of treatment, and had associated secondary benefits in decreased glycated hemoglobin (HgbA1c) and fasting plasma glucose. Additionally, 16 (38%) of the patients showed a drop in diastolic blood pressure of at least 5 mmHg. Further improvements were seen in weight loss, waist circumference, insulin resistance, depression, cognition, and quality of life. Among the 17 patients who had CD and visible tumors on MRI scans after initial surgery, tumor control was observed in 16 patients (94%) at 10 weeks and 24 weeks postenrollment.¹⁸

The novel 11 β -hydroxylase inhibitor LCI699 is also receiving attention for its effect on urinary cortisol levels. In a recent study, patients whose CD was diagnosed biochemically (as urinary free cortisol levels > 1.5 the upper limit of normal) or those whose CD was histologically confirmed after resection received LCI699 for 10 weeks. All of the 12 patients enrolled exhibited reduction in their urinary free cortisol levels below the upper limit of normal or showed at least a 50% decrease from their baseline levels.⁴ The specific efficacy of this agent for recurrent CD remains unclear.

Bilateral Adrenalectomy

As a final resort, bilateral adrenalectomy, typically performed laparoscopically, may be used as a definitive treatment of hypercortisolemia in patients who have recurrent CD and in whom surgical, radiation, and pharmacotherapy-based strategies have failed or who are intolerant of the side effects of these treatment modalities. Despite the need for long-term mineralocorticoid and glucocorticoid replacement, recent studies suggest bilateral adrenalectomy is a treatment that provides durable long-term outcomes. However, its safety is a matter of debate: results from 20 studies of 505 patients treated for CD showed that during a median follow-up period of 49 months, bilateral adrenalectomy had a median mortality rate of 9% due to causes including stroke, myocardial infarction, and sepsis.⁴⁵ In this systematic review, CD and Cushing's syndrome were not disaggregated for analyses of biochemical outcome, but the overall rates of resolution of hypercortisolemia in the 7 included studies were 100% in 2 studies, and 3%, 21%, 24%, 27%, and 34% in the others.

In another study of long-term outcomes of bilateral adrenalectomy, 36 patients were followed up for a median period of 11 years.³⁶ In total, 23 patients (63%) experienced ≥ 1 adrenal crises, and 9 patients (24%) developed Nelson's syndrome. Notably, the mortality rate was also high (that is, 14%). All of the 36 patients showed tumor remission without relapse. Importantly, significant reductions were seen in blood pressure, diabetes mellitus, physical stigmata, and muscular weakness. The relatively high mortality rates associated with bilateral adrenalectomy underscore that the intervention should be undertaken as a last resort. Patients should be properly counseled on the risks and benefits of this procedure, especially if treatment strategies using radiation-based and pharmacotherapies are available and tolerated by the patients.

Conclusions

Given the high morbidity and mortality rates associated with CD, prompt diagnosis and treatment are paramount, and this applies to both the initial diagnosis and the identification of recurrent CD. The treatment of recurrent CD remains challenging, with recent evidence suggesting a wide variety of comparably effective strategies for managing recurrent tumors. When possible, repeat transsphenoidal resection should be the first step in retreatment, but patients should be counseled that the efficacy of the second operation in achieving biochemical remission is lower than that of the first operation. Radiation-based strategies may adequately match repeat surgery in achieving disease control and are probably more effective for tumors in the cavernous sinuses. Finally, medical therapy offers a useful adjunctive treatment and in many instances improves the rates of remission when combined with other therapies.

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