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ORIGINAL ARTICLE

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Synchronous bilateral adrenalectomy in ACTH-dependent hypercortisolism: predictors, biomarkers and outcomes

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Abstract

Introduction Hypercortisolism requires a prompt therapeutic management to reduce the risk of development of a potential fatal emergency. A synchronous bilateral adrenalectomy (SBA) is effective in recovering hypercortisolism. However, specific indications for an SBA are not available. We aimed to evaluate the outcome of patients who underwent an SBA and to identify biomarkers able to predict the requirements of an SBA.

Patients and methods A mono-centric and longitudinal study was conducted on 19 consecutive patients who underwent SBA for ACTH-dependent hypercortisolism between December 2003 and December 2017. This study population was compared to two control groups composed of patients cured after the resection of the ACTH secreting pituitary adenoma (Group A: 44 patients) and of the ACTH-secreting neuroendocrine tumours (Group B: 8 patients).

Results Short- or long-term SBA complications or the recurrence of hypercortisolism did not occur. A single patient experienced Nelson syndrome. Clinical features after SBA showed improvement in the glico-metabolic assessment, hypertension, bone metabolism and the occurrence of hypokalaemia and infections. The younger the age at the time of Cushing's disease diagnosis, the longer the duration of active hypercortisolism, higher values of plasmatic ACTH and Cortisol (1 month after pituitary neurosurgery) and higher values of Ki67 in pituitary adenomas were detected in this study population as compared to Group A.

Conclusions SBA is an effective and safe treatment for patients with unmanageable ACTH-dependent hypercortisolism. A multidisciplinary team in a referral centre with a high volume of patients is strongly recommended for the management of these patients and the identification of patients, for better surgical timing.

Keywords Cushing · Pituitary adenoma · Neuroendocrine tumour

Introduction

Hypercortisolism is a systemic disorder characterized by hypertension, diabetes mellitus, hypokalemia, alkalosis, bone loss and bone fractures [1]. Hypercortisolism can evolve in acute emergency cases such as the development of intractable hypokalaemia, opportunistic infection, sepsis, uncontrolled hypertension, heart failure, hyperglycaemia, ketoacidosis, gastrointestinal haemorrhage, glucocorticoid-induced acute psychosis and thromboembolism [1].

An effective treatment of hypercortisolism is necessary, in order to reduce the morbidity due in most cases to infection, myocardial infarction and venous thromboembolism.

First-line treatment should be addressed to the removal of the primary source of ACTH hyper-secretion. However, in ACTH-dependent Cushing's syndrome, the source of ACTH overproduction may not be completely removed in

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cases of un-resectable or metastatic tumours or in cases of occult neoplasia. A synchronous bilateral adrenalectomy (SBA) is a therapeutic option in patients with ACTH-dependent hypercortisolism in whom the complete surgical resection of the primary tumour is not possible and medical therapy with steroidogenesis inhibition is not able to control the cortisol hyper-secretion or it is contraindicated, as in pregnancy or as other side effects. In fact, steroidogenesis inhibition normalizes cortisol levels in only half of patients and relieves symptoms of cortisol excess in around one-third [2]. An SBA can be also indicated after long periods of uncontrolled Cushing's disease leading to catastrophic situations with debilitating complications, such as stroke, myocardial infarction, osteoporotic fractures, even if cortisol secretion is not extremely high. In such conditions, in fact, the duration of uncontrolled mild hypercortisolism is considered a damaging factor [3]. Until now, an SBA has often been considered an *ultima ratio* after the failure of other therapies and was performed in emergency conditions or life-threatening complications of severe hypercortisolism [4]. By the removal of the end-organ of the ACTH stimulation, an SBA is effective in the control of hypercortisolism. In fact, <10% of cases may resume endogenous cortisol secretion, because of the presence of adrenal rests as remaining after surgery [5]. In recent years, an SBA was increasingly used and considered an essential treatment option, due to its low morbidity and mortality rates [6]. In previous series, post-surgery mortality ranged from 3 to 22% of cases [4–7]. In a recent study conducted on a large cohort of patients affected by Cushing's Disease, 18% of cases were treated with an SBA [6]. Specific indications for this procedure are currently not available [3].

The aim of this study was to evaluate the outcome of patients who underwent an SBA and to compare these patients to a control group in order to identify biomarkers which are able to predict the patients that will require an SBA, to reach the ACTH-dependent hypercortisolism control.

Patients and methods

A mono-centric cross sectional, longitudinal and retrospective study was conducted among consecutive patients who underwent an SBA for ACTH-dependent hypercortisolism between December 2003 and December 2017.

Patients were enrolled if they met all the following inclusion criteria:

- Diagnosis of ACTH-dependent hypercortisolism, conducted at the Pituitary Unit, Department of Endocrinology of the Gemelli Foundation, IRCCS Università Cattolica del Sacro Cuore, Rome;
- Treatment with an SBA conducted at the Department of Endocrine Surgery of Fondazione Policlinico Gemelli, Università Cattolica del Sacro Cuore, Rome, for unresponsiveness to
- Other treatments for ACTH-dependent hypercortisolism

The study population was compared with two control groups:

- Group A: patients diagnosed with Cushing's disease and cured through pituitary neurosurgery
- Group B: patients affected by ectopic or occult ACTH secreting neuroendocrine tumours (NET) and considered cured/controlled through the surgical removal of the NET and/or medical treatment, at the last examination.

Patients of the control groups were diagnosed and followed-up during the same period of time as the study population.

Diagnosis of ACTH-dependent hypercortisolism, Cushing's disease and Cushing's syndrome was conducted according to guidelines [8]. In particular, in patients with negative/not-diagnostic pituitary MR and with dynamic tests suggestive for an ectopic secretion of ACTH, a total body contrasted computerized tomography (CT) and 68-Gallium somatostatin analogues positron emission tomography (PET). The cytological or histological examination was conducted in order to confirm the diagnosis of ACTH-secreting NET. Patients affected by ACTH-dependent Cushing's syndrome but with an undetectable NET were considered to be affected by an ACTH secreting occult NET.

Patients were defined cured or controlled for ACTH-dependent hypercortisolism according to guidelines [8].

Follow-up evaluation

According to our clinical practice, patients are evaluated with biochemical (dosage of electrolytes) and hormonal tests (dosage of ACTH, plasmatic and urinary cortisol levels) within at least 15 days after the pituitary neurosurgery, after the resection of an ACTH-secreting NET, after the SBA or after the introduction of a steroidogenesis inhibition therapy (such as ketoconazole or mitotane). Subsequent evaluations are conducted after one and three months and then every six months. Morphological examinations are conducted 3 months after surgery and then at least annually.

Statistical methods

We collected the clinical and metabolic features of the study population and control groups both at the time of

hypercortisolism diagnosis and at the time of the last examination. We compared the data of the diagnosis with those of the last examination visit.

Data are presented as median ± interquartile ranges (IQR). Chi square test (or Fisher exact test when necessary) and non-parametric test (Kruskall-Wallis) were used to compare categorical and quantitative data. Logistic regression analysis was performed to identify the factors able to predict the requirement of an SBA for reaching a hypercortisolism biochemical control. To obtain the optimal threshold of quantitative variable, the receiver operating characteristic (ROC) analysis was performed. Statistical significance was assumed when $p < 0.05$. Data was analysed using the SPSS Software, version 22.

Results

The study population consists of 19 consecutive patients who underwent an SBA between December 2003 and December 2017.

Eleven patients were affected by Cushing's disease and underwent first-line treatment with the neurosurgical removal of the pituitary adenoma. All patients underwent medical treatment, for the persistence of hypercortisolism after pituitary neurosurgery. Ten cases were treated with ketoconazole, two with mitotane and two with Pasireotide short acting (s.a). Moreover, gamma-knife radiotherapy was conducted in three cases on the residual of the pituitary adenomas.

Out of the 19 enrolled patients in the study population group, 8 were affected by a ACTH-dependent Cushing's syndrome, due to an ACTH secreting occult NET and underwent an SBA, after the failure of medical treatment with ketoconazole or mitotane.

No patients experienced short or long-term complications of an SBA, or the recurrence of hypercortisolism. Among the 11 patients affected by Cushing's disease and who underwent an SBA, Nelson syndrome occurred in a single case.

The median duration of follow-up after an SBA was of:

- 72 months (IQR: 72) in patients affected by Cushing's disease and who underwent an SBA;
- 216 months (IQR: 60) in patients affected by Cushing's disease and who were cured through pituitary neurosurgery (Group A);
- 156 months (IQR: 117) in patients affected by ACTH-dependent Cushing's syndrome and who underwent an SBA;
- 126 months (IQR: 89) in patients affected by ACTH-dependent Cushing's syndrome and who were cured through other treatments (Group B).

Clinical assessment before SBA

At the last visit conducted before the SBA, two patients were diagnosed for glucose intolerance and treated with oral hypoglycemic drugs. Mellitus diabetes was detected in 10 patients and treated with oral hypoglycemic drugs and insulin. Mixed dyslipidaemia was identified in 10 patients and treated in five cases with a hypolipidic diet and in five cases with statin drugs. Thirteen patients carried mild/severe hypokalaemia and 10 patients neutrophilic leukocytosis. Recurrent infections were diagnosed in three cases. Systemic arterial hypertension was identified in 15 patients and treated with a single anti-hypertensive drug in three cases, two anti-hypertensive drugs in twol cases, three anti-hypertensive drugs in three cases, four anti-hypertensive drugs in five cases and five anti-hypertensive drugs in two cases.

Clinical assessment after an SBA

After the SBA, two patients were still affected by glucose intolerance, two patients by mellitus diabetes and six patients by mixed dyslipidaemia. However, neither the hypokalaemia nor the neutrophilic leucocytosis nor the recurrent infections still occurred. Systemic arterial hypertension persisted in six patients but required a single anti-hypertensive drug in all cases. With regard to bone metabolism, we found that bone densitometry both of the spine and at the femoral neck improved after SBA (femoral T-score: −0.9; spine T-score: −0.8), with respect to pre-surgical values (femoral T-score: −1.3; spine T-score: −1.04).

Hormonal replacement therapies

All 19 patients who underwent an SBA were on hormonal replacement treatment with hydrocortisone (median dosage: 30 mg/daily IQR: 0, range: 20–40 mg/daily) and fludrocortisone (median dosage: 1.5 mg/weekly). Among the 11 patients who underwent pituitary neurosurgery for Cushing's disease, 4 patients were affected by central hypothyroidism and a single patient by growth hormone deficit and diabetes insipidus. Central hypothyroidism and diabetes insipidus were compensated by hormonal replacement therapies.

Analysis of patients affected by Cushing's Disease

In Table 1, are summarized the results of the comparative analysis of the demographic, clinical and morphological features between the 11 patients of the study population and the control group A that was composed of 44 patients cured through pituitary neurosurgery. We found a younger age at

Table 1 Comparative analysis between demographic, clinical and morphological features of Cushing's disease affected patients who underwent a synchronous bilateral adrenalectomy (study population) and patients cured with pituitary neurosurgery: univariate analysis

	Patients affected by Cushing's disease		
	Pts who underwent a synchronous bilateral adrenalectomy (11 pts)	Control group A (44 pts)	*p*-value
Gender			
Male *n* (%)	4 (36.3%)	31 (70.4%)	0.6
Female *n* (%)	7 (63.7%)	13 (29.6%)	
Median age at Cushing's disease diagnosis (IQR)	26.5 (21.2)	42 (19.7)	**0.02**
Median ACTH value at Cushing's disease diagnosis (IQR)	55.5 (44.7)	73.3 (39.7)	0.06
Median plasmatic cortisol value at Cushing's disease diagnosis (IQR)	260 (165)	261 (107)	0.9
Median urinary cortisol value at Cushing's disease diagnosis (IQR)	609 (318)	611.9 (317.8)	0.1
Median duration of active hypercortisolism months (IQR)	9 (42)	3 (5)	**0.001**
Pituitary histological diagnosis			
Pituitary adenoma *n* (%)	5 (45.5%)	44 (100%)	Ref.
Negative/Not diagnostic *n* (%)	4 (36.3%)	0	**<0.001**
Pituitary ACTH cells hyperplasia *n* (%)	2 (18.2%)	0	**<0.001**
Pituitary adenoma dimensions			
Macroadenoma	3 (60%)	3 (6.8%)	**0.01**
Microadenoma	2 (40%)	41(93.2%)	

Bold values indicate statistical significance $p < 0.05$

the time of Cushing's disease diagnosis and a longer duration of active hypercortisolism, among patients of the study population as compared to those of the control group A. Interestingly, the biochemical tests (conducted 1 month after pituitary neurosurgery) showed higher values of plasmatic ACTH and cortisol in the study population as compared to those of control group A (Fig. 1). In particular, we detected that the requirement of an SBA can be predicted by an ACTH value higher than 40 ng/mL (AUC: 0.92; sensitivity: 80%, specificity: 100% $p = 0.001$), a plasmatic cortisol value higher than 190 ng/mL (AUC: 1; sensitivity: 80%, specificity: 100% $p < 0.001$), a urinary cortisol value higher than 40 mcg/24 h (AUC: 0.8; sensitivity: 100%, specificity: 28.1% $p = 0.04$) and a duration of active hypercortisolism longer than 6 months (AUC: 0.82; sensitivity: 100%, specificity: 65% $p < 0.001$).

With regard to morphological features, we found that patients affected by Cushing's disease with undetectable pituitary lesions or patients affected by pituitary hyperplasia require in most cases an SBA to reach a biochemical control of the disease, after the failure of the explorative pituitary neurosurgery and medical therapy (Table 1).

Among the patients who carried a pituitary adenoma, we found a higher value of Ki67 in patients of the study population group as compared to control group A (Fig. 1d). In particular, a Ki67 value higher than 4% (AUC: 1; sensitivity: 100%, specificity: 84% $p = 0.02$) suggests the requirement of an SBA for reaching the biochemical control of ACTH-dependent hypercortisolism.

Analysis of patients affected by ACTH-dependent Cushing's Syndrome

Comparative analysis between demographic, clinical and morphological features of ACTH-dependent Cushing's syndrome affected the study population and control group B is summarized in Table 2. The control group was composed of eight patients: six were affected by typical and two by atypical carcinoids. Among this control group, two patients (25%) were cured through lung lobectomy and the remaining six patients (75%) required medical treatment for the control of the disease. We found that the percentage reduction of the cortisol after the midnight administration of 8 mg dexamethasone was significantly higher in patients that required the SBA (study population), as compared to patients of control group B. Particularly, a cortisol percentage reduction higher then 73% after the midnight administration of 8 mg dexamethasone (AUC: 0.93; sensitivity: 100%, specificity: 87.5% $p = 0.007$) suggests the requirement of an SBA for reaching the biochemical control of the ACTH-dependent Cushing's syndrome.

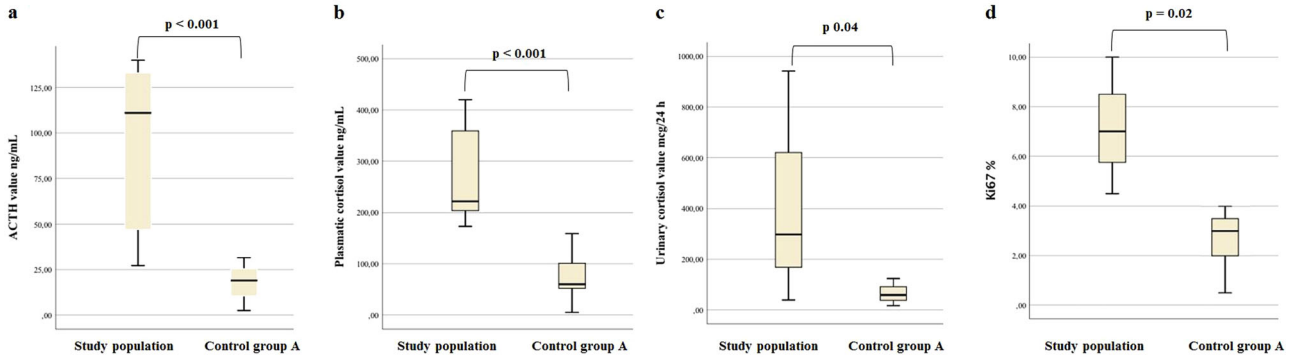

Fig. 1 Boxplot of **a** ACTH value, **b** plasmatic cortisol, **c** urinary cortisol and **d** Ki67% (median and IQR), among the study population and control group A. ACTH, plasmatic and urinary cortisol value (evaluated one month after pituitary neurosurgery) and Ki67 Li were significantly higher in the study population as compared to the control group A

Table 2 Comparative analysis between demographic, clinical and morphological features of ACTH-dependent Cushing's syndrome affected study population and control group B. Univariate analysis

	Patients affected with Cushing's syndrome		
	Pts who underwent a synchronous bilateral adrenalectomy (8 pts)	Control Group B (8 pts)	*p*-value
Gender			
Male *n* (%)	3 (37.5%)	4 (50%)	0.9
Female *n* (%)	5 (62.5%)	4 (50%)	
Median age at Cushing's disease diagnosis (IQR)	49 (16.7)	42 (21)	0.3
Median ACTH value at Cushing's disease diagnosis (IQR)	26 (84)	108 (80)	**0.03**
Median plasmatic cortisol value at Cushing's disease diagnosis (IQR)	256 (82)	318 (53)	**0.02**
Median urinary cortisol value at Cushing's disease diagnosis mcg/24 h (IQR)	533 (445)	120 (1005)	0.5
Median percentage reduction of plasmatic cortisol after 1 mg midnight dexamethasone (IQR)	28 (138)	34 (70)	0.6
Median percentage reduction of plasmatic cortisol after 8 mg midnight dexamethasone (IQR)	126 (70)	57.4 (35)	**0.005**
Primary NET			
Occult	8 (100%)	0	Ref
Typical bronchial carcinoid	0	7 (87.5%)	<0.001
Atypical bronchial carcinoid	0	1 (12.5%)	0.1
Median duration of active hypercortisolism months (IQR)	8 (27)	2 (5)	0.4
Median plasmatic cortisol value during medical therapy after pituitary neurosurgery (IQR)	248 (309)	52 (72)	**0.004**

Bold values indicate statistical significance $p < 0.05$

Logistic regression analysis

As showed in Table 3, logistic regression analysis confirmed that the main predictors for the requirement of an SBA to reach the biochemical control of the Cushing's disease were a Ki67 Li 4% and an ACTH value 40 ng/mL tested a month after the pituitary neurosurgery.

Mortality

A total of six patients died during the follow-up period. Two of these had undergone an SBA: one patient died for a malignant mammary adenocarcinoma and the other for the occurrence of a pancreatic NET with liver synchronous metastasis (G2, cT2N1M1, IV stadium). Two patients of

Table 3 Factors predicting the requirement of a synchronous bilateral adrenalectomy for reaching the biochemical control of the Cushing's disease

	p-value	OR (95%CI)
Age at Cushing's disease diagnosis <29 years	0.24	5.6 (1.4–22.6)
Duration of active hypercortisolism >6 months	0.5	2.7 (1.8–4)
Ki67 ≥ 4%	**0.04**	4 (1.1–21.8)
ACTH value at 1 month after pituitary neurosurgery ≥ 40 ng/mL	**0.04**	7.2 (2.8–18.3)
Plasmatic cortisol value at 1 month after pituitary neurosurgery ≥200 ng/mL	0.06	11.2 (3.5–36.3)

Logistic regression; *OR* odds ratio, *CI* confidence interval

Bold values indicate statistical significance $p < 0.05$

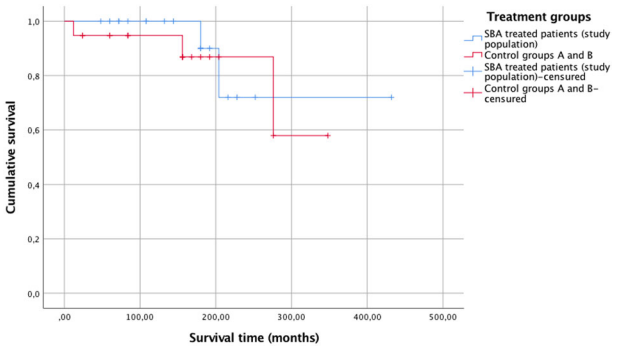

Fig. 2 Survival time. Kaplan Maier plot showed superimposable survival time among the study population and the control Group A and B ($p = 0.46$; HR: 1.89 95% IC: 0.3–10.5)

group B died due to the metastatic progression of atypical ACTH-secreting bronchial carcinoids The survival rate was similar among the study population and the control group A and B ($p = 0.46$ (HR: 1.89 95% IC: 0.3–10.5 Fig. 2).

Discussion

Our study described a homogeneous series of patients who underwent an SBA for ACTH-dependent hypercortisolism. In this series, 11 patients were affected by Cushing's disease and 8 patients by ACTH-dependent Cushing's syndrome. All the enrolled cases failed to reach the biochemical control of hypercortisolism with other treatments such as surgery or medical therapy, with ketoconazole or mitotane. In most of the previously described series, the patient cohort was heterogeneous, for the different adrenal diseases, such as bilateral Cushing's syndrome or pheochromocytoma or metastasis [9, 10]. Among patients affected by Cushing's disease, we found that those that required the SBA were younger at the time of hypercortisolism diagnosis, were affected by an active disease for a longer time and carried a higher value of serum ACTH and cortisol. This suggested a more aggressive disease, as compared to patients that reached the cure/control of Cushing's disease through pituitary neurosurgery or medical treatments.

Similarly, the Ki67 value was higher in pituitary adenoma of patients that required an SBA. Ki67 indicates the proliferative activity in neoplasia and, also, in pituitary adenoma where a higher value of Ki67 can predict the aggressiveness and recurrence risk [11]. The patients described in our series represent two different types of disease: a group of patients carried large, invasive and proliferative ACTH secreting pituitary adenoma and a second group of patients carried the corticotroph cell hyperplasia or small and not identified ACTH secreting pituitary adenoma. In fact, in our series, the large majority of patients who carried an ACTH-secreting micro-adenoma were cured only through pituitary neurosurgery (93.2% of cases). Moreover, the Ki-67 Li resulted higher in larger and invasive pituitary adenoma (median value: 3% IQR: 8) as compared to Ki-67 detected in smaller ones (median value: 2% IQR: 3).

Our data confirm that an SBA is effective both for an immediate control of hypercortisolism and for the improvement of hypercortisolism-related symptoms, as already shown in previous studies [4–13]. In a recent review, Ritzel et al. [6] showed partial or full remission of signs and symptoms that are associated with Cushing's syndrome, after an SBA: arterial hypertension improved in 82% of cases and diabetes mellitus in 70% of reviewed cases. The remission rate of obesity, depression and muscle weakness ranged from 32 to 43% of cases. Hypertension, obesity and depression improved within 7 to 10 months after the SBA, instead weakness and acne can persist until 12–17 months [14]. However, it was also reported that the improvement of morbidities after an SBA may be underestimated, due to the length of exposure to high cortisol levels or to the supra-physiological dosage of substitutive corticosteroids, particularly in the early post-surgical phase [15]. In fact, the optimal dose of corticosteroids for restoring the normal cortisol diurnal rhythm are difficult to achieve, but the impact of an over- or under-treatment is well described [16]. Data regarding the long-term clinical outcome, prognosis and quality of life after an SBA in patients with ACTH-dependent hypercortisolism still remain limited. This is, in part, because of the rarity of these conditions. With regard to the long-term outcome of patients in this series, we found that the mortality rate was superimposable among study population and control groups.

As previously reported by our group [17, 18], this series confirmed the effectiveness and safety of an SBA as no

patients died due to post-surgical complications, no adverse events occurred and all patients showed a long-term recovery of hypercortisolism, in the absence of post-surgery residual of the adrenal gland in all cases. A single patient developed Nelson syndrome, but she carried a cavernous sinus invasive residual pituitary adenoma. However, this patient underwent pituitary neurosurgery a second time with the stabilization of the residual pituitary adenoma. The better results in term of efficacy and safety in our study population may also be due to our protocol for the management of the pre-surgical and post-surgical phases. In fact, all patients are treated with steroidogenesis inhibitors (ketoconazole or mitotane) in order to reduce or normalize the cortisol hyper-secretion, before undergoing an SBA. Previous researches showed that treatment with steroidogenesis inhibitors can reduce the mortality rate of SBA and the risk of the occurrence of post-surgical thromboembolic events [15–20].

Similarly, according to our protocol, since the induction of anaesthesia to all the post-surgical phase, all patients are treated with adequate glucocorticoid replacement therapy, with the intravenous administration of hydrocortisone and a subsequent slow dose titration.

The limits of this study are the retrospective design and the absence of a randomization that reflect our real life practice. Another limit of our study was the absence of data on the patients' subjective idea of their quality of life (QoL). Our data consequently can't be compared with those of the most recent studies that suggested a worsening of QoL in patients who underwent an SBA, as compared to patients cured with other treatment choices [21–24]. Patients who underwent an SBA seem to be at a greater risk of suffering an impaired QoL for the more prolonged time with imperfectly controlled hypercortisolism. However, data on QoL still remain controversial, as an improvement of emotional-behavioural symptoms was also reported [25].

In conclusion, our data suggested that an SBA is an effective and safe treatment for patients with unmanageable primary sources of ACTH hyper-secretion and with a reasonable life expectancy from their primary disease. In particular, our data suggest that patients affected by Cushing's disease due to pituitary macroadenoma with a Ki-67 higher than 4% and patients with an plasmatic ACTH value higher than 40 ng/mL one month after pituitary neurosurgery may require an SBA and should benefit from an early treatment in their clinical history. A multidisciplinary team including endocrinologists, endocrine surgeons, oncologists and anaesthesiologists and a referral centre with a high volume of patients are strongly recommended for the management of these patients, in order to identify the better surgical time, to integrate the biology and behaviour of the tumour with all the cancer-directed available therapies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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