

A critical reappraisal of bilateral adrenalectomy for ACTH-dependent Cushing's syndrome

Martin Reincke, Katrin Ritzel, Andrea Oßwald, Christina Berr, Günter Stalla¹, Klaus Hallfeldt², Nicole Reisch, Jochen Schopohl and Felix Beuschlein

Medizinische Klinik und Poliklinik IV, Klinikum der Ludwig-Maximilians-Universität München, Ziemssenstraße 1, D-80336 Munich, Germany, ¹Max-Planck-Institut für Psychiatrie, Munich, Germany and ²Chirurgische Klinik und Poliklinik – Innenstadt, Klinikum der Ludwig-Maximilians-Universität München, Munich, Germany

Correspondence should be addressed to M Reincke

Email
Martin.Reincke@med.uni-muenchen.de

Abstract

Objective: Our aim was to review short- and long-term outcomes of patients treated with bilateral adrenalectomy (BADx) in ACTH-dependent Cushing's syndrome.

Methods: We reviewed the literature and analysed our experience with 53 patients treated with BADx since 1990 in our institution.

Results: BADx is considered if ACTH-dependent Cushing's syndrome is refractory to other treatment modalities.

In Cushing's disease (CD), BADx is mainly used as an ultima ratio after transsphenoidal surgery and medical therapies have failed. In these cases, the time span between the first diagnosis of CD and treatment with BADx is relatively long (median 44 months). In ectopic Cushing's syndrome, the time from diagnosis to BADx is shorter (median 2 months), and BADx is often performed as an emergency procedure because of life-threatening complications of severe hypercortisolism. In both situations, BADx is relatively safe (median surgical morbidity 15%; median surgical mortality 3%) and provides excellent control of hypercortisolism; Cushing's-associated signs and symptoms are rapidly corrected, and co-morbidities are stabilised. In CD, the quality of life following BADx is rapidly improving, and long-term mortality is low. Specific long-term complications include the development of adrenal crisis and Nelson's syndrome. In ectopic Cushing's syndrome, long-term mortality is high but is mostly dependent on the prognosis of the underlying malignant neuroendocrine tumour.

Conclusion: BADx is a relatively safe and highly effective treatment, and it provides adequate control of long-term co-morbidities associated with hypercortisolism.

European Journal of Endocrinology
(2015) 173, M23–M32

Invited Author's profile

Prof. Martin Heinrich Reincke is Director of the Medizinische Klinik und Poliklinik IV, Ludwig-Maximilians-Universität München, and Chair of the Department of Endocrinology and Diabetology. His research specialities include adrenal physiology and pathophysiology, endocrine hypertension, pituitary disease, mineralocorticoid and glucocorticoid action and stress research. Professor Reincke heads a research team that specifically explores the prevalence and relevance of Cushing's syndrome at the epidemiological, clinical, genetic and molecular levels. The research teams of his clinic have particular expertise in assay development and validation for endocrine disease and in the development of genetically manipulated animals as models for human adrenal disease.



Introduction

Endogenous Cushing's syndrome is defined as chronic exposure to inadequate high levels of plasma cortisol. Cushing's syndrome is rare, with an estimated annual incidence that ranges from 1.2 to 2.7 per million (1, 2). The stigmata of Cushing's syndrome include phenotypic changes in fat distribution (truncal obesity, moon face, etc.), myopathy and skin manifestations, such as plethora, skin fragility and infections, ecchymosis and striae. The signs and symptoms of Cushing's syndrome overlap with those that occur in patients with the metabolic syndrome. Because of the epidemic dimension of the metabolic syndrome, in Western societies, identifying Cushing's syndrome in an early stage is becoming increasingly challenging.

Cushing's syndrome is divided by aetiology into adrenocorticotrophin (ACTH)-dependent and ACTH-independent forms. In the former, pituitary corticotroph adenomas and ectopic ACTH-producing neuroendocrine tumours cause hypercortisolism by stimulating both adrenals. The majority of the ACTH-independent causes of Cushing's syndrome are unilateral adrenal adenomas and, much less frequently, carcinomas. Rare causes of adrenal Cushing's syndrome include macro- and micro-nodular bilateral adrenal hyperplasia. Macronodular and micronodular hyperplasia mostly affect both glands equally. Table 1 shows the distribution by aetiology in our own institution from 1990 to 2014.

Bilateral adrenalectomy (BADx) is a complex surgical procedure that results in a lifelong dependency on glucocorticoid substitution and a risk of developing Nelson's syndrome. On the other hand, BADx is an essential treatment option for patients with Cushing's syndrome when previous treatments have failed. We have recently systematically evaluated the immediate outcome and the long-term consequences of BADx in Cushing's

syndrome (3) and reported our results in 36 patients treated with BADx in Munich (4). The present review addresses the practical aspects of BADx and is based on recent evidence and the outcome of 53 BADx treatments in our institution.

Primary goal in Cushing's syndrome: control of hypercortisolism by surgery

The primary treatment goal in patients with endogenous Cushing's syndrome is to terminate excess cortisol production by removing the autonomous ACTH or cortisol-producing tumour tissue without permanently damaging the pituitary–adrenal axis.

First-line treatment of ACTH-independent Cushing's syndrome that results from an adrenal adenoma is unilateral adrenal surgery. In contrast, bilateral micro- or macro-nodular adrenal hyperplasia is treated by BADx, although there have been recent reports of successful long-term outcomes following unilateral adrenalectomy in selected patients (5, 6).

In ACTH-dependent forms of Cushing's syndrome, the first-line treatment focuses on the surgical removal of the site of ACTH production (7). Transsphenoidal microsurgery has become the primary treatment for Cushing's disease (CD) when ACTH response to corticotrophin-releasing hormone, imaging and/or inferior petrosal sinus sampling indicate pituitary ACTH production. Transsphenoidal surgery by an expert neurosurgeon achieves remission in 42–97% of cases (median 78%) (reviewed by Petersenn *et al.* (8)). Remission and recurrence rates after transsphenoidal surgery vary widely and are influenced by pituitary morphology, the invasiveness of the pituitary tumour, the patient's age and the experience of the surgeon. In a significant percentage of patients,

Table 1 Causes of Cushing's syndrome, rate of BADx and surgical mortality in the endocrinology department, Medizinische Klinik IV, Klinikum der Ludwig-Maximilians-Universität, from 1990 to 2014.

Cause of Cushing's syndrome	n (%)	Patients treated by BADx (n (%))	Surgical (30-day) mortality of BADx
ACTH-dependent Cushing's syndrome	184 (74)		
Cushing's disease	154 (62)	34 (22)	1
Ectopic Cushing's syndrome	30 (12)	11 (37)	0
ACTH-independent Cushing's syndrome	64 (26)		
Cortisol-producing adenoma	46 (19)	0	0
Cortisol producing carcinoma	5 (2)	0	0
Bilateral adrenal hyperplasia	13 (5)	8 (61)	1
Total	248 (100)	53 (21)	2 (4)

hypercortisolism persists or recurs after a few years. Recurrence occurs in 3–47% of cases, with a median of 12% (8), and there are higher recurrence rates with long-term follow-up.

The primary approach to ACTH-producing neuroendocrine tumours that cause ectopic Cushing's syndrome is resection or tumour debulking. In this context, BADx is applied in two situations: In 8–16% of patients, the primary tumour site cannot be identified and remains occult during follow-up (9, 10, 11). The second common clinical situation is the incomplete removal of the tumour, local recurrences or metastatic disease without further surgical options, and this occurs in 71–88% of patients (9, 10).

Treatment options in persistent or recurrent CD: the case for BADx

As indicated in the previous section, persistence and recurrence in CD affects a substantial percentage of patients. According to a meta-analysis by Petersenn *et al.* (8), 31% of patients are in need of secondary treatment options, either because they are not controlled by a first pituitary surgery (22% of patients) or because they develop recurrence (9% of patients). Second-line therapeutic options consist of second transsphenoidal surgery, pituitary irradiation, medical therapy and BADx. Each of these strategies has advantages and disadvantages (Fig. 1) that

have been recently reviewed (7, 12). In many instances, they are used in combination or sequentially.

Repeat transsphenoidal surgery is advocated in most centres but has a lower success rate and a higher recurrence rate than first surgery does. Remission rates may be as high as 70% in selected patients in highly specialised centres (7). However, more recent series report a lower success rate of around 40% (13). In a recent study of 64 patients with persistence or recurrence, 43% did not undergo repeat surgery surgical because of tumour invasion into the cavernous sinus, which was not amendable to complete resection, because of other contraindications to surgery or because of patient preference. In total, 36 patients underwent repeat transsphenoidal surgery, and remission was achieved in 42%. Second recurrence occurred in 40% of patients after a mean of 27 months (14). In our institution, we consider second transsphenoidal surgery in all cases of persistent or recurrent CD following a careful review by our multidisciplinary pituitary tumour board.

Second-line treatment by pituitary radiation is widely used if repeated transsphenoidal surgery fails or is not feasible. In one previous study, fractionated radiotherapy was shown to have induced remission in 60 percent at 18 months and 91 percent at 5 years follow-up, but also hypopituitarism in 57% of patients (15). Cranial nerve neuropathy occurred in up to 5% of patients. Stereotactic radiosurgery appears to have lower success rates (16): in one

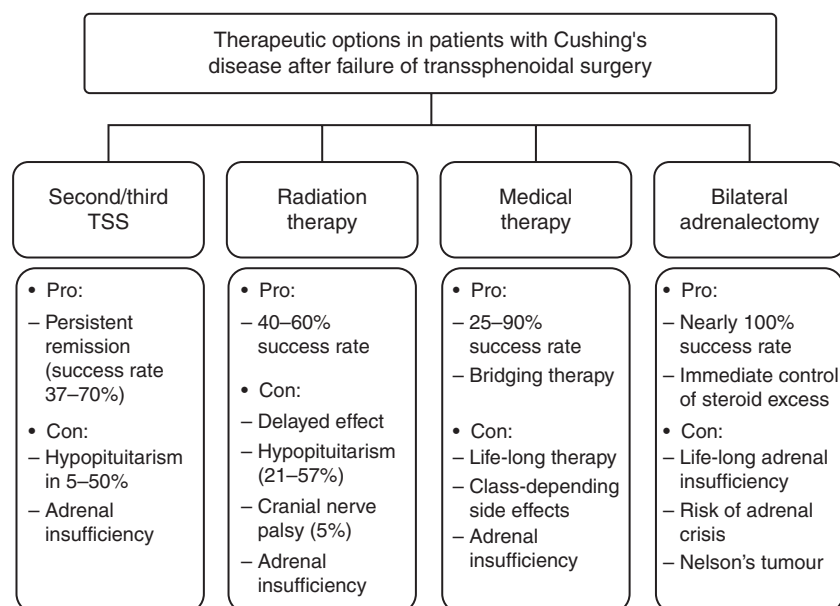


Figure 1

Strategies in recurrent or persistent Cushing's disease after first transsphenoidal surgery. TSS, transsphenoidal surgery.

study that included 18 patients with CD, 50% of the patients were in remission after 28 months, two patients developed recurrence after 6 and 8 years and 21% of patients developed hypopituitarism during the observation period (17). Our institution uses fractionated pituitary radiation and stereotactic radiosurgery mainly for local tumour control of growing corticotroph tumours but not for biochemical control of Cushing's syndrome.

Medical therapies have been used for 50 years in Cushing's syndrome with variable success. Evidence of success has mainly been based on retrospective case series, and efficacy has rarely been assessed prospectively in randomised controlled trials. This has recently changed because three drugs were formally approved for the treatment of Cushing's syndrome. Several further compounds are currently under investigation. Pituitary-directed approaches include the dopamine agonist cabergoline (18) and the multi-receptor somatostatin-analogue pasireotide (19). Inhibitors of steroidogenesis that inhibit cytochrome P450 enzymes include metyrapone, ketoconazole and LCI699 (20, 21). Hypercortisolism can also be controlled by the adrenolytic agent mitotane (22, 23, 24) and by the glucocorticoid receptor antagonist mifepristone (25). Currently, the approved drugs have limited efficacy because monotherapies and side effects limit their long-term use. A combination of several pituitary and adrenal-directed therapeutic approaches has been shown to increase efficacy (26), but long-term outcome has not been well established. Therefore, the exact status of medical treatment remains to be defined and is evolving. In many places, including our institution, medical treatment is frequently used as an adjunctive or bridging measure until definite therapy can be performed.

When is BADx in ACTH-dependent Cushing's syndrome indicated?

In general, two scenarios can be distinguished: elective and emergency BADx. Elective BADx is used in patients with CD in whom the ACTH excess is not amendable to other second-line treatments. In such a setting, BADx is generally considered to be the ultima ratio after other attempts to establish safe cortisol levels have failed or have been contraindicated. The latter may be the case in a female patient with CD who wishes to become pregnant and cannot be treated medically or by pituitary radiation. It is typical that time until BADx for patients in this category is rather long. In fact, in the Munich cohort of 34 CD patients, the median time between diagnosis of CD and BADx was 44 months. The patients underwent BADx

after one (62%) or several (38%) transsphenoidal surgeries, radiation (21%) and medical therapies (45%) (4).

Emergency BADx is performed in patients with very severe Cushing's syndrome. The characteristic scenario in this category consists of patients with massive ACTH and cortisol excess, which causes the most severe forms of Cushing's syndrome. These patients typically suffer from ectopic Cushing's syndrome. They might develop, in addition to classical Cushing's stigmata, life-threatening complications of hypercortisolism, such as bacteraemia and sepsis (27, 28, 29), thromboembolic complications, intractable hypokalaemic hypertension, heart failure, gastrointestinal haemorrhage, psychosis, debilitating myopathy, uncontrolled hyperglycaemia or a combination of these conditions (30). Serum cortisol levels generally reach 41 µg/dl (1100 nmol/l) and may be even higher than 100 µg/dl (2700 nmol/l). Emergency BADx can also be indicated after long periods of uncontrolled CD that have led to catastrophic situations with debilitating complications (stroke, myocardial infarction, osteoporotic fractures, etc.), even when cortisol secretion is not extremely high. In such a situation, the duration of uncontrolled hypercortisolism is the damaging factor. Timing of BADx is important because the course is generally fatal if hypercortisolism cannot be controlled and BADx is delayed or postponed (30). Therefore, we use the term 'malignant' or 'catastrophic' Cushing's syndrome to characterise this emergency scenario, and in such cases,

Table 2 Diagnostic criteria and specific treatment of emergency BADx in catastrophic Cushing's syndrome.

Clinical criteria

A patient with Cushing's syndrome and recent onset of one or more of the following:

- sepsis, opportunistic infection;
- intractable hypokalaemia, uncontrolled hypertension;
- heart failure;
- gastrointestinal haemorrhage;
- glucocorticoid-induced acute psychosis;
- progressive debilitating myopathy;
- thromboembolism; and/or
- uncontrolled hyperglycaemia and ketoacidosis.

Biochemical criteria

A patient with Cushing's syndrome and at least one of the following conditions:

- serum cortisol of ≥ 41 µg/dl (1100 nmol/l) (27); and/or
- severe hypokalaemia (< 3.0 mmol/l).

Treatment

Consider transfer to ICU

Control hypercortisolism with 2.5–3.0 mg/h etomidate i.v. (safe cortisol levels: in physiologically stressed patients, 500–800 nmol/l; in non-stressed patients, 150–300 nmol/l) (31)

Treat complications

Plan BADx at the next available possibility

BADx has to be performed in the shortest possible time span. Table 2 summarises the signs and symptoms of catastrophic Cushing's syndrome and the action that was taken. As expected, the median time from the diagnosis of ectopic Cushing's syndrome to BADx was short, at 4 months (4). Our approach to patients with catastrophic Cushing's syndrome who are scheduled for BADx includes a pre-surgical phase that aims to stabilise the patient with parenteral adrenostatic treatment. The patient is treated for 5–10 days with the 11 β -hydroxylase inhibitor etomidate in a non-sedative dose. I.v. low-dose etomidate infusion rates for the treatment of hypercortisolaemia are 0.04–0.05 mg/kg per h, which equates to 2.5–3 mg/h with dose titration according to serum cortisol levels (31), and a maximum dose of up to 5 mg/h in selected cases. Based on the pharmacokinetic properties of etomidate, cortisol levels fall within 12–24 h (32). Monitoring of serum cortisol levels is necessary to achieve the desired blockade and to prevent hypoadrenalism. The aim is to titrate serum cortisol levels to 500–800 nmol/l in physiologically stressed patients and to 150–300 nmol/l in unstressed patients (31). The treatment goals depend on the patient's presentation, and they include the normalisation of hypokalaemia, the control of hypertension and myopathy, the amelioration of psychosis and immunosuppression. Whether ICU stay during etomidate application should be mandatory remains controversial (31, 33). Our approach requires the initiation of etomidate in the ICU for 2 days and transfer to a normal ward thereafter when cortisol levels are in a safe and stable range and surgery cannot be performed immediately.

An alternative to i.v. etomidate followed by emergency BADx might be an oral combination therapy that consists of mitotane, metyrapone and ketoconazole. The two fast-acting steroidogenesis inhibitors metyrapone and ketoconazole provide rapid clinical and biological control of severe hypercortisolism, which thus covers the lag period before mitotane starts to act. The safety and efficacy of this regimen has been demonstrated recently (23). In that study, all 11 patients had ACTH-dependent Cushing's syndrome associated with clinical disorders such as severe cardiovascular, respiratory or infectious complications that precluded the surgical removal of the source of excessive ACTH as well as bilateral surgical adrenalectomy. UFC excretion fell within 48 h after the initiation of oral steroidogenic blockade into the normal range and remained controlled long-term. Five of the 11 patients eventually underwent successful transsphenoidal surgery. Rapid control of hypercortisolism was reported when a combination of metyrapone and ketoconazole was used

in 14 patients with ectopic Cushing syndrome and in eight patients with adrenocortical carcinomas. After 1 week of treatment, median 24 h urinary cortisol fell from 40 to three times the upper limit of normal in the patients with ectopic Cushing's syndrome and from 16 to one times the upper limit of normal in patients with adrenocortical carcinomas respectively. After 1 month of treatment, 73 and 86% of patients were controlled respectively (34).

Surgical outcome

Laparoscopic adrenalectomy was introduced in 1992 (35), and it has now replaced the open posterior and anterior approaches, which are associated with more wound complications and prolonged hospital stays. Only a small number of studies have directly compared open vs laparoscopic bilateral procedures in patients with Cushing's syndrome (36, 37, 38). Those studies demonstrated reduced blood loss and shortened hospital stays but similar mortality, morbidity and quality of life. Currently, the most commonly used technique is simultaneous bilateral laparoscopic BADx with the lateral trans-abdominal transperitoneal laparoscopic approach, although posterior retroperitoneoscopic adrenalectomy is advocated in some centres (30, 39). Because of the severe co-morbidities and the bilateral approach, patients with Cushing's syndrome have a higher risk for surgery-related morbidity and mortality than do patients with

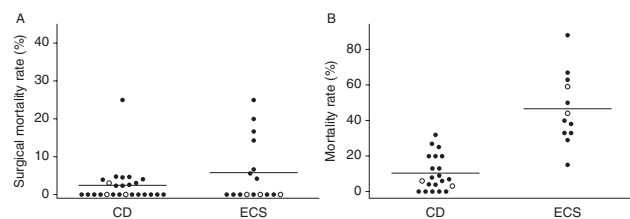


Figure 2

Mortality in patients with ACTH-dependent Cushing's syndrome following BADx. (A) Surgical (30-day) mortality. (B) Long-term mortality after undergoing BADx. The closed circles represent data from the 2013 systematic review by Ritzel *et al.* (3). The open circles depict studies published since 2013, including surgical mortality (4, 30, 41) and total mortality (4, 30). Mortality is lower in studies that involved patients with Cushing's disease than it is in patients with ectopic Cushing syndrome (surgical mortality 2.4 vs 5.7% respectively; total mortality 10.2 vs 46.3% respectively). CD, Cushing's disease; ECS, ectopic Cushing syndrome.

pheochromocytoma or aldosterone-producing adenomas who undergo unilateral adrenalectomy (40). Fig. 2A summarises the studies that have examined the surgical mortality of BADx in patients with Cushing's syndrome. As evident from Fig. 2A, patients with ectopic Cushing's syndrome have an adverse outcome because of more severe hypercortisolism and an underlying malignant tumour (CD: 2.1% vs ectopic Cushing's syndrome: 3.6%).

Long-term mortality

Long-term mortality is reported heterogeneously, as has been pointed out in the review by Ritzel *et al.* (3). Figure 2B shows non-adjusted mortality data of BADx in ectopic Cushing's syndrome (12 studies) as compared to CD (21 studies). Ectopic Cushing's syndrome is associated with higher mortality, likely as a result of the progression of the underlying malignancy. We recently reported that long-term mortality in a large series ($n=50$) with a long follow-up was 14% (4). The Kaplan–Meier curve (Fig. 3) showed excellent survival in CD (mortality at 1, 2, 5 and 10 years: 2.9%). Mortality was high in ectopic Cushing's syndrome (22% at 1 year and 44% at 2, 5 and 10 years).

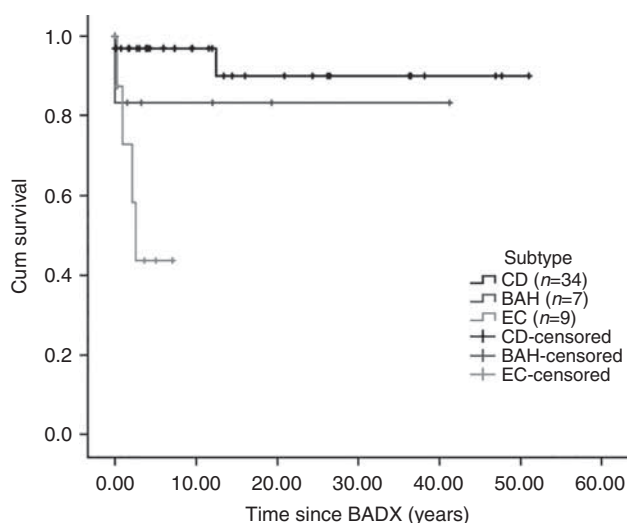


Figure 3

Long-term mortality of the Munich cohort (reprinted with permission from the European Society of Endocrinology from Osswald *et al.* (4)). Survival in patients with Cushing's syndrome according to Cushing's subtype (Kaplan–Meier method). CD, Cushing's disease; BAH, bilateral adrenal hyperplasia; ECS, ectopic Cushing's syndrome.

Clinical outcomes and complications

BADx is an effective means of reducing Cushing's-associated morbidity. Because of the immediate termination of glucocorticoid excess, its effect becomes evident instantly. All of the studies reviewed by Ritzel *et al.* (3) showed partial or full remission of Cushing's-associated signs and symptoms. Phenotypic stigmata decreased in 85% of the patients, arterial hypertension decreased in 82% and diabetes mellitus decreased in 70%. Symptoms and co-morbidities such as obesity, depression and muscle weakness showed the lowest overall remission rate of 32–43%. According to Sipple *et al.* (41) hypertension, obesity and depression improved in 7–10 months, whereas weakness and acne persisted for 12–17 months. Although functional remnant or ectopic adrenal tissue has been reported in some studies, clinical recurrence of Cushing's syndrome after BADx is very rare, at <2% (3). However, in a recent study, three out of 21 patients had clinical recurrence based on unilateral or bilateral single adrenal bed nodules (30).

Five studies have formally addressed quality of life after successful BADx in patients with Cushing's syndrome (4, 38, 42, 43, 44). Significant improvement in quality of life after BADx was achieved in 82–89% of the patients. Although quality of life in patients with Cushing's syndrome significantly improved in all of the studies after BADx, it was still definitely and permanently reduced as compared to a matched healthy control population (4, 43, 44). This appears to be unrelated to BADx itself, seeing as patients with CD following successful transphenoidal surgery are similarly affected by an impaired quality of life.

Procedure-related long-term complications after BADx include adrenal crisis and Nelson's syndrome. Addisonian crisis is caused by a total lack of endogenous glucocorticoid production. It can be prevented by glucocorticoid substitution with an adequate increase in dosage in situations of increased physical stress (45). As in all patients with adrenal insufficiency, patients who are treated with BADx should undergo structured education. Table 3 shows the incidence of adrenal crisis in patients after BADx. Incidences of 4.1–9.1 per 100 patient-years are within the range of adrenal crisis that results from other causes of glucocorticoid deficiency, such as Addison's disease, secondary adrenal insufficiency and congenital adrenal hyperplasia (46, 47, 48).

Nelson's syndrome is a potentially life-threatening condition that can occur following BADx for the treatment of CD (49). The diagnosis of Nelson's syndrome has

Table 3 The incidence of adrenal crisis in patients after BADx as compared to other causes of adrenal insufficiency.

Author	Study type	No.	Causes of adrenal insufficiency	Median follow-up (months)	Addison's crisis	Death
BADx						
Ritzel <i>et al.</i> (3)	Retrospective (review of six manuscripts)	203	BADx	42	9.3 per 100 patient-years	ND
Osswald <i>et al.</i> (4)	Retrospective	50	BADx	132	4.1 per 100 patient-years	1 (2%) (0.2 per 100 patient-years)
Primary and secondary adrenal insufficiency						
Hahner <i>et al.</i> (45)	Retrospective	444	Primary AI, <i>n</i> =254; secondary AI, <i>n</i> =190	6092 patient-years	6.3 crises per 100 patient-years	Not reported
Hahner <i>et al.</i> (46)	Prospective	434	Primary AI, <i>n</i> =221; secondary AI, <i>n</i> =202	24 months (768 patient-years)	8.3 crises per 100 patient-years	4 (0.9%) (0.5 adrenal crisis-related deaths per 100 patient years)
Congenital adrenal hyperplasia						
Reisch <i>et al.</i> (47)	Retrospective	122	CAH	35 years (4456 patient-years)	5.8 crises per 100 patient-years; salt wasting: 8.8; simple virilising: 2.5	Not reported

AI, adrenal insufficiency; ND, not determined.

changed over the past few decades. In early studies, the detection of Nelson's syndrome depended on clinical observation and conventional skull radiography. Thus, tumours were frequently diagnosed late in their clinical manifestation. With the more widespread application of tomographic imaging modalities, the direct identification of tumours has become possible at an earlier stage. An additional variable that has influenced the incidence of Nelson's syndrome in different studies is the length of follow-up, seeing as Nelson's syndrome can occur as late as 24 years after BADx (50). The incidence of Nelson's syndrome that occurred following BADx in 24 studies with 768 patients ranged from 0 to 47%, with a median of 21% and a median follow-up of 61 months (3). Nelson tumours occurred in 24% (7/29) of our patients with CD (4) and required repeated transsphenoidal surgery and radiation therapy. In all instances, Nelson's syndrome could be well controlled by these measures. A recent study by Assié *et al.* (51) conceptually revised the often arbitrary criteria that is used to define Nelson's syndrome (the presence of a pituitary adenoma and high ACTH concentration). Using short pituitary MRI imaging intervals (median 12.4 months) in 53 patients, they evaluated corticotroph tumour progression during a median follow-up after adrenalectomy of 4.6 years. Corticotroph tumour progression was defined as the occurrence of an adenoma in a patient without visible adenoma at baseline MRI or by

the progression of an existing adenoma. Three years after adrenalectomy, the proportion of patients who presented with corticotroph tumour progression reached 39%, and the proportion plateaued at 47% after 7 years. In multivariate analysis, a shorter duration of hypercortisolism and high plasma ACTH concentration in the 1st year after adrenalectomy were found to be independent predictive factors for corticotroph tumour progression. That study demonstrates that corticotroph tumour progression is not constant; rather, it occurs early after BADx and is predictable by ACTH determination and close MRI monitoring.

Conclusion

BADx is used in two instances: elective adrenalectomy in CD as an ultima ratio after the failure of (repeated) transsphenoidal surgery, pituitary radiation, medical therapy or a combination of these therapies and in cases of contraindications (pregnancy, side effects of medication, etc.). In these situations, many years have typically elapsed between the first diagnosis of Cushing's syndrome and the final decision to perform BADx. In contrast, emergency adrenalectomy in severe, life-threatening (so-called 'catastrophic') Cushing's syndrome is a medical emergency. In this situation, BADx is often performed shortly after a diagnosis of Cushing's syndrome has been

established. Patients typically suffer from ectopic Cushing's syndrome that is either caused by an aggressive neuroendocrine tumour or by an occult ACTH source. Clinically, patients have a high risk of severe complications, such as infections, myopathy, hyperglycaemia, psychosis or hypokalaemic hypertension. In both elective and in emergency BADx, the surgical procedure can be performed with manageable morbidity and a 30-day mortality in the lower single-digit range. Long-term outcome depends on the underlying cause of ACTH hypersecretion. In refractory CD, long-term outcome is excellent and can be superior to medical treatment (30). The available data support early use of BADx in (ACTH-dependent) Cushing's syndrome. In ectopic Cushing's syndrome, the overall prognosis is limited by the biological behaviour of the underlying malignancy. More than 40% of patients have died after 24 months, mainly because of tumour progression. In ectopic Cushing's syndrome, life expectancy and procedure-related complications have to be carefully weighed. In summary, BADx is a safe and highly effective therapy for ACTH-dependent Cushing's syndrome. Its effectiveness has been proven in elective BADx and in the most severe forms of ectopic Cushing's syndrome. It is our conviction that BADx should be used more frequently.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

Funding

The symposium was sponsored by unrestricted scientific grants from the DFG (grant number Re 752/22-1), the European Science Foundation (grant number 5551) and the Carl Friedrich von Siemens Stiftung. M Reincke was supported by a grant from the Else Kröner-Fresenius Stiftung (grant number 2012_A103).

Acknowledgements

This paper forms part of a special issue of European Journal of Endocrinology on Cushing's syndrome. This article is adapted from work presented at the IMPROCUSH-1: Improving Outcome of Cushing's Syndrome symposium, 12–14 October 2014. The meeting was supported by the European Science Foundation, Deutsche Forschungsgemeinschaft, Carl Friedrich von Siemens Stiftung, European Neuroendocrine Association and the Deutsche Gesellschaft für Endokrinologie. The opinions or views expressed in this special issue are those of the authors, and do not necessarily reflect the opinions or recommendations of the European Science Foundation, Deutsche Forschungsgemeinschaft, Carl Friedrich von Siemens Stiftung, European Neuroendocrine Association and the Deutsche Gesellschaft für Endokrinologie.

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Received 7 March 2015

Revised version received 16 May 2015

Accepted 20 May 2015