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# Are Cushing's disease patients curable?

## *Peut-on guérir les patients atteints de la maladie de Cushing ?*

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**Abstract**

Treatment of Cushing's disease remains a challenge. Whereas pituitary surgery can "*cure*" the patient and restore a completely normal pituitary adrenal axis, there are immediate failures and late recurrences which ultimately require alternate therapeutic approaches. These are numerous, but so are their drawbacks, and all appear to be "default options". For the future, pituitary adenoma has to remain the "reasonable obsession" of efficient and optimistic therapists. . .


*Keywords:* Cushing's disease; Pituitary adrenal axis; Pituitary surgery

**Résumé**

Le traitement de la maladie de Cushing reste un défi. La chirurgie hypophysaire a la capacité de « *guérir* » le patient et de rétablir une fonction hypophyso-surrénalienne strictement normale. Cependant, les échecs immédiats et les récidives tardives réclament des approches thérapeutiques alternatives. Leur grand nombre est en corrélation directe avec leurs inconvénients, car elles ne sont que des « options par défaut ». Dans l'avenir, c'est bien l'adénome hypophysaire qui doit rester « *l'obsession raisonnable* » d'un thérapeute efficace et optimiste. . .


*Mots clés :* Maladie de Cushing ; Chirurgie surrénalienne ; Fonction hypophyso-surrénalienne

## 1. Introduction

Whereas PRL-, GH-, and TSH-secreting adenomas have long found their "medical solutions" with dopaminergic and somatostatin (SST) analogs, the ACTH-secreting pituitary adenoma is still something of an orphan with regard to targeted medical therapy. It is, however, an appealing orphan, stimulating numerous investigators, and pharmaceutical firms, to explore different therapeutic strategies against the various actors composing the pituitary-adrenal-glucocorticoid receptor axis [1]. They often succeed in controlling chronic hypercortisolism; lasting restoration of a "normal" pituitary adrenal axis, however, is another question. The Holy Grail for Cushing's disease is yet to be found. . .

## 2. What criteria for a "cure"?

Four criteria should be met simultaneously:

- "chronic hypercortisolism" should be suppressed:
  - any treatment should, at least, bring 24-hour urinary cortisol (UC) below the upper limit of normal (ULN). Almost all therapeutic trials, these days, use this purely biochemical target as their primary end-point;
- a normal pituitary-adrenal axis should be restored:
  - the objective is not only to suppress the hypersecretion but also to restore the normal circadian pattern of cortisol secretion, with normal early morning and late evening serum values. The overall pituitary-adrenal axis should regain its ability to react to stress;
- the clinical peripheral features and complications of "chronic hypercortisolism" should be reversed:

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- the clinical features and complications of "chronic hypercortisolism" are not all of equal significance and clinical impact: after successful treatment, diabetes may disappear within days, menses resume within weeks, but height loss due to vertebral collapse. . .never. Patient age and disease duration are important factors, which determine the reversibility – or irreversibility – of complications;

- the culprit tumor should be ablated:
  - in Cushing's syndrome, whatever its cause, we always have two enemies, invariably present together at the same time: a hormone, cortisol, and a tumor which is directly or indirectly causing overproduction of cortisol. Anatomical difficulties and tumor invasion do not always allow easy total resection, ruling out the ideal of vanquishing both enemies at once by a single efficient and definitive approach.

## 3. The only way to "cure" patients with Cushing's disease is. . . surgery

### *3.1. Pituitary surgery is the "cure-all"*

There is nothing like it: within hours of successful pituitary surgery, cortisol plasma values drop below the detection threshold and within months the overall pituitary adrenal axis is back to normal, indistinguishable from that in normal subjects.

When it works: yet very small adenomas are not always detected and invasive adenomas cannot always be resected entirely: pituitary surgery is not always a cure-all and immediate failure and late recurrence are not unknown.

### *3.2. All other therapeutic approaches are. . ."default options" with inescapable limitations [1–23]*

Medical treatment targeting the pituitary (dopaminergic, SST analogs), adrenal cortex (synthesis inhibitors, adrenolytics) or glucocorticoid receptor (mifepristone), pituitary radiotherapy, and, finally, bilateral total adrenalectomy are alternative therapeutic approaches, but all with inescapable limitations:

- they almost always induce a second (and sometimes third) disease:
  - Addison's disease with the adrenolytic mitotane or after bilateral adrenalectomy,
  - adrenocortical blockade with steroid synthesis inhibitors, and the problems of excess precursors, fine-tuning of daily dosage, and risk of adrenal insufficiency,
  - the inescapable features of general resistance to glucocorticoids (excess androgens, mineralocorticoids), and even a third problem (progesterone blockade) with mifepristone. And the many difficulties of adapting and monitoring treatment,
  - pituitary insufficiency with radiotherapy,
  - or else the original disease, the pituitary adenoma, remains, with its own possibilities of growth, if not irradiated;
- they often incur further adverse events (AEs):
  - diabetes is a big concern when using pasireotide,
  - significant gastrointestinal and CNS AEs, and many other possible side-effects with chronic mitotane treatment;
- they never restore normal pituitary-adrenal function:
  - none of these approaches can restore a normal pituitary adrenal axis;
- they reduce or eliminate "chronic hypercortisolism" . . .most of the time:
  - apart from total bilateral adrenalectomy – which unsurprisingly has a success rate of 100% – all other therapeutic options have much lower rates of successful control of "chronic hypercortisolism".

### *3.3. Assessing the efficacy of medical treatments may be a challenge*

Assessing the efficacy of any therapeutic option in Cushing's disease patients is difficult; and this is particularly true when new medical options are tested:

- recruiting a sufficient number of patients with a rare disease may be difficult;
- UC is the usual – and logical – primary end point. Yet, in order to recruit enough patients, it is convenient to include cases with only mildly elevated UC, at just 1.5-fold ULN, a range in which spontaneous fluctuation may be enough to normalize UC [5]. Surprisingly, some studies also assess treatment efficacy by counting patients in whom UC is still above the ULN, but is reduced by at least half below baseline – although the same authors have stated in parallel publications that the "degree of hypercortisolism. . .is not related to its severity" [6].

For these reasons it seems particularly important to design well-controlled trials. However, because of the supposed intrinsic severity of Cushing's disease, most if not all therapeutic trials carried out so far have been non-controlled.

In real life, what patients complain of are the peripheral consequences of their disease – and not their UC concentration! These clinical features (obesity, diabetes, high blood pressure, gonadal dysfunction, etc.) may be difficult to evaluate, since they are usually given concomitant symptomatic treatments.

## 4. Future directions

For obvious theoretical reasons, no treatment can be expected to be better than that which specifically controls/ablates the ACTH-secreting pituitary adenoma.

### *4.1. Can we improve the efficiency of pituitary surgery/radiotherapy?*

Better and more precise (and intra-operative) MRI imaging of the pituitary? More efficient surgical approaches, through

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