Utility of the Immediate Postoperative Cortisol Concentrations in Patients With Cushing’s Disease

BACKGROUND: Several investigators have recommended serial measurements of serum cortisol in the days following pituitary surgery to identify patients at risk of recurrence.

OBJECTIVE: We systematically reviewed the literature on this topic and analyzed the usefulness of this test in our own patient population.

METHODS: We identified studies publishing data regarding recurrence rates after transsphenoidal surgery for Cushing’s disease, focusing on studies with data regarding patients with early postoperative cortisol levels. We determined a cumulative relative risk of having a subnormal vs normal cortisol level postoperatively using a fixed-effects meta-analysis model. Additionally, we analyzed our own patients with Cushing’s disease undergoing transsphenoidal surgery and performed Kaplan-Meier analysis of recurrence-free survival for patients with undetectable, subnormal but detectable, and normal immediate 8 AM serum cortisol levels.

RESULTS: Fourteen studies met inclusion criteria. The length of follow-up varied between 32 and 115 months. The cumulative rate of recurrence in the group of patients with subnormal cortisol levels was 9% (95% confidence interval: 6%-12%). The cumulative rate of recurrence in the group with normal cortisol levels was 24% (95% confidence interval: 17%-31%). We analyzed 73 of our own patients and found similar recurrence rates in patients with subnormal vs normal early postoperative cortisol levels (4% vs 22%, χ² test, \( P < .05 \)).

CONCLUSION: Although a subnormal early postoperative cortisol level is predictive of improved outcome after transsphenoidal surgery for Cushing’s disease, it is not analogous with cure, nor is a normal level completely predictive of future failure.

KEY WORDS: Adenoma, Cortisol, Cushing’s disease, Pituitary, Recurrence

T he determination of whether patients with Cushing’s disease have been rendered disease free and are likely to remain in remission after pituitary surgery remains one of the most difficult challenges facing clinicians treating Cushing’s disease. The hypercortisolism associated with Cushing’s disease results in profound suppression of the normal or nontumoral corticotrophs of the anterior pituitary gland.¹⁻⁴ When an adrenocorticotropic hormone (ACTH)–producing pituitary tumor is completely removed, ACTH levels decrease and cortisol production rates decrease to extremely low levels, leading to hypocortisolism.¹ The hypocortisolism, also referred to as central adrenocortical insufficiency, typically resolves in 10 to 18 months as the normal corticotrophs of the anterior pituitary recover from the prolonged period of glucocorticoid-induced suppression.¹ After recovery, and in the absence of tumoral ACTH production, cortisol levels typically exhibit a normal diurnal variation, are suppressed by low doses of dexamethasone, and increase as a consequence of insulin-induced hypoglycemia. This expected physiology has led to an abundance of studies and subsequent reports detailing recommended approaches to the evaluation of patients with Cushing’s disease after pituitary surgery.¹⁻⁵⁻⁹

Although most physicians agree that complete restoration of normal physiology of the hypothalamic-pituitary-adrenal axis is consistent with a remission or cure of Cushing’s disease, there is still no consensus as to the most appropriate
diagnostic approach to evaluate these patients in the postoperative period. Several investigators have recommended serial measurements of serum cortisol in the days after pituitary surgery to identify patients with persistent Cushing’s disease. Some have also suggested early repeat surgery based on a detectable serum cortisol level early in the postoperative period, interpreting this finding as evidence of persistent disease. There are, however, several clinical scenarios that complicate the interpretation of diagnostic tests in the postoperative period. In some patients, long-standing ACTH excess results in marked adrenal hyperplasia and somewhat autonomous cortisol hypersecretion by the adrenal glands. Cortisol levels may therefore not decrease immediately after successful resection of an ACTH-producing pituitary tumor. Alternatively, near-total resection of an ACTH-producing pituitary tumor may result in a marked decrease in ACTH hypersecretion and, in the setting of suppression of normal corticotrophs, a temporary period of adrenocortical insufficiency. The adrenocortical insufficiency ultimately resolves as tumoral ACTH secretion gradually increases as a consequence of growth and progression of the residual tumor. These patients typically experience a temporary phase of “normal” cortisol levels followed by the development of recurrent hypercortisolism. Notably, this phase of normocortisolemia is often characterized by the lack of a normal diurnal variation in cortisol secretion. Failure of suppression of cortisol levels in response to dexamethasone may not become apparent until the increasing tumor burden becomes significant.

We systematically reviewed the literature on this topic, as well as our own experience with these tests. In doing so, we raise the idea that the assessment of immediate postoperative cortisol levels is helpful but not entirely reliable in making the determination as to which patients have been rendered disease free and which patients are probably going to experience a recurrence. Inappropriate use and misinterpretation of this simple test may lead to unnecessary repeat surgery or a false sense of success in patients who, in fact, have persistent disease.

MATERIALS AND METHODS

Meta-analysis

Article Selection

Articles were identified via a PubMed search using the key words “cortisol,” “Cushing’s disease” “Cushing’s syndrome” “pituitary,” “surgery,” “transsphenoidal,” “recurrence,” “remission,” and “hypercortisolism,” alone and in combination. This search was performed by physicians familiar with pituitary disorders and transsphenoidal surgery on numerous occasions with the most recent search date being June 20, 2008. We then searched all references in these articles to ensure that we included as many articles as possible.

Articles were then screened using the following inclusion criteria: (1) The articles must state that patients had a preoperative endocrinologic evaluation demonstrating the presence of Cushing’s disease. (2) Data for patients with Cushing’s disease must be presented separately from those of patients with other causes of Cushing’s syndrome (ie, adrenal and ectopic sources). (3) All patients must have undergone technically successful transsphenoidal surgery for their disease. Adenomectomy, hemihy-
cases in which postoperative hypocortisolemia occurred in cases that ultimately were proved to result from causes other than pituitary adenoma such as ectopic corticotropin-releasing hormone, pseudo-Cushing’s disease, and ACTH cell hyperplasia. Thus, patients whose final pathologic analysis did not reveal an ACTH-secreting adenoma were excluded from further analysis.

**Data Analysis**

All patients with a preoperative diagnosis of Cushing’s disease undergoing transsphenoidal surgery at our institution are placed on dexamethasone perioperatively. The doses that we use would not be expected to be suppressive in patients with ACTH-secreting pituitary tumors, so there would be little effect on cortisol levels. Dexamethasone was chosen instead of hydrocortisone because hydrocortisone is cortisol and would be measured in the assay, whereas dexamethasone is not detected as cortisol by current cortisol assays. At 8 AM on postoperative day 1, all patients with Cushing’s disease had cortisol levels determined. The normal levels for 8:00 AM serum cortisol in our laboratory during the study period were 8 to 25 µg/dL. Generally, this measurement is taken approximately 24 hours after the last steroid dose. Those with supranormal levels had an additional 8 AM cortisol test the following day to determine whether the cortisol level would trend downward. If it remained supranormal on this second test, the patient was considered to be not in remission and was excluded from further analysis. All patients with normal or subnormal levels were considered to be in remission and were included in our analysis. Postoperative magnetic resonance imaging was performed on all patients 3 to 6 months postoperatively and as warranted by the clinical situation thereafter. Given evidence suggesting that postoperative ACTH levels are poor predictors of recurrence and disease remission, we do not routinely obtain these levels in the immediate postoperative period.10

Patients were considered to have a recurrence if at some point after normalization of their postoperative cortisol level, new hypercortisolemia not caused by glucocorticoid therapy developed or by other known etiologies other than Cushing’s disease. This could be evidenced by increased 8 AM serum cortisol levels off of hydrocortisone or other confounding therapies or increased 24-hour urine free cortisol levels. Recurrence of Cushing’s disease in these patients was confirmed with a dexamethasone suppression test.

**Statistical Analysis**

Continuous variables were compared using analysis of variance after statistical tests confirmed that the data behaved normally. Between-group comparisons of binary data were performed using Pearson’s χ² test. Kaplan-Meier analysis was used to compare recurrence-free survival among patients with undetectable, subnormal detectable, and normal immediate 8:00 AM cortisol levels. For all tests, the P value was considered significant at the 5% (ie, P < .05) level. All continuous data are presented as mean ± standard error.

**RESULTS**

**Results of the Literature Search**

A total of 1127 articles were screened for inclusion criteria. Eighteen articles were identified that presented recurrence data for adult patients undergoing transsphenoidal surgery for Cushing’s disease with early postoperative 8 AM cortisol measured and reported. Four of these articles were excluded. Two were excluded because data presentation did not permit segregating patients with normal postoperative cortisol levels from those with subnormal levels. Two articles were excluded because the normal ranges of cortisol at the relevant institution were not presented, making analysis impossible. In the remaining studies, a total of 13 patients were excluded for reasons described in the Materials and Methods section.

In the remaining 14 included studies,2-10,13-17 there were 786 patients reported to have subnormal cortisol levels and 319 patients had postoperative cortisol levels in the normal range. Ten studies included data for patients with both normal and supranormal values, and these were included in the meta-analysis. Mean or median range of follow-up in these studies ranged from 2.0 to 9.6 years (mean range 32-115 months, median range 24-115 months). These data are summarized in Table 1.

**Results of the Meta-analysis**

The cumulative rate of recurrence in the group of patients with subnormal cortisol levels was 9% (95% confidence interval [CI], 6%-12%). The cumulative rate of recurrence in the group with normal cortisol levels was 24% (95% confidence interval: 17%-31%). The cumulative relative risk of recurrence for patients with subnormal cortisol levels vs those with normal levels was 0.35 (95% CI, 0.25%-0.47%, P < .001). Forest plots depicting the 95% CIs for the relative risk of recurrence in patients with subnormal cortisol levels for each of the 10 studies providing data for both groups are shown in Figure 1.

**Relationship Between Postoperative Cortisol Levels and Rates of Recurrence at Our Institution**

A total of 88 patients underwent transsphenoidal surgery for histopathologically proven Cushing’s disease between 2001 and 2008. The cortisol level remained persistently supranormal in 15 patients, and these patients were excluded from our analysis. The demographic data for patients in our analysis are compared in Table 2. The median length of follow-up for all patients in this study was 58 months (range 9-100 months). There was no significant difference in age, tumor size, rate of cavernous sinus invasion, rate of suprassellar extension, and length of follow-up among patients with undetectable, subnormal but detectable, and normal immediate postoperative cortisol levels.

Our rates of recurrence for patients with normal and subnormal immediate postoperative cortisol levels very closely mirrored those found in the meta-analysis (Table 1). Patients with subnormal cortisol levels had a lower rate of recurrence than those with normal levels (4% vs 22%, χ² test, P < .05). The 2 patients with subnormal levels who experienced recurrence had postoperative day 1, 8 AM serum cortisol levels of 2 µg/dL and 7 µg/dL.

Twenty-three patients in our analysis had immediate postoperative 8 AM cortisol levels below the limits of detection (<2 by the assay used at our institution). There were no known episodes of recurrence in any of these patients, and this group had a marginal improvement in recurrence rates over patients with subnormal but detectable levels (0% vs 6% vs 22%, χ² test, P < .05). Kaplan-Meier analysis confirmed that there was a difference in recurrence-free survival between these groups (P < .05) (Figure 2).
Numerous investigators have discussed their findings relating the value of immediate postoperative cortisol determinations in patients with Cushing’s disease. Many early reports depicted a low or undetectable early postoperative cortisol level as analogous with “cure.” For example, Trainer et al reported that hypercortisolism did not recur in any patient with Cushing’s disease who demonstrated an undetectable postoperative 9 AM cortisol level after withdrawal of hydrocortisone. Their overall cure rate based on this criterion was 42%. This result is in contrast to higher cure rates reported by other centers and suggests that their criterion may have been too strict. McCance et al demonstrated that there is a reasonable chance of cure in patients who have subnormal 8 AM cortisol levels, especially when the cortisol levels suppress with low-dose dexamethasone. Pereira et al reported long-term remission in 86% of those with cortisol levels less than 50 nmol/L 2 weeks after surgery.

Our meta-analysis suggests that Cushing’s disease patients with subnormal 8 AM cortisol levels measured within 2 weeks after transsphenoidal surgery clearly have reduced risk of long-term recurrence compared with those with postoperative cortisol levels in the normal range. Additionally, we performed a prospective analysis of our own patient population and found nearly identical results, although the timing of testing and length of follow-up differed among these studies and the current meta-analysis. Despite this fact, the recurrence rates in patients with subnormal immediate postoperative cortisol levels is not 0%, and as many as 12% of patients with subnormal values are at risk of recurrence within 2 to 8 years of surgery. Further, analyzing the 95% CIs at their extremes reveals that the absolute difference between the rates of recurrence between these groups could be as little as 5%. Thus, while somewhat reassuring, a subnormal postoperative cortisol level does not guarantee long-term remission and an “inappropriately normal” cortisol level after surgery, although associated with a higher risk of recurrence, does not always imply active persistent disease. Those with high levels are considered to have persistent disease and are treated as such.
Although our data suggest that undetectable cortisol levels might be more predictive of cure, this result is obtained in a minority of patients, and it is unclear how knowing this fact changes the plan of care for these patients. However, there is not enough cumulative experience published on this to confirm this finding (Figure 3). These patients represent a minority of patients undergoing surgery for Cushing’s disease, and yet most patients without undetectable levels do not go on to recurrence. Thus, although a better marker of cure, the question of what to do with everyone else with detectable cortisol levels is probably more important.

We fully understand the interests of physicians and patients alike when it comes to making a rapid and early determination of whether a patient with Cushing’s disease has been rendered disease free as a result of surgery. We firmly believe, however, that the most appropriate course of action is one of careful and deliberate evaluation of these complex patients who are experiencing wide variations in postoperative pathophysiology and cortisol secretion. In fact, when we combined all studies available to us that explicitly published these data, we found the recurrence rate in patients with biochemical profiles claimed by many to imply “cure” to be approximately 6% to 12% in this patient population (Table 1). Further, patients with normal cortisol levels are not destined to recur because between 69% and 83% of these patients will experience lasting remission for several years. Thus, although having a normal as opposed to subnormal cortisol level seems to be a risk factor for recurrence, neither measure is definitive enough to trigger an early second operation because this value is at best a moderate marker of prognosis, and these patients do not have frank hypercortisolemia at the time of the measurement.

Furthermore, given the significant variability in results reported in the literature, we believe that it is premature to use isolated immediate postoperative cortisol levels to make clinical decisions regarding patient management. This is especially true with patients with normal immediate postoperative cortisol levels who are deemed by the present dogma to be at high risk of recurrence. Although outcomes for this group are less often reported in the literature, our analyses found the recurrence rate to be 17% (95% CI, 14%-21%) in these patients.

Ram et al\textsuperscript{12} suggested that early reoperation, triggered by higher than expected postoperative cortisol levels and performed within 1 to 6 weeks, can induce sustained remission in more than one half of patients. Locatelli et al\textsuperscript{18} outlined a strategy of repeat surgery for

| TABLE 2. Demographic Characteristics of Patients in This Study\textsuperscript{a} |
|-----------------|-----------------|-----------------|-----------------|
| Cortisol Level  | Normal          | Sub-normal      | Undetectable    | P Value |
| No. of patients | 18              | 32              | 23              | NS      |
| Age at surgery, y | 39 ± 4.0       | 42 ± 2.0        | 33 ± 3.1        | NS      |
| Tumor size, mm   | 7.2 ± 2.0       | 6.2 ± 0.6       | 6.4 ± 0.8       | NS      |
| No. (%) with cavernous sinus invasion | 4 (22) | 6 (19) | 1 (4) | NS |
| No. (%) with suprasellar extension | 2 (11) | 2 (6) | 0 (0) | NS |
| No tumor seen on magnetic resonance imaging, no. (%) | 4 (22) | 5 (16) | 2 (7) | NS |
| Total follow-up, y | 4.5 ± 0.5 | 4.9 ± 0.4 | 4.1 ± 0.5 | NS |

\textsuperscript{a}NS, not significant.
patients with Cushing’s disease in the immediate postoperative period when cortisol levels remain greater than 2 µg/dL during the first 3 days after initial surgery. However, they do maintain that therapy should be individualized, given the many variables to consider when evaluating and treating patients with Cushing’s disease. Several reports suggest that postoperative complications, including hypopituitarism and diabetes insipidus, are more common after repeat surgery for Cushing’s disease than usually seen after initial surgery. This is especially true when hemi- and total hypophysectomy are performed as opposed to a selective adenomectomy.12,18,19

In addition, several investigators support withholding empirical glucocorticoid replacement therapy postoperatively, or until symptoms and signs of adrenal insufficiency develop, to permit an early assessment of the probability of cure.8,18 In at least 2 reports, the motivation behind this therapeutic plan is so that a decision can be made regarding the need for immediate repeat surgery.8,18 One rationale for this approach is that perioperative steroids may suppress residual tumoral ACTH-producing cells and mask persistent disease, therefore making it difficult to establish the disease state immediately after surgery. In general, 80% to 90% of patients with Cushing’s disease caused by ACTH-producing microadenomas can be expected to enter early remission provided they have been treated by an experienced neurosurgeon.3,13,20 The likelihood of remission after surgery in patients with ACTH-producing macroadenomas is slightly lower at 50% to 65%.1 Interpreted differently, in a majority of the patients who undergo surgery for Cushing’s disease, postoperative central adrenocortical insufficiency will indeed develop. Why deliberately withhold glucocorticoids in a patient population at some risk because of omission of therapy simply for the purpose of obtaining a value whose utility is questionable? We have seen hyponatremia, hypotension, and other symptoms and signs of adrenal insufficiency develop in several hospitalized patients as a consequence of inadvertent omission of their glucocorticoid doses. We do not recommend withholding glucocorticoids in postoperative Cushing’s patients because we believe that this practice puts patients at unnecessary risk, is not worth the yield given that only 1 to 2 patients out of every 10 will have persistent disease, and because we believe that the reliability of the immediate postoperative cortisol levels in these patients remains debatable. We contend that there is little to no harm in treating the 10% to 20% of patients who have persistent disease with a replacement dose of a glucocorticoid for as long as 6 weeks.

Although the simple idea that removal of a constitutive source of ACTH should lead to nearly complete absence of cortisol production in the case of cure, our data suggest that the true picture is more complex than that theory. Interestingly, Rollin et al21 found that cortisol levels 10 to 12 days after surgery permitted a better differentiation of the groups of patients with persistent disease and remission. Toms et al17 found cortisol levels 6 to 12 weeks after surgery to be lower than those obtained 5 to 14 days after surgery in the 7 of 11 patients who had a sustained remission. Pereira et al10 also reported that 7% of their patients had cortisol levels greater than 138 nmol/L immediately after surgery that decreased to less than 50 nmol/L 6 to 12 weeks later; these patients experienced sustained remission. These reports support the hypothesis that select patients may have adrenal hyperplasia and a period of autonomous cortisol production. Alternatively, it is conceivable that some of these patients had residual tumor tissue that became ischemic and later underwent necrosis as a result of vascular injury at the time of initial surgery. Regardless of the pathophysiology, in our experience, this pattern of cortisol level is not uncommon. Thus, caution is advised in the timing of evaluation to make the determination regarding the outcome of initial surgery in these patients.

A review of the articles referenced here leads us to believe that the assessment of a morning serum cortisol within a few days of surgery is not a reliable enough test on which to base the need for
subsequent immediate treatment. More specifically, based on the best existing published data, a subnormal immediate postoperative level has a specificity for lasting disease freedom of approximately 88% to 94%, which, although positive, is not exactly analogous with “cure,” as many believe. More importantly, a value in the normal range has a positive predictive value of predicting recurrence of only approximately 17% to 31%. Even cases of persistent supranormal cortisol values may not always represent patients with residual tumor. Based not only on these data, but also on our own experience, it can be concluded that a significant proportion of patients with detectable or normal cortisol levels after surgery do not have persistent or recurrent disease, nor do all patients with elevated values need immediate aggressive management of residual disease. Rather, these findings suggest that the error rate of early repeat surgery based on early postoperative cortisol levels would be sufficiently high to call for abandonment of this practice in all but those patients who remain profoundly hypercortisolemic. Several reports clearly show that cortisol levels reach their nadir weeks to months after initial surgery.10,13,17,21 These observations suggest that if one wishes to rely on serum cortisol levels after surgery, the immediate postoperative period is not the time to conduct the assessments and plan additional interventions.

Although meta-analysis can be a powerful tool for reducing the biases and limited statistical power of individual reports, as with any meta-analysis, there are significant limitations regarding the use of the data produced. Most notable for the current meta-analysis is the significant heterogeneity with regard to the length of follow-up, which likely leads to an underestimation of recurrence rates in some studies. A close look at our methods will reveal our attempts to address the potential for individual study bias affecting the ultimate odds ratio for recurrence. More specifically, the calculation of the Q-statistic allows assessment of between-study heterogeneity, and our use of the fixed-effects meta-analysis model was based on the statistical confirmation that the data from individual studies were relatively homogeneous or at least that individual studies did not significantly influence the eventual conclusions. We think that this minimizes the risk that different lengths of follow-up alone produced these results; however, this possibility cannot be completely eliminated with any statistical method. Replication of these findings in our own data set also suggests that our methodology is at least not markedly flawed. Also, the definition of recurrence in these studies is similarly heterogeneous, with many studies using urine free cortisol as evidence of recurrence, and others using return of hypercortisolemia not suppressed with dexamethasone, raising the possibility of imperfections in estimations of recurrence rates in many of these studies. In addition, the timing of the cortisol measurement was quite variable and delayed by as much as 4 weeks in 1 case. Given the low morbidity of contemporary endonasal transsphenoidal surgery, our current patients typically go home the next day and cortisol levels are usually measured on the morning of postoperative day 1, raising questions regarding the clinical relevance of cortisol levels measured on postoperative day 14. Even though measuring the cortisol level at a follow-up visit is feasible, it is unclear whether prognostically this is the best time point to assess hypothalamic-pituitary-adrenal axis function, and this study does not aim to answer this question.

The diagnosis of residual or recurrent Cushing’s disease is perhaps more challenging than making the initial diagnosis of Cushing’s disease. Postoperative patients are physiologically much more complex. Normal cortisol levels postoperatively may remain stable for several years, but later recurrences are significant. We believe that taking shortcuts and arriving at conclusions based on limited information about this very complex disease process can lead to major errors in the prescription of therapy. However, obtaining this value is not harmful and has some prognostic value. Even though the immediate postoperative cortisol level has cavets, it should still be routinely obtained in patients with Cushing’s disease who undergo transsphenoidal tumor resection, until better tools to identify early remission are available.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENTSThe determination of remission after transsphenoidal surgery for CD remains, as this article notes, problematic, which influences the recommendation for, and timing of, additional treatment. Postoperative cortisol production can be a function of variably suppressed normal pituitary tissue, possible residual adrenocorticotropic hormone adenoma, partially autonomous adrenal glands, and the vagaries of cortisol assays. This article reports that assessment of cure, as determined by immediate postoperative serum cortisol measurement, is in many cases inaccurate and argues that additional treatment should be withheld until data can be obtained over a longer follow-up period. It specifically addresses the question of whether early postoperative cortisol levels are predictive of cure and finds a correlation between undetectable postoperative cortisol levels and long-term remission. However, the authors also report a measurable incidence of persistent long-term remission, even in cases in which the postoperative serum cortisol is only normal (rather than low), although the risk of recurrence is higher in this group overall, and use this to argue that these patients should not undergo early reoperation. Presumably the issue has arisen as reports in the literature argue for early reoperation if the first procedure is unsuccessful, but in fact the National Institutes of Health article referenced actually argues for reoperation if cortisol levels remain elevated at 1 to 6 weeks postoperatively. In most centers with pituitary expertise, however, it is unlikely that clinicians recommend additional treatment on the basis of data obtained on the first or second postoperative day.

The time course over which postoperative hypocortisolemia develops is variable for the reasons noted previously. Our own recent data, compiled in association with Italian colleagues, showed that 5.6% of 620 postoperative CD patients experienced a delayed decrease in cortisol at times up to 6 weeks, which would support the contention of these authors that delaying additional therapy in uncertain cases is warranted. In addition, however, our own unpublished data show that, in 115 patients undergoing transsphenoidal surgery for Cushing’s disease between 1998 and 2006, 7 of 12 recurrences occurred in patients whose postoperative 24-hour urine free cortisol levels were 0 or 1 [mu]g/24 h. In contradistinction to the authors, we found no statistical correlation between the risk of recurrence and whether the postoperative 24-hour urine free cortisol level was undetectable or simply subnormal, as opposed to the data presented here showing a significant correlation between undetectable and subnormal postoperative serum cortisol levels and risk of recurrence. Differences in patient populations, cortisol assays, use of perioperative steroids, and measurement dates in relation to surgery may account for the disparate findings.

Finally, we agree with the authors that better tools are needed to measure outcome in this challenging disease. A recent article describes the use of midnight salivary cortisol levels in the determination of remission and reports improved sensitivity and specificity over both fasting cortisol and 24-hour urine cortisol levels, promising technique that merits further investigation and correlation with recurrence data.

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POSTOPERATIVE CORTISOL LEVELS IN CUSHING’S DISEASE