RESULTS AND PREDICTORS OF OUTCOME OF ENDOSCOPIC ENDO Nasal SURGERY IN CUSHING’S DISEASE: 20-YE A-R EXPERIENCE OF AN ITALIAN REFERRAL PITUITARY CENTER

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Received: 20 September 2019 / Accepted: 16 March 2020 / Published online: 25 March 2020 © Italian Society of Endocrinology (SIE) 2020

Abstract
Purpose To assess outcomes and predictors of early and long-term remission in patients with Cushing’s disease (CD) due to ACTH-secreting adenomas treated via endoscopic endonasal approach (EEA).

Methods This is a retrospective study. Consecutive patients operated for CD from 1998 to 2017 in an Italian referral Pituitary Center were enrolled. Clinical, radiological, and histological data at enrollment and follow-up were collected.

Results 151 patients (107 F) were included; 88.7% were naïve for treatment, 11.3% had been treated surgically and 11.2% medically. At pre-operative magnetic resonance imaging (MRI), 35 had a macroadenoma and 80 a microadenoma, while tumor was undetectable in 36 patients. Mean age at surgery was 41.1 ± 16.6 years. Diagnosis was confirmed histologically in 82.4% of the cases. Patients with disease persistence underwent second surgery and/or medical and/or radiation therapy. Mean follow-up was 92.3 ± 12.0 (range 12–237.4) and median 88.2 months. Remission rate was 88.1% after the first surgery and 90.7% at last follow-up. One patient died of pituitary carcinoma. Post-surgical cortisol drop (p = 0.004), tumor detection at MRI (p = 0.03) and size < 1 cm (p = 0.045) increased the chance of disease remission; cavernous sinus invasion was a negative predictor of outcome (p = 0.002). Twenty-seven patients developed diabetes insipidus and 18 hypopituitarism. Surgery repetition increased the risk of hypopituitarism (p = 0.03), but not of other complications, which included epistaxis (N = 2), cerebrospinal fluid leakage (1), pneumonia (3), myocardial infarction (1), and pulmonary embolisms (2).

Conclusions Selective adenomectomy via EEA performed by experienced surgeons, supported by a multidisciplinary dedicated team, allows long-term remission in the vast majority of CD patients with low complication rate.

Keywords Cushing’s disease · ACTH-secreting pituitary adenoma · Transsphenoidal surgery · Outcome · Cortisol · Predictor · Pituitary unit
Introduction

Cushing’s disease (CD) is a rare but severe condition due to chronic hypersecretion of cortisol. It typically affects people in the 4th decade of life, with an estimated female-to-male ratio of 5:1 [1, 2]. The great majority of the cases are caused by ACTH-secreting pituitary adenomas, 90% of which are microadenomas; hyperplasia of corticotroph pituitary cells, pituitary carcinoma, and ectopic ACTH-producing tumors are very rare [1, 2].

Early diagnosis and successful treatment are advisable to reduce the dramatic and often permanent psychophysical alterations induced by CD, responsible for the associated systemic comorbidities and disability, thus poor quality of life and increased mortality [3]. The ideal treatment should aim at normalizing cortisol secretion and reversing disease-associated comorbidities and manifestations, while preventing further complications, preserving pituitary function and avoiding recurrences [2].

Selective endoscopic pituitary adenoidectomy represents the first-line treatment for the associated high chance of cure and low occurrence of major complications [3, 4], although medical comorbidities make CD patients at higher risk of surgical complications than those with other pituitary adenomas [5, 6]. Rates of disease remission and recurrence largely vary among studies, mainly depending on tumor and patient features, surgical technique and neurosurgeon experience, follow-up duration and criteria to define CD remission and recurrence [2]. In case of disease persistence/recurrence, treatment options include surgery repetition, medical and radiation therapy and, eventually, bilateral adrenalectomy [2, 7].

The aims of our retrospective study were to assess outcomes and identify potential predictors of early post-surgical remission and long-term cure in a large and homogeneous cohort of patients with ACTH-secreting adenoma, treated via endoscopic endonasal approach (EEA) over 20 years in an Italian tertiary care referral center.

Patients and methods

Patients affected by CD, consecutively treated by surgery via EEA from May 1998 to August 2017 at the Pituitary Unit of the IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy, and with at least 12-month follow-up, were included in the study. Diagnosis was based on clinical, biochemical, and radiological criteria according to international guidelines [2, 8]. Patients naïve for treatment or who had already undergone surgery and/or medical therapies were included. Patients with Nelson’s syndrome and silent ACTH-secreting adenomas were excluded. All surgeries were performed by a multidisciplinary team composed by an expert pituitary neurosurgeon and a dedicated ENT surgeon.

Before surgery, patients underwent biochemical, endocrinological and neurological evaluation, visual field examination and 1.5 T MRI with gadolinium contrast medium. In case of clinical and/or biochemical suspicious features for CD, or histological evidence of ACTH-secreting pituitary adenoma/cell hyperplasia at previous surgery, but negative 1.5 T MRI, patients underwent a 3 T contrast MRI and, in case of negative imaging, to inferior petrosal sinus sampling (IPSS) [8].

According to MRI features, lesions were divided into microadenomas (Ø < 1 cm) and macroadenomas (Ø > 1 cm), classified according to Hardy–Wilson score [9], and MRI-negative cases or undetectable adenomas. Cavernous sinus (CS) invasion was suspected at pre-operative MRI and classified according to Knosp grade [10], and confirmed by direct surgical inspection [11].

Clinical, biochemical, radiological and pathological data were retrospectively collected from patient records dating from the first hospital access to the last follow-up evaluation.

Neurosurgical procedure

The surgical technique had already been reported [11–15]. Briefly, surgery was performed under general anesthesia with orotracheal intubation with the patient placed in a semi-sitting position, using rod lens endoscopes (0° and 30° scopes; Hopkins II model, Ø 4 mm, length 18 cm; Karl Storz Endoscopy America, Inc., Culver City, CA) with a high-definition camera. Surgical approach was patient-tailed based on tumor extension. Direct mid-line transsphenoidal approach to the sella was sufficient to remove the great majority of sellar tumors. Extended ethmoido-pterygospheno- or transplanum/transstuberculum approaches were reserved to adenomas involving the lateral or antero-inferior compartment of cavernous sinus, ectopic stalk lesions or to those with a sub-frontal extension or dumbbell shape, respectively [15]. Tumor was preferentially dissected from the surrounding structures using both hands, as with the standard microscopic technique. Whenever possible, the pseudo-capsule was removed, as suggested by Oldfield et al. [16] to increase the chance of cure, despite the potentially increased risk of complications. At the end of tumor removal, a careful watching of the surgical field, using also the angled scope, together with the inspection of the medial wall of the CS, was performed to detect possible tumor remnants or pit-hole tumor invasion. Finally, a cottonoid was twisted inside the surgical cavity to clear the surgical cavity [11–15].
Watertight plastic repair was performed in case of cerebrospinal fluid (CSF) leakage using multilayer technique. External spinal drainage was not adopted to reduce the risk of tense pneumocephalus. In the absence of complications, patients were immediately awakened after surgery, resumed oral feeding on the same day, were mobilized in the first 24 h, and discharged after 3 days.

**Histological evaluation**

All slides were reviewed by an expert pituitary pathologist (S.A.). Histochemical stains included periodic acid Schiff (PAS) and Gordon–Sweet silver stain for reticulin, followed by immunohistochemistry for pituitary transcription factor-1 (Pit-1), steroidogenic Factor-1 (SF-1) and estrogen receptor alpha (ER), adrenocorticotropic hormone (ACTH), growth hormone (GH), prolactin (PRL), beta-thyrotropin (βTSH), beta-folliculotropin (βFSH), beta-luteotropin (β-luteinizing hormone; βLH), and cytokeratin CAM 5.2 [17]. Tumor invasion and proliferation were defined as ≥ 2/10 mitosis high-power fields (HPF; 0.30 mm², 400X magnification), Ki-67 ≥ 3% and p53 expression > 10 strongly positive nuclei/10 HPF, and the latest evaluated on cells located in the areas with the highest nuclear labeling or ‘hotspots’ [17].

**Post-operative evaluation**

Potential complications occurring intra- or post-operatively were reported to determine surgical morbidity rate. According to international guidelines, 8 a.m. cortisol levels were assessed at post-operative days 1 and 2 and early disease remission was defined for values < 5 μg/dl [7]. Hydrocortisone replacement therapy was started only in this circumstance and/or in case of manifestations suggestive of adrenal crisis. Cortisol basal levels were re-checked at 1-, 3-, 6- and 12-month follow-up, then annually, and anticipated in case of manifestations suggestive for hypocortisolism. At follow-up, cortisol levels < 2 μg/dl was used as cut-off to define CD remission. Low-dose ACTH test was performed in case of cortisol levels falling in the ‘gray zone’ pre- and at follow-ups performed from 3 months after surgery [7]. Screening for cortisol hypersecretion was performed in case of manifestations suspicious for disease recurrence [2, 7]. Following international guidelines for the assessment and management of hypopituitarism [18], all patients underwent basal evaluations for the other axis; dynamic tests were performed for somatotroph axis post-operatively after at least 3-month follow-up only in patients with negative MRI for tumor residue or, in whom replacement treatment could be considered.

Patients underwent surgical and neurological evaluations at 1-month follow-up; surgical, neurological, ophthalmological, and MRI evaluations at 3-, 6- and 12-month follow-up, then annually. Controls were anticipated in case of manifestations suspicious for mass effect secondary to tumor remnant growth [2, 7].

The study was approved by an inter-hospital Ethical Committee of Bologna City (Protocol No. CE17143, February 2018). All patients gave written informed consent after detailed explanation of the study purpose and procedures.

**Statistical analysis**

Descriptive data are presented as median [quartiles] when non-normally distributed, and as mean ± SD when normally distributed. Kolmogorov–Smirnov test was used to test the parameter distribution. Correlations were assessed using Pearson’s or Spearman’s method for normally or non-normally distributed data, respectively. Chi-square test (Fisher’s exact test for small numbers) was used for comparisons of categorical variables. Univariate regression logistic models, specific for each variable, were initially created to evaluate factors potentially affecting CD remission. Subsequently, a stepwise backward regression analysis was performed to select those variables that mostly influenced outcomes. Significance threshold was fixed at 0.2. Finally, multivariate regression analyses, including these variables, were performed. A p value < 0.05 was considered statistically significant. Statistical analysis was performed using STATA—Statistical software, Version 13—StataCorp LP. College Station, Texas.

**Results**

One hundred fifty-five patients with CD were treated surgically via EEA at our Center. Four were lost at follow-up, while 151 (107 F) were included in the study, for a total of 170 surgical procedures. Mean follow-up was 92.3 ± 12.0 months (median 81.1 yr; range 12–237.4; F 88.7 ± 12.5; M 107.7 ± 27.1) (Table 1).

**Pre-operative evaluation**

Mean age at first surgery performed at our Center was 41.1 ± 16.6 years (range 14–76; M 38.1 ± 18.0; F 42.3 ± 15.8). One hundred thirty-four patients (88.7%; 95 F) were naïve for surgery; 17 (11.3%; 12 F) had been operated once (8 by micro-trans-sphenoidal approach, 3 by EEA and 2 by craniotomy), while 4 had undergone multiple surgeries using different approaches; 17 (11.2%) had received medical therapy (Table 1; Fig. 1). Thirty patients (19.8%) presented with hypopituitarism, 9 (6%) with visual disturbances, and 6 (4%) with ophthalmoplegia (Table 1).

Pituitary adenoma was identified by pre-operative MRI in 115 patients (76.2%; 1.5 T MRI identified 113 adenomas, 35
macros and 78 micros; 9 patients with undetectable adenomas underwent 3 T MRI, available from the most recent years only, demonstrating a micro-adenoma in 2 patients). Eighty (5.3%; 60 F) were microadenomas, 2 of which were ectopic, one located in the cavernous sinus (CS) without connection to the gland, the other in the pituitary stalk. Thirty-five (23.2%; 22 F) were macroadenomas; 6 presented CS invasion (Knosp score ≥ 3) (Table 1).

Surgical approach and histological findings

Standard midline transsphenoidal approach was performed in 167 cases (98.2%). Two macroadenomas (1.2%) extended to the antero-inferior and lateral compartments of the CS required ethmoido-pterygo-sphenoidal approach. The microadenoma located in the pituitary stalk was removed through supra-diaphragmatic approach.

The presence of an ACTH-secreting adenoma was confirmed in 82.4% of the cases, although the chance varied according to tumor detection at pre-operative MRI, tumor dimensions and number of surgeries (Table 2). Sixteen patients with MRI-undetectable adenoma were positive at histological examination. Based on surgical reports, adenoma was detected in 9 patients with negative pre-operative MRI and negative histology; the reliability of surgical information is supported by the fact that all these patients were cured by surgery only.

Surgical complications consisted in one case of epistaxis (0.6%) that occurred on the day of surgery and treated with nasal packing, and one case of CSF leakage that occurred 2 days after surgery and was treated with endoscopic endonasal plastic repair, without long-term sequelae. Medical complications included 3 cases (1.8%) of pneumonia, 1 (0.6%) of myocardial infarction and 2 (1.2%) of pulmonary embolisms, for which patients received appropriate treatment in other Hospital Units and were discharged after complete recovery.

Early surgical and long-term outcome

Overall, gross tumor removal was achieved in 137 cases (90.8%). Post-surgery remission rate was 88.1%. The best results were achieved in microadenomas (76/80; 95%), followed by macro- (29/35; 82.6%) and MRI-undetectable adenomas (28/36; 77.8%) (Table 3; Fig. 1). Disease persisted in 18 (11.9%) patients, 6 with a macro-, 4 with a micro- and 8 with MRI-undetectable adenoma. Eleven patients were re-operated via EEA, 10 at our center; 8 patients underwent radiation therapy, 5 medical therapy, and 7 bilateral adrenalectomy. Twenty-five (20 F; 6 with micro-, 11 with micro- and 8 with MRI-undetectable adenoma) out of 137 (18.2%) patients who had achieved remission after the first surgery performed at our center had disease recurrence, after a mean of 5 years (range 1–16; median 4.8; mean age at...

Table 1 Main demographics, clinical and radiological features, and previous treatments at the time of first surgery performed at our Center

|                      | Total (N = 151) | Males (N = 44) | Females (N = 107) |
|----------------------|----------------|---------------|------------------|
| Age at diagnosis (mean ± SD; range) | 39.7 ± 2.7 (14–79) | 35.2 ± 5.5 (14–79) | 41.8 ± 3.1 (14–79) |
| Age at surgery (mean ± SD; range) | 41.1 ± 16.6 (14–76) | 38.1 ± 18.0 (14–76) | 42.3 ± 15.8 (14–76) |
| MRI features         |                |               |                  |
| Macroadenoma (Ø > 1 cm) (N; %) | 35 (23.2) | 13 (29.5) | 22 (20.6) |
| Hardy ≥ 3 (N; %)     | 5 (0.33) | 5 (11.4) | 0 (0) |
| Wilson E (N; %)      | 12 (7.9) | 4 (9.0) | 8 (7.5) |
| Knosp ≥ 3 (N; %)     | 6 (0.4) | 4 (9.0) | 2 (1.9) |
| Microadenoma (Ø < 1 cm) (N; %) | 80 (53.0) | 20 (45.5) | 60 (56.1) |
| Intrasellar (N; %)   | 78 (51.7) | 18 (41.0) | 60 (56.1) |
| Ectopic (N; %)       | 2 (1.3) | 2 (4.5) | 0 (0) |
| Undetectable adenoma (N; %) | 36 (23.8) | 11 (25) | 25 (23.3) |
| Previous medical therapy (N; %) | 18 (11.9) | 6 (13.6) | 12 (11.2) |
| Previous surgery (N; %) | 17 (11.3) | 5 (11.4) | 12 (11.2) |
| Endocrinological alterations |                |               |                  |
| Partial hypopituitarism (N; %) | 28 (18.5) | 11 (25) | 17 (15.8) |
| Panhypopituitarism (N; %) | 2 (1.3) | 1 (2.3) | 1 (0.1) |
| Visual alterations    |                |               |                  |
| Bitemporal hemianopia (N; %) | 6 (4%) | 2 (4.5) | 4 (0.4) |
| Bitemporal quadrantanopia (> 2 quadrants) (N; %) | 1 (0.7) | 1 (2.3) | 0 (0) |
| Neurological alterations |                |               |                  |
| Ophthalmoplegia (III cranial nerve palsy) (N; %) | 6 (4) | 3 (6.8) | 3 (2.8) |

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diagnosis: 32.4 ± 4.1 years; mean age at disease recurrence: 37.2 ± 0.4 years). In 5 cases (3 macro- and 2 microadenomas) the disease involved the cavernous sinus. Twelve of these patients were re-operated (8 at our center), 10 underwent radiation therapy, 4 medical therapy, and 6 bilateral adrenalectomy (Fig. 1) (Table 4).

Eighteen patients (11.9%) developed pituitary deficiency, that was partial in 16 cases and complete in 2. In particular, 9 patients developed GH deficiency, 11 hypogonadotroph hypogonadism, and 14 central hypothyroidism. Twenty-seven patients (18%) developed central DI, which was permanent in 6 (4%) and transient in 21 (13.9%) cases (Table 5).
No ophthalmological complication was observed. On the contrary, all the 7 patients with pre-operative bitemporal hemi-/quadrantanopia improved after surgery, six (86%) completely and one (14.2%) partially; ophthalmoplegia resolved in 4 (66.7%), and improved in 2 (33.3%) of the 6 patients with pre-operative alterations (Table 5).

At last follow-up, 137 (90.7%) patients were biochemically cured, 110 (72.8%; 71.4% of macro- and 83.8% of microadenomas, 66.7% of MRI-negative cases) after single/multiple surgeries, 21 (13.95) after multiple treatments (i.e., radiation therapy: 9; radiation and medical therapy: 5; bilateral adrenalectomy: 7). Disease was controlled by medical treatment in 9 patients (6%). Four (2.6%) patients with uncontrolled disease were not treated because of poor general conditions or personal choice. One (0.7%) patient died of pituitary carcinoma (Table 4; Fig. 1).

Variables of interest (i.e., age at surgery, age, adenoma visible at pre-operative MRI, cavernous sinus invasion, adenoma size, the presence of visual/neurological/endocrinological alterations at diagnosis) defined by univariate regression logistic analysis were included in the stepwise analysis. Adenoma visible at pre-operative MRI, adenoma size, CS invasion, and visual/neurological/endocrinological alterations at diagnosis remained significant.

According to multivariate analysis, chance of early postsurgical and long-term remission was higher for adenomas visible at pre-operative MRI (OR: 3; p = 0.03). Moreover,

### Table 3
 Outcome of the first surgery performed at our Center, according to radiological features

| Total (N=151) | Macroadenoma (N=35) | Microadenoma (N=80) | MRI negative (N=36) |
|---------------|----------------------|----------------------|---------------------|
| Remission (N; %) | 133 (88.1) | 29 (82.6) | 76 (95) | 28 (77.8) |
| Persistence (N; %) | 18 (11.9) | 6 (17.4) | 4 (5) | 8 (22.2) |

### Table 4
 Outcome at last follow-up (considering all types of treatment), according to pre-operative MRI features

| Microadenoma (N=80) | Macroadenoma (N=35) | MRI negative (N=36) | Total (N, %) |
|---------------------|----------------------|---------------------|--------------|
| Remission after surgery (N, %) | 67 (83.8) | 25 (71.4) | 24 (66.7) | 116 (76.8) |
| Single (N, %) | 65 (81.2) | 23 (65.7) | 20 (55.6) | 108 (71.5) |
| Multiple (N, %) | 2 (2.3) | 2 (5.7) | 4 (11.1) | 8 (5.3) |
| Remission after surgery and complementary treatments (N, %) | 6 (7.5) | 5 (14.3) | 10 (27.8) | 21 (13.9) |
| Radiation therapy (N, %) | 3 (3.8) | 3 (8.6) | 3 (8.3) | 9 (6%) |
| Bilateral adrenalectomy (N, %) | 2 (2.3) | 1 (2.9) | 4 (11.2) | 7 (4.6) |
| Combined treatments (N, %) | 1 (1.3) | 1 (2.9) | 3 (8.3) | 5 (3.3) |
| Disease control with medical therapy (N, %) | 4 (5) | 3 (8.6) | 2 (5.6) | 9 (6) |
| Uncontrolled disease (N, %) | 3 (3.8) | 1 (2.9) | 0 (0) | 4 (2.6) |
| Death for pituitary carcinoma (N, %) | 0 (0) | 1 (2.9) | 0 (0) | 1 (0.7) |

### Table 5
 Impact of surgical treatment on pituitary function, visual and neurological manifestations

| Pre-surgery alterations | Normalization/ improvement\(^a\) | Stability\(^b\) | New onset\(^b\) |
|-------------------------|-------------------------------|----------------|----------------|
| Pituitary function      |                               |                |                |
| Partial hypopituitarism (N; %) | 13 (46.4) | 15 (53.6) | 16 (10.6) |
| Panhypopituitarism (N; %) | 2 (100) | 0 (0) | 2 (1.3) |
| Permanent diabetes insipidus (N; %) | 0 (0) | 0 (0) | 6 (4.0) |
| Transient diabetes insipidus (N; %) | 0 (0) | 0 (0) | 21 (13.9) |
| Visual                  |                               |                |                |
| Bitemporal hemianopia (N; %) | 6 (86) | 0 (0) | 0 (0) |
| Bilateral quadrantanopia (N; %) | 1 (0.6) | 0 (0) | 0 (0) |
| Neurological            |                               |                |                |
| Ophthalmoplegia/III c.n. palsy (N; %) | 6 (100) | 0 (0) | 0 (0) |

\(^a\)Based on the number of patients presenting with the specific alteration pre-operatively

\(^b\)Based on the total of 151 patients operated at our Center
patients with microadenomas had a 75% higher chance to be cured than those with macroadenomas (OR: 0.25; \( p = 0.045 \)). On the contrary, CS invasion increased the risk of disease persistence after surgery in both patients treated at our (OR: 3.35; \( p = 0.002 \)) and other Centers (OR: 4.41; \( p = 0.005 \)). Surgery repetition increased the risk of hypopituitarism (OR: 2.32; \( p = 0.03 \)) that doubled at each intervention.

The assessment of cortisol levels at 1–2 days after surgery was available for 89 patients. In 64 (71.9%) of them—8 with macro-, 42 with micro- and 14 with MRI-undetectable adenoma—cortisol levels dropped under 5 μg/dl. Sixty-one (95.3%) had long-term disease remission, 56 (87.5%) after a single surgery, and 5 (8%) after two surgeries, while 3 (5%) had disease persistence. Of the 25 patients without early cortisol level drop, 12 (48%) had disease remission after a single surgery and 6 (24%) after two surgeries, for a total of 18 (72%) patients with long-term disease remission. Cortisol drop was associated with higher chance of early (i.e., after first surgery) \(( p = 0.0002 \)) and long-term (last follow-up) \(( p = 0.004 \)) disease remission.

The chance of cure with surgery only in patients naïve for surgery who underwent the first intervention at our Center tended was similar in microadenomas while it improved in macroadenomas, although it did not reach statistical significance \(( p = 0.07 \)) possibly because of the low number of observations.

No other significant association between pre-operative characteristic and outcome was detected. Results obtained in the first and second decades of surgical activity were similar (data not shown).

**Discussion**

Our data, deriving from one of the largest and homogenous series of patient with CD due to ACTH-secreting pituitary adenoma, treated in a tertiary care referral Center over a 20-year period and with a long follow-up, demonstrated the efficacy and safety of selective adenomectomy performed by EEA.

In the last decades, EEA has progressively demonstrated its pivotal role in the treatment of skull base tumors, including pituitary adenomas [18–20]. As demonstrated in a previous study by our group, EEA allows similar cure rate with respect to standard microscopic transsphenoidal approach for microadenomas or sellar macroadenomas, with the advantage of a large panoramic view of the surgical field, which is particularly useful to detect possible tumor remnants [17, 21, 22]. Moreover, it allows the surgeon to tailor the surgical approach on each case, following tumor extension on the supra- or parasellar region [12]. To date, surgical outcome in ACTH-secreting adenomas remains highly variable among series adopting different surgical approaches, but also among studies performed via EEA [2, 23]. Tumor pre- and intra-operative detection, dimensions, localization and invasion, as well as pre-operative ACTH and urinary cortisol levels, histological confirmation, early post-surgery drop of cortisol levels, and surgeon abilities have been suggested as outcome predictors [2, 23]. However, despite initial clinical and biological remission, disease recurrence is reported in 2–35% of the patients, depending on definition criteria and follow-up duration, with a risk that appears to increase with time [15, 24].

Literature review of the studies focusing on surgical outcome in CD patients treated via EEA [4, 13, 23, 25–32] was performed. Main study features are tabulated (Supplementary Table 1) to facilitate the comparison of study results. Overall, age at first surgery, gender, and tumor size distribution were similar between our and other studies. Remission rate after first surgery was in line with the other studies, confirming the indication of EEA as first-line treatment in CD and its reproducibility. Finally, we confirmed the higher chance of remission associated with tumor detection at pre-operative MRI [4, 23, 29, 30] and adenoma size <1 cm [4, 23, 26, 28, 30]. This could depend on a more targeted and complete adenoidectomy, sparing a more aggressive pituitary manipulation to identify the lesion or enlarged resection, up to hemihypophysectomy, thus reducing the risk of post-operative pituitary dysfunction [14, 26]. Consequently, and as for other series, disease recurrence typically occurred in non-visible lesions some years after surgical remission.

The presence of ACTH-secreting adenoma cells was confirmed in the great majority of the cases, being the chance was higher in macro- than in microadenomas and MRI-negative cases, likely because of the higher chance of collecting sufficient tissue sample. Moreover, surgical remission in case of visible adenoma but negative histology was suspicious for accidental aspiration of the tiny pathological tissue portions. To improve the chance of successful tissue collection, we have proposed to connect a filter to the suction tube during EEA [14].

In agreement with the previous studies [25, 30], cortisol levels drop under 5 μg/dl on post-operative day 1 or 2 was a strong predictor of post-surgery and long-term remission. Differently from Shin et al. 2017 [31], we did not identify any correlation between surgical outcome and gender nor age at first intervention.

Our study also supported the validity of EEA for disease recurrence. At the same time, if compared to first surgery, the chance of disease remission was significantly lower and the risk of hypopituitarism higher, underlining the importance of referring patients to Pituitary Centers since the diagnosis [31, 33]. Finally, we confirmed the safety of EEA when performed by experienced surgeons. Indeed, surgical and medical complications were unusual and reversible with appropriate treatment. CSF leakage is the most
common intra- and post-operative complication [4, 13, 23, 25–32, 34] and requires prompt repair by dural plastic and antibiotic treatment to avoid meningitis due to contamination from nasal cavities. In our experience, the collaboration with ENT surgeons expert in EEA prevented other complications to the upper airways (i.e., nasal dysventilation, sphenoid mucocele or sphenopalatine artery hemorrhage) often reported in patients undergoing transsphenoidal surgery [5, 13, 29].

Moreover, our study confirmed the cavernous sinus invasion as a negative predictor of surgical cure. At this purpose, we would like to remark that EEA has not only a therapeutic but also diagnostic role. Indeed, Knosp classification is not highly reliable, especially for lower grade tumors, to detect the effective CS invasion that should, therefore, be assessed by direct surgical inspection [11, 13].

Pituitary manipulation was associated with the new onset of hypopituitarism, partial in the majority of the cases, and central diabetes insipidus, typically transient, whose prevalence was in line with the literature [4, 13, 23, 25, 26, 28, 31]. In our experience, repeated surgery increased the risk of hypopituitarism, but not of neurological, visual alterations of other complications, nor was a predictor of negative outcome, as reported by others [24]. On the contrary, residual anterior pituitary function, as well as visual and neurological alterations, resolved or improved after surgery in many cases.

Five patients presented cardiovascular and pulmonary complications that should be attributed to pre-existing comorbidities that make CD patients more vulnerable, than to surgery itself, as previously reported [14]. Different from other studies, we did not detect significant differences in the incidence of medical complication not directly associated with surgery between macro-, micro or non-detectable adenomas [35].

Since CD is a rare condition, difficult to be diagnosed and requiring long-term expert management for the significant impact on patient health and quality of life and for the risk of recurrence, main strengths of the study are the high sample number and homogeneity in terms of surgical approach and team, together with the patient-tailored approach, the multidisciplinary dedicated management, and the long-term follow-up. Main limitation is the retrospective design.

**Conclusions**

Patients with CD should always be managed in Pituitary Centers of excellence with multidisciplinary dedicated team and advanced diagnostic (MRI and histological) techniques to maximize the chances of early disease identification and cure, reduce complications, and, eventually, provide prompt and adequate treatment. EEA ensures high rate of cure with low rate of complications and mortality zero. Therefore, whenever allowed by patient conditions, it should be privileged as first treatment, and also considered for recurrences. At the same time, all patients deserve long-term follow-up since disease can recur after several years from initial remission, independently of tumor and patient features.

**Acknowledgements** We thank Dr. Giorgio Frank for his fundamental clinical and scientific support over the past 20 years. The study received no financial support.

**Funding** The authors declare that the study has received no funding.

**Compliance with ethical standards**

**Conflict of interest** All 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 inter-hospital Ethical Committee of Bologna City (Protocol No. CE17143, February 2018) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** All patients gave written informed consent after detailed explanation of the study purpose and procedures.

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