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ORIGINAL ARTICLE

Determinants of outcome of transsphenoidal surgery for Cushing disease in a single-centre series

A. L. Serban[1,2] · G. Del Sindaco[1,3] · E. Sala[1] · G. Carosi[1,3] · R. Indirli[1,3] · G. Rodari[1,3] · C. Giavoli[1,3] · M. Locatelli[4,5] · G. Carrabba[4] · G. Bertani[4] · G. Marfia[4] · G. Mantovani[1,3] · M. Arosio[1,3] · E. Ferrante[1]

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Abstract

Background First-line therapy of Cushing disease (CD) is transsphenoidal surgery (TSS) aimed to obtain a complete removal of the pituitary adenoma and remission of disease.

Purpose To analyse the surgical outcome of patients with CD who underwent TSS in our Centre.

Methods Retrospective analysis on patients with CD who underwent TSS between 1990 and 2016.

Results We analysed 102 TSS that included: 84 first TSS and 18 second and third TSS. The overall remission rate after surgery was 76.5%, with a significant higher percentage of remitted patients after the first TSS compared to the subsequent TSS (82% vs 50%, $p=0.014$). The remission after the first TSS was significantly higher when performed by a dedicated surgical team (DST) (89.8% vs 71% $p=0.04$) and when the immunohistochemical examination confirmed the adrenocorticotropic adenoma (87% vs 55%, $p=0.04$). Neuroradiological findings influenced the surgical outcome in a non-significant manner. Post-TSS complications were reported in 32 patients, with no significant variation when TSS was performed by DST. In case of reintervention, remission of disease was obtained in 72.7% of microadenoma, while no remitted patients were observed in case of macroadenomas. The DST did not significantly improve the outcome.

Conclusion Cushing disease is characterized by a broad spectrum of neuroradiological presentation. Despite the availability of a DST make the TSS a safe and effective first-line treatment among all these patients, a precise pre-treatment evaluation is needed in order to define the aim of neurosurgery and to schedule the management of recurrent disease.

Keywords Hypercortisolism · Cushing disease · Transsphenoidal surgery · Remission

Introduction

Cushing disease (CD) represents the most frequent cause of endogenous hypercortisolism in adults and is caused by an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma. The prevalence of CD is close to 40 cases per million inhabitants with a female:male ratio of 3:1 [1, 2]. Chronic hypercortisolism is related to many severe complications such as cardiovascular disease, diabetes, osteoporosis and fractures, infections and thromboembolic events, leading to an excess mortality [3, 4]. Clayton and colleagues in a recent multicentre retrospective cohort study showed that patients affected by CD who achieved cure for 10 years still have an increased overall mortality risk, in particular from cardio- and cerebrovascular diseases. Notably, this risk correlates with number of treatments required to achieve the remission of disease, with normalization occurring only in patients cured by pituitary surgery alone [5].

M. Arosio and E. Ferrante are co-last authors.

✉ G. Mantovani
giovanna.mantovani@unimi.it

1 Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Endocrinology Unit, Via Francesco Sforza, 35, Milan 20143, Italy

2 Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy

3 Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy

4 Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Neurosurgery Division, Milan, Italy

5 Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

First-line therapy of CD is transsphenoidal surgery (TSS) aimed to obtain a complete removal of the pituitary adenoma and remission of disease. Previous data show that the remission rate after surgery varies from 42 to 96.6% with a median of 77.9% [6]. The outcome of the surgical intervention may be influenced by several factors such as: the type of neurosurgical method used (microscopic/endoscopic) [7], the tumour localization prior to surgical intervention [8, 9], the size of pituitary adenoma [10], the histological confirmation of ACTH-secreting adenoma [11]. As for other pituitary diseases such as acromegaly, the surgical outcome can be also influenced by the surgical learning curve and, therefore, by the experience of the neurosurgeon [12]. Data on CD confirmed that neurosurgery performed by an experienced pituitary surgeon is related to a better outcome and to fewer side effects such as hypopituitarism [13, 14]. Despite the high prevalence of remission rate after surgery, CD requires lifelong follow-up because about one-third of patients may experience a recurrence during their lifetime [15]. Both recurrence and persistence of the disease after pituitary surgery require additional therapies: surgical reintervention, radiotherapy, medical therapy or bilateral adrenalectomy. As multiple therapies seem to reduce life expectancy of cured CD patients, strategies that aim to increase the success of first-line approach should be adopted.

Aim of this study was to retrospectively analyse the surgical outcome of patients affected by CD who underwent TSS in our Centre between 1990 and 2016 with particular focus on the influence of surgeon's experience on postoperative remission rate.

Materials and methods

We performed a retrospective analysis of all patients affected by CD who underwent a neurosurgical intervention at the Neurosurgery Unit of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan between 1990 and 2016 and with a minimum follow-up of 1 year after surgery.

The diagnosis of CD was based on patients' medical history, characteristic clinical features, laboratory data, magnetic resonance imaging, and histopathological findings, according to the Endocrine Society Guideline and Consensus Statement [1, 16].

All neurosurgical interventions were performed with a TSS approach combined with the microscopic method until 2008 and with the endoscopic method after 2008. After TSS, all patients received a standard therapy with 25 mg of cortisone acetate per day divided in two or three doses. The substitutive therapy was started the day of TSS.

The first endocrinological evaluation was performed 2 months after TSS. All the patients withdrew the cortisone replacement therapy 24 h before the execution of blood tests. Patients were considered in early remission in the presence of adrenal insufficiency or eucortisolism. The diagnosis of AI was based on morning serum cortisol levels < 3 µg/dL or lack of cortisol response to 1 µg/250 µg Synacthen stimulation test, using a cut-off value of 18 µg/dL. In particular, until 1998 adrenal function was studied with a 250 µg Synacthen test. After 1998, after the demonstration at our institution of its precision [17], the 1 µg Synacthen test was adopted as the routine test in patients with pituitary diseases.

Those patients with apparent normal cortisol secretion after surgery were screened for hypercortisolism. Persistence of CD after TSS was defined as elevated UFC levels in at least two samples and/or a positive dexamethasone suppression test (1 mg overnight or 2 mg 48-h dexamethasone suppression test, for both cortisol levels > 1.8 µg/dL denoted a positive test).

Central hypothyroidism was diagnosed in the presence of low free thyroxine level associated with low or normal thyroid-stimulating hormone values. Central hypogonadism in men was defined by low total testosterone levels associated with normal or low gonadotropins (luteinizing hormone, follicle-stimulating hormone) in women of fertile age by clinical findings (amenorrhea or oligomenorrhea) associated with low 17-beta estradiol levels and low or normal gonadotropins and in postmenopausal women by the absence of high follicle-stimulating hormone levels. Growth hormone secretion was evaluated using the following stimulation tests: insulin tolerance test or growth hormone-releasing hormone–arginine test, considering for the insulin tolerance test a cut-off value of 5.1 µg/L and for the growth hormone-releasing hormone–arginine test 4.1 µg/L [18]. Central diabetes insipidus was defined as emission of a high volume (> 40 mL/kg/day) of hypoosmotic urine.

In patients with adrenal insufficiency at 2 months after TSS, a Synacthen stimulation test for the assessment of adrenal function recovery was performed every 6 months for the first 3 years and then once a year. In case of regain of the adrenal function, patients were immediately screened for CD recurrence. If hypercortisolism was excluded, they were further evaluated with the same frequency as patients with AI.

Statistical analysis

We summarized the collected data using mean ± standard deviation for normally distributed continuous variables, median and interquartile range (IQR) for non-Gaussian data and proportion for categorical parameters. The latter were analysed using the χ^2 test or the Fisher exact test if the expected value was < 5. Continuous parameters with normal distribution were compared using the *t* test and non-Gaussian data using the non-parametric test of Mann–Whitney. We assessed the relation between two or more variable through logistic regression in case of binary dependent variable and linear regression in case of continuous dependent variable.

All statistical analyses were performed using SPSS, version 24 (IBM, Cary, NC, USA).

Results

In the present study, we analysed 102 transsphenoidal surgical interventions (TSS) performed in 87 patients. In 84 out of 102 TSS, neurosurgery represented the first procedure, in 17 the second procedure and in 1 the third. The overall remission rate after surgery was 76.5%, with a significant higher percentage of cured patients after the first TSS compared to the subsequent surgical interventions (82% vs 50%, $p=0.014$). Then, we decided to analyse separately the two groups of patients.

First TSS in patients with CD

Early outcome

The general characteristics of 84 patients with CD who underwent TSS as first procedure are summarized in Table 1. The female/male ratio was 4:1 (67 females and 17 males), with a mean age at diagnosis of 39.4 ± 14.8 years. MRI study showed a microadenoma in 60 cases (71.4%) and a macroadenoma in 9 (10.7%), while a negative imaging was recorded in 15 patients (18.1%). Of 75 patients with microadenomas and negative imaging, IPSS was executed and confirmed the diagnosis in 13 patients, in the remaining cases the CD diagnosis was confirmed by the immunohistochemical analysis and the occurrence of adrenal insufficiency after TNS.

The early remission rate after the first TSS was 82% (69/84).

The proportion of cured patients significantly increased after 2004, when a dedicated and experienced surgical team performed the TSS (89.8% (44/49) vs 71% (25/35) $p=0.04$). The positive impact of the dedicated surgical team (DST) on the remission rate was statistically confirmed with the logistic regression study (OR 3.56, 95% CI 1.1–11, $p=0.037$). Furthermore, from 2008 the surgical method changed from microscopic to endoscopic approach. However, the new approach did not lead to a significant improvement of the remission rate (90.7% (39/43) with endoscopic vs 80% (4/5) with microscopic approach, $p=0.43$).

Neuroradiological findings influenced the surgical outcome in a non-significant manner: in particular, the remission rate was of 83% (41/49) in case of microadenomas, 77.7% (7/9) for macroadenomas and 84.6% when no pituitary tumour was visible at MRI (Table 1). The success rate in macroadenoma was related to parasellar extensions of macroadenomas. Therefore, according to the Knosp classification in the remitted group 4 patients presented a 0 grade macroadenomas, 1st grade 2 patients and 1 patient 2nd grade. On the other side, the 2 patients with persistent disease had Knosp 4th grade macroadenomas.

In almost all cases (81/84, 96.4%) the neurosurgeon performed a selective adenomectomy, while total and subtotal hypophysectomy were carried out in two and one case, respectively. The immunohistochemical analysis was available in 65 patients and confirmed the diagnosis of ACTH-secreting adenoma in 56 cases (86.1%). The immunohistochemical confirmation of adrenocorticotropic adenoma was positively associated with remission rate (OR 5.6, 95% CI 1.2–26, $p=0.028$). Only two patients had a high proliferation index (Ki67 of 7% and 14%, respectively): the first had persistent CD after TSS, while in the second case, despite adrenal insufficiency after TSS, the disease relapsed after 6 months. The other patients had a Ki67% less than 3%.

Post-TSS complications were reported in 32 patients (38,5%). The most frequent complication was diabetes insipidus (DI) recorded in 21 patients (25%), among which

Table 1 General characteristics of patients who underwent first TSS

	All cases ($n=84$)	Early remission ($n=69$)	Persistence of CD ($n=15$)	p value
Age at TNS (years) (mean ± SD)	40.4 ± 15.6	41 ± 16.1	37 ± 12	0.35
Female (n, %)	67 (80%)	53 (76.8%)	14 (93.3%)	0.28
BMI (kg/m^2) (mean ± SD)	27.6 ± 6	27 ± 6.2	26 ± 6	0.48
Biochemical features				
ACTH (pg/ml) (mean ± SD)	57.4 ± 28	55.6 ± 27	64 ± 31.7	0.31
Mean baseline cortisol (μg/dL) (mean ± SD)	25 ± 9.8	24.7 ± 9.6	26 ± 10.8	0.62
Median relative UFC (median, IQR)	2.3 (1.3–4.3)	2.2 (1.3–4.3)	3.1 (1.6–4.4)	0.44
Radiological features				
Microadenoma (n, %)	60 (71.4%)	49 (71%)	11 (73.3%)	0.83
Macroadenoma (n, %)	9 (10.7%)	7 (10.1%)	2 (13.3%)	0.5
Negative imaging (n, %)	15 (18.1%)	13 (18.8%)	2 (13.3%)	0.6

13 cases had transient DI and 8 permanent DI (9%). Diagnosis of diabetes insipidus was more frequent in patients with persistent disease after TSS with respect to those cured after surgery (53.8% (7/13) vs 14.54% (8/55), $p=0.041$). The second most common complication was cerebrospinal fluid leak (7 patients, 8.3%) followed by hyponatremia (3 cases, 3.5%) and pulmonary embolism (2 cases, 2.3%). The rate of TSS complications did not significantly changed when performed by DST (12/35 vs 20/49 $p=0.54$).

At the first endocrinological evaluation, 2 months after TSS, 65/69 (94%) of remitted patients had adrenal insufficiency, while the remaining four patients had a normal cortisol secretion.

Overall, 28/84 patients (33.1%) presented at least one pituitary deficit besides hypoadrenalism and 9 patients (10.7%) had panhypopituitarism (after excluding two cases of total hypophysectomy). Among anterior pituitary deficits, growth hormone deficiency was diagnosed in 21 cases (25%), central hypothyroidism in 18 (21.4%) and central hypogonadism in 17 patients (20.2%).

Late outcome

All the 15 patients with persistent hypercortisolism after first TSS needed further pharmacological, surgical or radiological intervention. The sequence of additional therapies executed in order to achieve disease control is outlined in Fig. 1.

All 69 patients considered to be in early remission were monitored for at least 1 year. The mean follow-up duration in this subgroup of patients was 5.6 ± 3.8 years. During follow-up, 12 patients (17.4%) showed a recurrence of CD. Two out of four subjects (50%) with normal cortisol secretion at first endocrinological evaluation presented a recurrence of disease. The median time between TSS and recurrence was 10.5 months, with a range of 6–84 months. These results are summarized in Table 2.

Subsequent TSS in CD patients with persistence of recurrence of disease

Early outcome

The general characteristics of patients that underwent a second or a third TSS are described in Table 3. The overall remission rate was 50% (9/18). Neurosurgical reintervention was scheduled in 13 patients with persistent disease and in 5 patients with CD recurrence. Four out of 5 patients with relapsed CD (80%) achieved early remission with respect to 5 of 13 (38.4%) cases with persistent CD, however the remission rate observed in the two groups was not statistically different ($p=0.29$). In these cases, the presence of the DST did not have a significant impact on the surgical outcome, with remission rate of 55.5% (5/9) after 2004 versus 44.4% (4/9) before 2004 ($p=1$). Considering all 102 TSS the influence of DST remain significative (see Fig. 2).

The proportion of remitted patients after the second and third TSS was significantly affected by the radiological characteristics of pituitary adenoma: in fact, the best outcome was seen in patients with visible microadenomas (8/11,

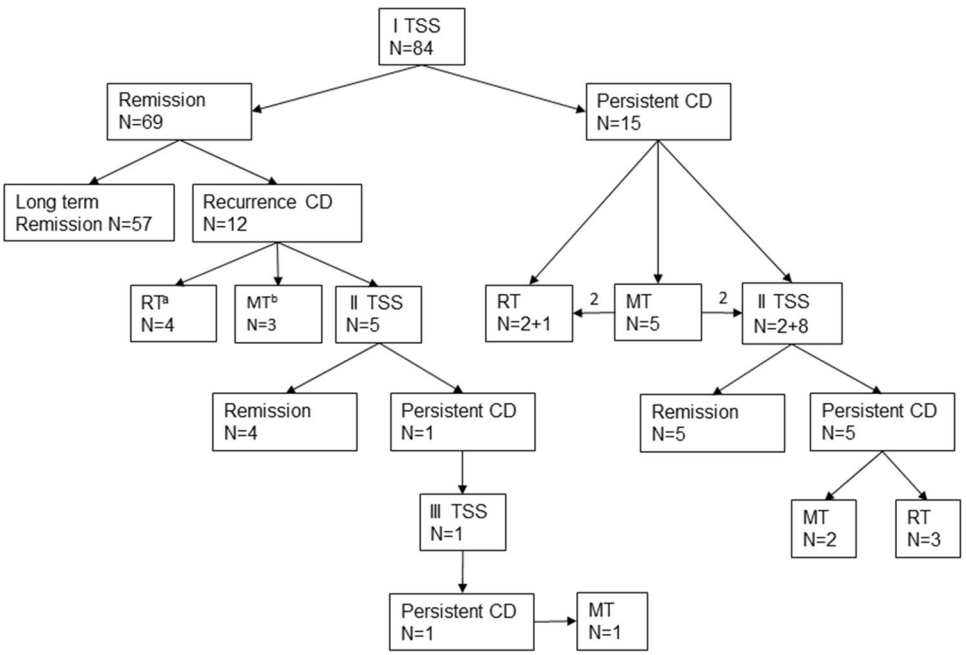

Fig. 1 Outcome of CD patients after first TSS and additional therapies needed to achieve CD remission

Table 2 General characteristics of patients in remission after first TSS

	Early remission ($n=69$)	Persistent remission ($n=57$)	Recurrence of CD ($n=12$)	p value
General characteristics				
Age at TNS (years) (mean ± SD)	41 ± 16.1	41.3 ± 15.3	40.3 ± 20.6	0.35
Female (n, %)	53 (76.8%)	44 (77.2)	9 (75%)	0.87
BMI (kg/m^2) (mean ± SD)	27 ± 6.2	27 ± 3.6	25 ± 3.6	0.2
Biochemical features				
ACTH (pg/ml) (mean ± SD)	55.6 ± 27	54.8 ± 28.3	59.5 ± 20.2	0.31
Mean baseline cortisol (μg/dL) (mean ± SD)	24.7 ± 9.6	21.3 ± 9	26.4 ± 12.1	0.62
Median relative UFC (median, IQR)	2.2 (1.3–4.3)	2.1 (1.2–4.1)	3.3 (1.6–5.3)	0.44
Radiological features				
Microadenoma (n, %)	49 (71%)	41 (72%)	8 (66.7)	0.73
Macroadenoma (n, %)	7 (10.1%)	5 (8.7%)	2 (16.6%)	0.6
Negative imaging (n, %)	13 (18.8%)	11 (19.3)	2 (16.6)	0.9

Table 3 General characteristics of patients who underwent second and third TSS

	All cases (18)	Cured (9)	Persistent CD (9)	p
General characteristics				
Age at TNS (years) (mean ± SD)	36.3 ± 11.3	38.5 ± 13	34.1 ± 9.7	0.42
Female (n, %)	17 (94.4%)	9 (100%)	8 (88%)	1
BMI (kg/m^2) (mean ± SD)	28 ± 5	30 ± 5.7	26 ± 3.4	0.1
Biochemical features				
ACTH (pg/ml) (mean ± SD)	48 (41–78)	41 (38–46.5)	71 (43–89)	0.065
Mean baseline cortisol (μg/dL) (mean ± SD)	25 ± 10.6	20 ± 8.3	28.1 ± 11.2	0.19
Median relative UFC (median, IQR)	1.6 (1–2.1)	1.44 (1.13–2.6)	1.8 (1.14–2)	1
Radiological features				
Microadenoma (n, %)	11 (61.1)	8 (88%)	3 (33%)	**0.05**
Macroadenoma (n, %)	4 (22%)	0	4 (44%)	0.08
Negative imaging (n, %)	3 (16.6%)	1 (22%)	2 (11.1%)	1

P value in bold is statistically significant

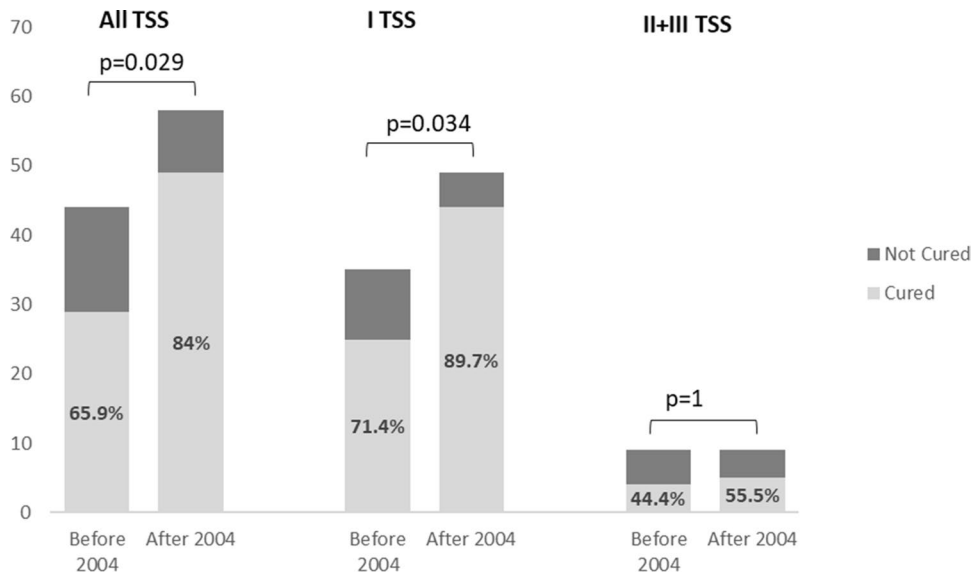

Fig. 2 The remission rates of TSS were higher after 2004, when surgery was performed by a dedicated surgical team (DST)

72.7%), while in case of negative imaging a lower remission rate was observed (1/3, 33%, $p=0.05$). No CD remission was obtained among patients with macroadenomas (0/4). The TSS was limited to adenomectomy in 11 cases. Otherwise, 1 patient underwent subtotal hypophysectomy and 4 patients total hypophysectomy.

Post-TSS complications were reported in eight cases (42%). Similarly to the first TSS group the most frequent complication was diabetes insipidus (6/18, 33.3%), with only one case of cerebrospinal fluid leak and one postoperative hematoma. The immunohistochemical analysis was available in 14 cases. All cases with negative immunostaining for ACTH showed a persistent active disease at the first evaluation after TSS. On the contrary, 8 out of 11 ACTH positive patients (72.7%) showed an early disease remission, although this difference did not reach a statistical significance (0/3 vs 8/11, $p=0.055$).

Late outcome

Among nine patients in early remission after second TSS, only one patient recurred during the follow-up which was shorter with respect to first TSS (median 2 years, IQR 1–3 years). The CD relapsed 21 months after surgical intervention.

The nine patients with active CD after the second TSS were further treated as follows: one patient underwent a third TNS, two patients conventional radiotherapy, two patients gamma knife radiosurgery, three patients pharmacological therapy. One patient was lost at follow-up.

Discussion

Transsphenoidal surgery (TSS) is the well-established first choice treatment of CD, aiming to obtain a surgical cure of this life-threatening condition.

As main result, our retrospective study show that neurosurgical intervention is a safe and effective option for these patients, with a positive impact of dedicated team in term of remission rate: in fact, the early remission rate after the first TSS observed in the present study was of 82%, which is within the range of 42–96.6% and relatively close to the median of 77.9%, data presented in the last review that assessed the outcomes of microscopic TSS in patients with Cushing disease [6]. This broad range of remission rate is probably related to the significant variety of assessments and methods used to define the TSS outcome, since a universal definition of postoperative CD remission, as far as persistence and recurrence of disease is now lacking. In our patients, we consider the first extensive endocrinological evaluation performed after 2 months from TSS to define the outcome of the surgery.

Moreover, the proportion of remitted cases after the first TSS significantly improved after the availability of an experienced, dedicated surgical team. This observation is in line with a previous study that analysed TSS outcome over three decades in acromegalic patients operated in the same neurosurgery unit [12]. Although the presence of a dedicated team is clearly recommended in the current guidelines [10], few specific data about CD, a condition characterized by the presence of a high percentage of microadenomas or negative imaging, are available so far. The positive impact of DST in CD was previously described by Rees and colleagues in a relatively strict cohort of 54 patients [13]. More recently, Brichard and colleagues reported a surgical remission rate of 100% in CD patients with negative MRI after 2011, when a better surgeon expertise was achieved [14].

On the other side, in our cohort of patients the replacement of the microscopic approach with the endoscopic one did not produce a significant effect on the efficacy of the TSS, observation that supports our previous data and the conclusions of a recent meta-analysis comparing the two neurosurgical approaches [7, 19]. Moreover, the same meta-analysis also affirmed that the endoscopic approach probably has better results for macroadenomas. Unfortunately, we were not able to verify this hypothesis in our study because of the small number of CD patient affected by macroadenoma.

Previous publications stated that some biochemical, radiological and histological features could impact on the TSS outcome. The presence of a macroadenoma is usually associated with a worse surgical outcome ratio [20–25], although in a recent series the remission rate in macroadenoma was similar to that obtained in visible microadenomas [14]. Similarly, a study conducted by Ming Feng and colleagues that included 22 macroadenomas showed that there was no significant difference in remission rate between microadenomas and macroadenomas [26]. However, a review that analysed 87 studies enrolling 8113 patients with CD treated with TSS showed that higher remission rates were observed with smaller size adenoma [27].

In the present study, the remission rate after first TSS is lower for macroadenomas with respect to microadenomas or nonvisible adenomas in a non-significant manner, but, again, the low number of macroadenomas (nine patients) did not allow a conclusive observation. On the contrary, in case of neurosurgical reintervention, the patients with macroadenomas had the worst outcome, with no remitted case. This could be explained by the fact that the invasiveness of neighbouring structures from macroadenomas that necessitate subsequent TSS make the disease hardly resectable or even unresectable. This result is quite similar to previous observations that found a direct correlation between the efficacy of first and second surgery exist [14, 28] and confirms that the choice of second-line treatment

should be weighted also on the basis of neuroradiological presentation of CD at baseline.

In our study 18.1% of patients were negative at MRI examination, a percentage in line with those previously reported in large series [29–32]. As for the negative imaging, its detrimental impact on the efficiency of TSS remains controversial. Several studies showed that remission rate is significantly lower in these patients [8, 26, 30, 33] ranging from 45 to 76%, while our study and other publications [25, 34] demonstrated that the proportions of remitted patients with visible adenoma and negative imaging did not differ significantly. Since our neurosurgical approach was to perform a selective adenomectomy, this result can be at least in part related to neurosurgeon's experience, as recently suggested [14]. On the other hand, the positive correlation between the histopathological confirmation of ACTH-secreting adenoma and the remission rate is in line with previous studies [9, 11, 33].

Regarding the surgical complications, diabetes insipidus is one of the most common conditions that occur immediately after TSS, with a prevalence that generally ranges between 20 and 30% [7, 9, 14, 34, 35]. In our study, DI occurred in 25% of patients, but with a significant higher proportion (53.8%) in patients with persistent disease. To our knowledge, this observation has never been stated before. In a recent study focused on the recurrence of CD, we observed that the post-TSS DI occurred more often in patients that relapsed during follow-up (30% vs 7.8%, $p = 0.08$). The underlying physiopathological mechanisms are unclear, but these observations need to be confirmed by studies with a larger number of patients.

In our series panhypopituitarism after TSS seems to be more frequent (10.7%) with respect to other studies published on this topic that reported rates of 1.4% and 6.5% [34, 36]. However, there are few studies that report the frequency of panhypopituitarism after TSS in patients affected by CS. As known, Cushing disease has a high morbidity and mortality and the alternative treatments to TSS (pharmacological therapy, radiotherapy) are less efficient compared to other pituitary tumours. Furthermore, in some cases Cushing disease may have a multifocal localization. For all these reasons it cannot be excluded that neurosurgeons tended to be more aggressive with respect to other pituitary tumours, even if the purpose was to perform a selective adenomectomy in almost all cases.

As for the late outcome of TSS, Fleseriu et al. performed a review of 74 studies showing that recurrence rates ranged from 0 to 65% with a median of 10.6% [15]. The wide range was likely a consequence of high variability of the population included in each study, definition of recurrence and duration of follow-up. The recurrence rates presented in our study—17.4% after first TSS and 11.1% after repeated TSS—are within this broad range and relatively close to the median.

Finally, we observed an overall remission rate after second TSS of 50%, with no remitted cases among macroadenomas. It is known that the repeated TSS is less successful than the initial intervention [36]; however, there are several factors that could increase the remission rate, such as the presence of a microadenoma at the first radiological evaluation, the success of the first TSS and the histopathological confirmation of ACTH-secreting adenoma, even if some of these features did not attain statistical significance in our study, probably because of the low number of cases. Our observation that patients with recurrent CD have a better prognosis than patients with persistent disease supports the results of Brichard and colleagues who described as the positive outcome of the first TSS with subsequent CD recurrence during follow-up is positively correlated with the efficiency of second TSS [14].

The main limitations of the present study are the retrospective nature of the analysis and the small number of patients presenting with macroadenomas.

In conclusion, our study confirms that TSS is a safe and extremely effective first-line treatment for CD. Its efficacy is maintained throughout the broad spectrum of neuroradiological presentation of the disease, although a dedicated surgical team is needed in order to reach this goal. In case of persistence or recurrence of disease, a careful and personalized evaluation is requested before choosing the second-line treatment.

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Author contributions ALS analysed the data, and wrote certain paragraphs (Materials and methods and Results) of manuscript. GD, ES, GC, and, RI and GR collected the data and draft the study protocol required by the Ethics Committee. ML, GC, GB, GM analysed the data and provided intellectual input. GM, MA, CG, and revised the project and critically reviewed the manuscript. EF designed the study and wrote the remaining paragraphs. All authors approved the final version of the manuscript.

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Compliance with ethical standards

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

Ethical approval The study was approved by the Ethics Committee of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan (Comitato Etico Milano Area 2, number 651_2019).

Informed consent Subjects gave their written informed consent for the use of their clinical data for research purposes.

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