

PANOMEN-3 grading score is reliable in predicting a pituitary adenoma behaviour and prognosis: a single center cohort validation study

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Supplementary Data

Age and sex analyses

The PANOMEN-3 panelists recognized a prognostic role of these features in pituitary adenomas but were not included in the score due to a variable effect on different adenoma subtypes. We decided to assess their role in our cohort, together with the PANOMEN grade.

Female sex predicted initial surgical remission (*Supplementary Table 3*), but on the long term it was also related to an increased risk of recurrence (grade distribution did not differ among sexes in our cohort, $p=0.28$) (*Supplementary Figure 4*); in case of persisting disease after surgery females were also more frequently referred to further adjuvant treatments (*Supplementary Figure 4*).

Age did not provide useful information, except for the NFPA group where younger patients presenting persistent disease post-operatively were more likely to receive additional treatments ($p<0.01$).

Age and sex were not relevant in predicting final disease status after a multimodal therapeutic approach (whole cohort) or response to medical treatment.

Grade items analyses

We also performed analyses on grade items in order to define whether some of them played a pivotal role in specific settings (e.g., surgical outcome, recurrence risk).

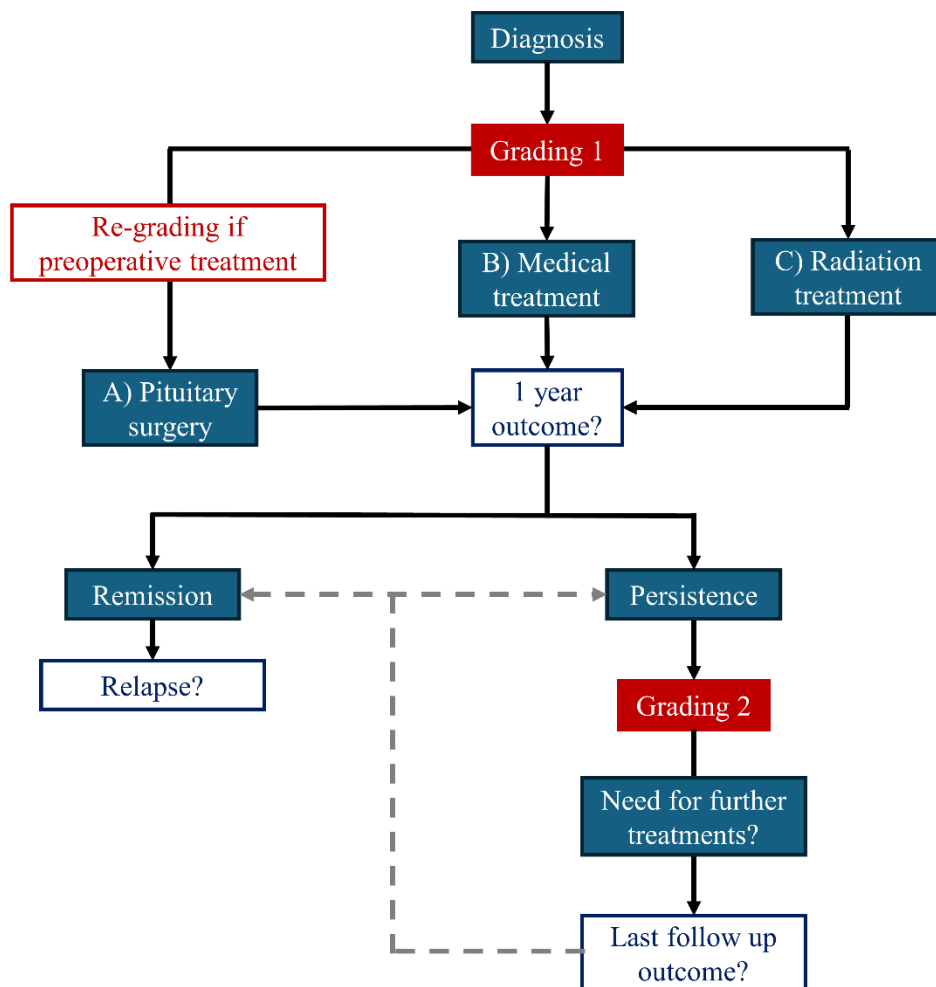
Considering a multimodal therapeutic approach in our whole cohort, some items of the grade could predict disease remission at the last available visit at the Pituitary Unit: patients with Cushing's Disease (CD) were more prone to reach remission (OR 3.07, 95%CI [1.71; 5.59], $p<0.01$), while cavernous sinus invasion predicted a persisting disease on the long-term (OR 0.14, 95%CI [0.04; 0.39], $p<0.01$).

Regarding the surgically treated patients, grade could not predict the outcome. From the analysis of items used for grade calculation a significant role of adenoma phenotype and cavernous sinus invasion emerged (*Supplementary figure 5*), without any significant interaction between these two parameters. Regarding cases achieving disease remission following first-line surgery, pre-operative biochemical control in hyperfunctioning adenomas led to a recurrence risk reduction (*Supplementary Figure 6*). Moreover, Cox regression highlighted a pivotal role of phenotype, with CD patients presenting a higher risk of recurrence (OR 12.5, 95%CI [2.22; 50.0], $p<0.01$). In case of persistent disease following surgery, CD phenotype increased probability of further treatments (OR 7.69, 95%CI [3.33; 16.67], $p<0.01$).

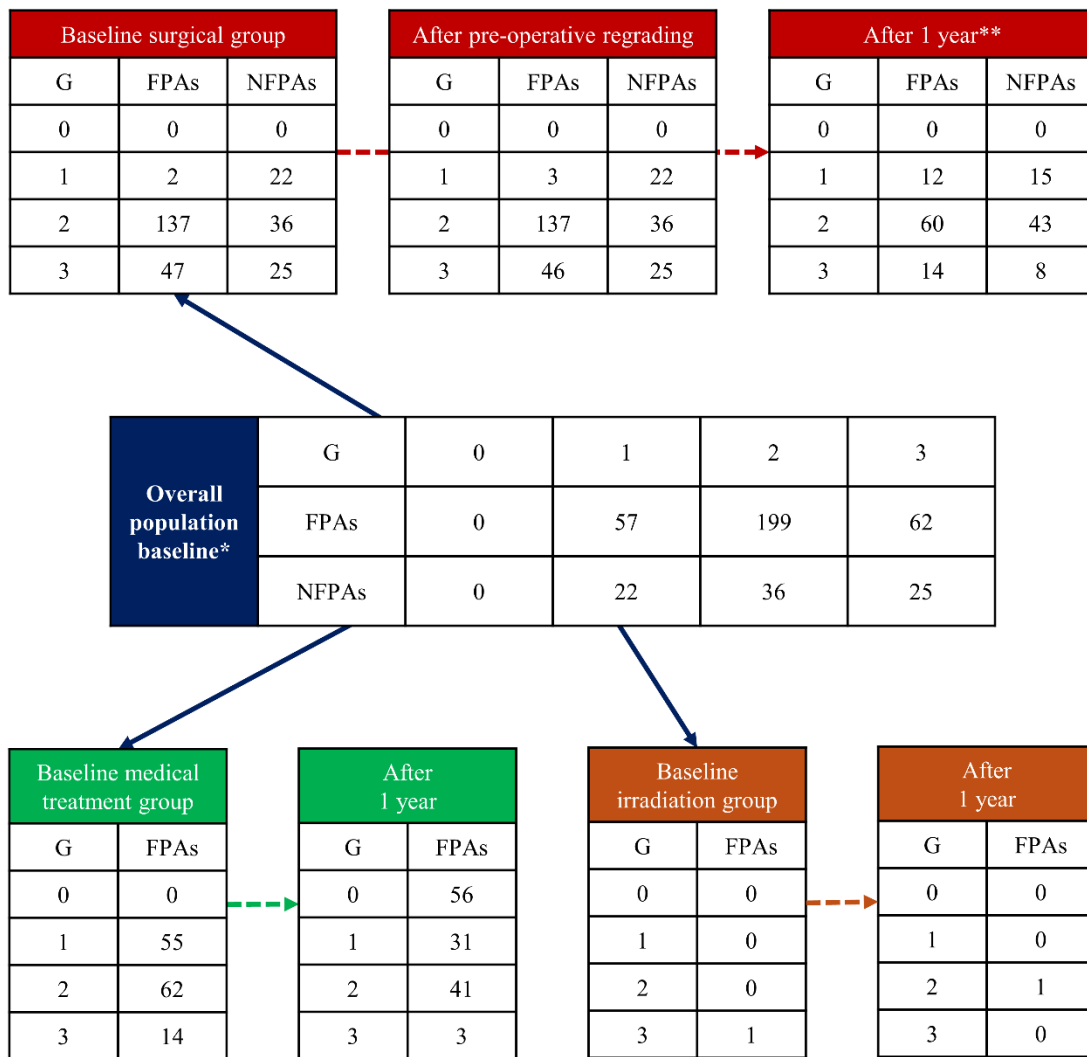
Regarding primary medical treatment, prolactinomas presented a higher response rate at 1 year (i.e., biochemical control) than acromegaly (OR 3.77, 95%CI [1.44; 10.02], $p<0.01$); CD presence trended to the need of second-line curative approaches following medical treatment failure (OR 12.5, 95%CI [1.2; 211.8], $p=0.05$). Regarding medially-induced disease remission, only non-significant trends to remission in case of prolactinomas, microadenomas, and non-invasive adenomas emerged ($p=0.07$, 0.05 and 0.08 respectively) without reciprocal interactions.

Note that genetic syndrome was excluded from these analyses due to the limited data available.

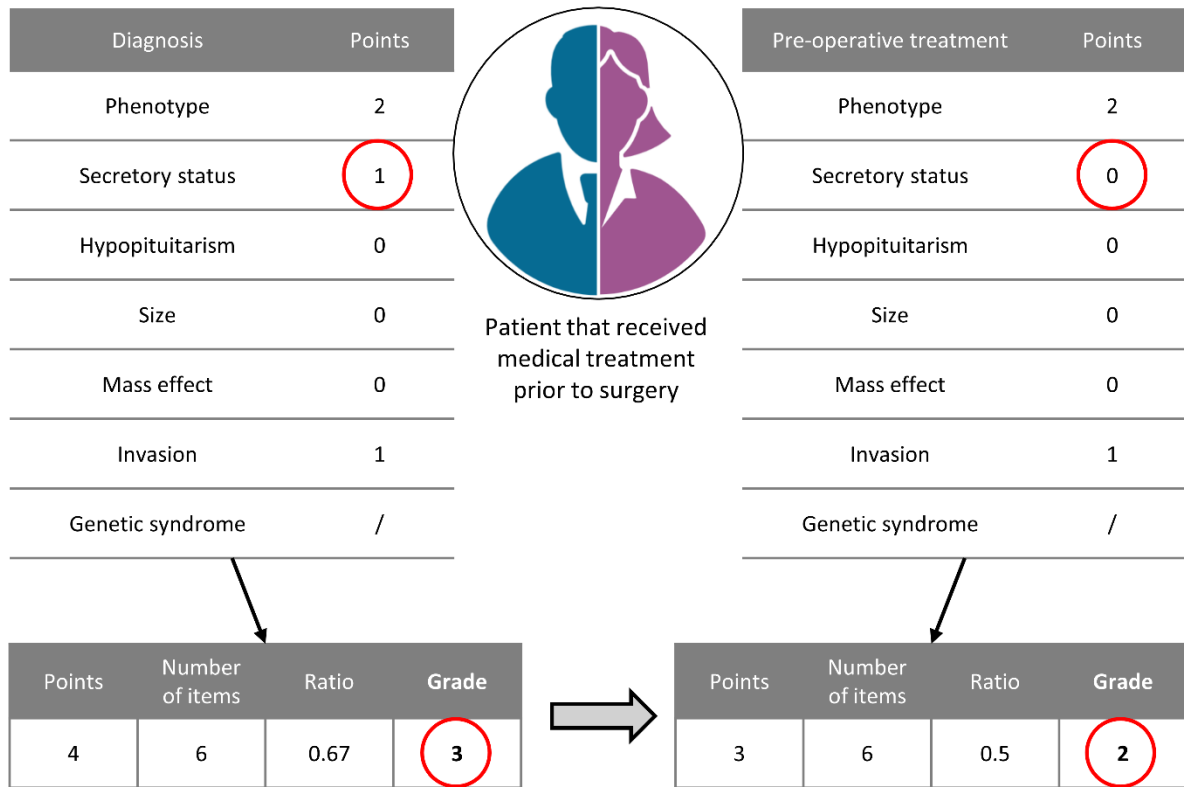
Supplementary Figure 1. A first grading was assigned at diagnosis, with patients undergoing surgery receiving a re-grading if preoperatively treated based on biochemical control. Treatment's outcome was evaluated at 1 year and, in case of persisting disease, a second grading was performed. Patients were further evaluated based on their 1-year outcome, analysing recurrences in cured patients and the need for further curative treatments (see methods) in persisting cases. Disease status (i.e., disease remission or persistence) and disease control (for persisting cases) were assessed at the last follow-up.



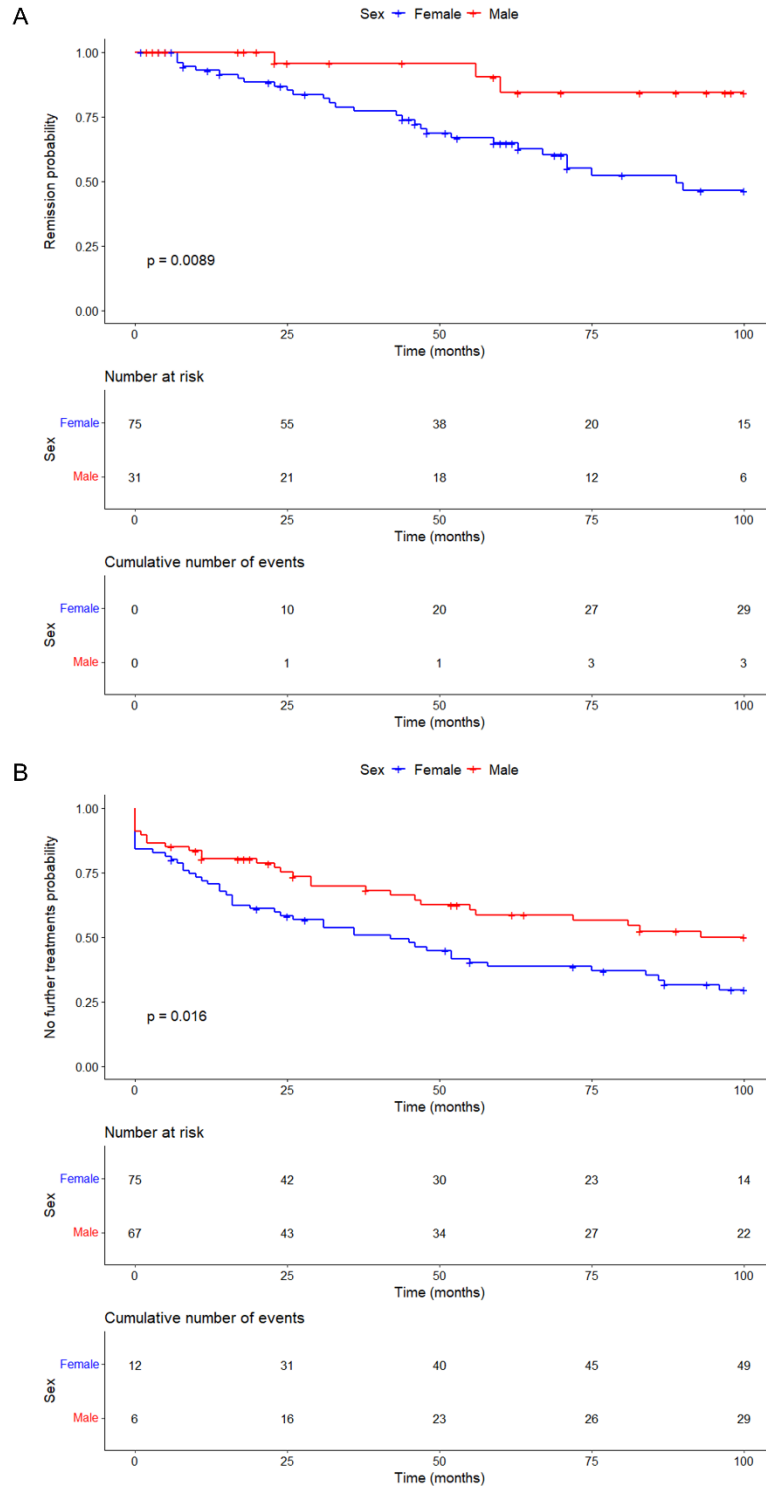
Supplementary Figure 2. Grade distribution at baseline and 1 year after first line treatment based on the primary treatment chosen; for the surgical group the effect of pre-operative treatment is also reported. *401 included patients. **only the 152 patients with persisting disease were assigned a grade at this time point in the surgical cohort as the others achieved disease remission. G: PANOMEN-3 grade; FPA: hyperfunctioning pituitary adenomas; NFPA: non-functioning pituitary adenomas.



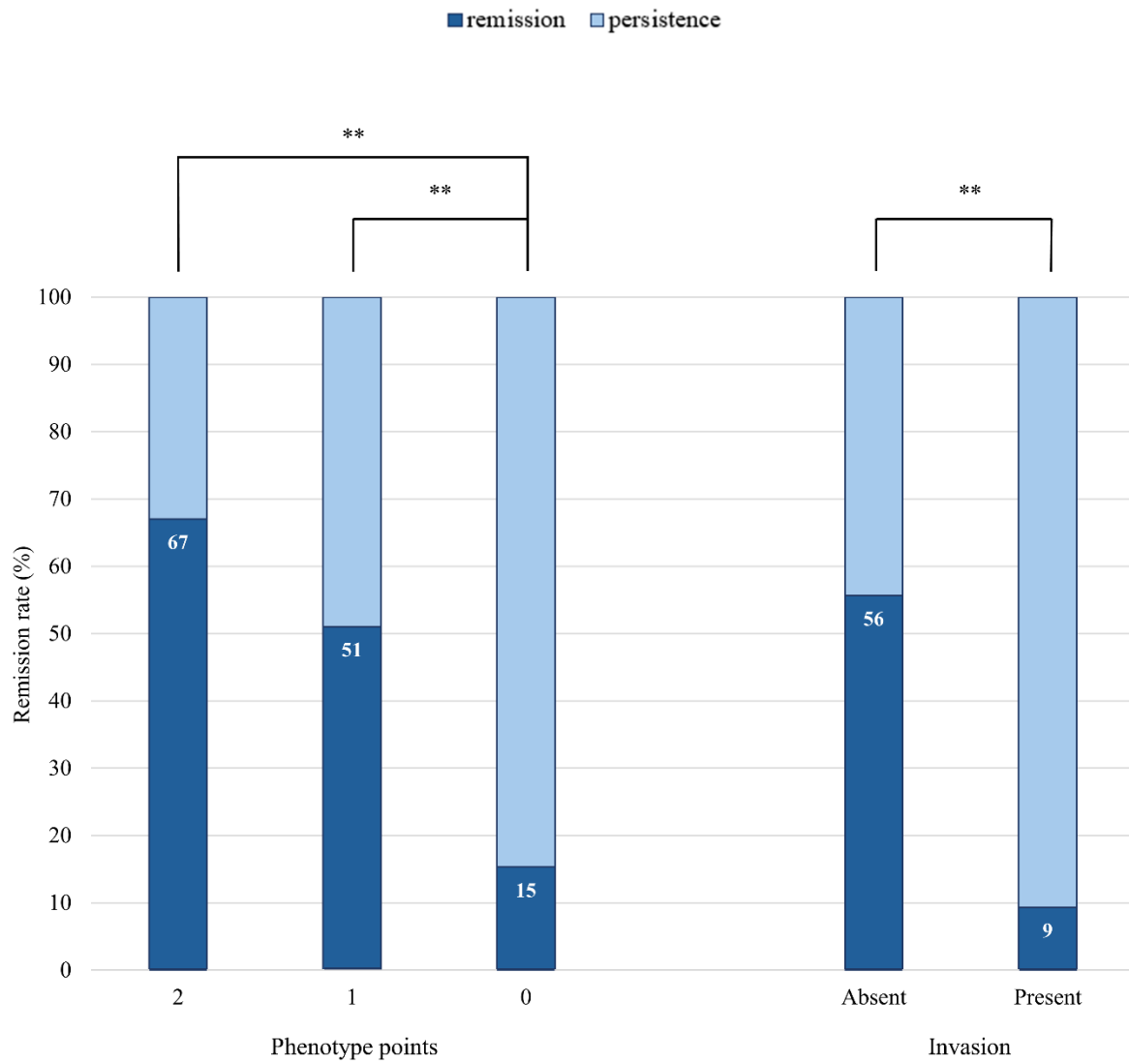
Supplementary Figure 3. Illustrative case of pre-operative re-grading (grade 3 to 2) following biochemical control via pre-operative medical treatment. Created with biorender.com.



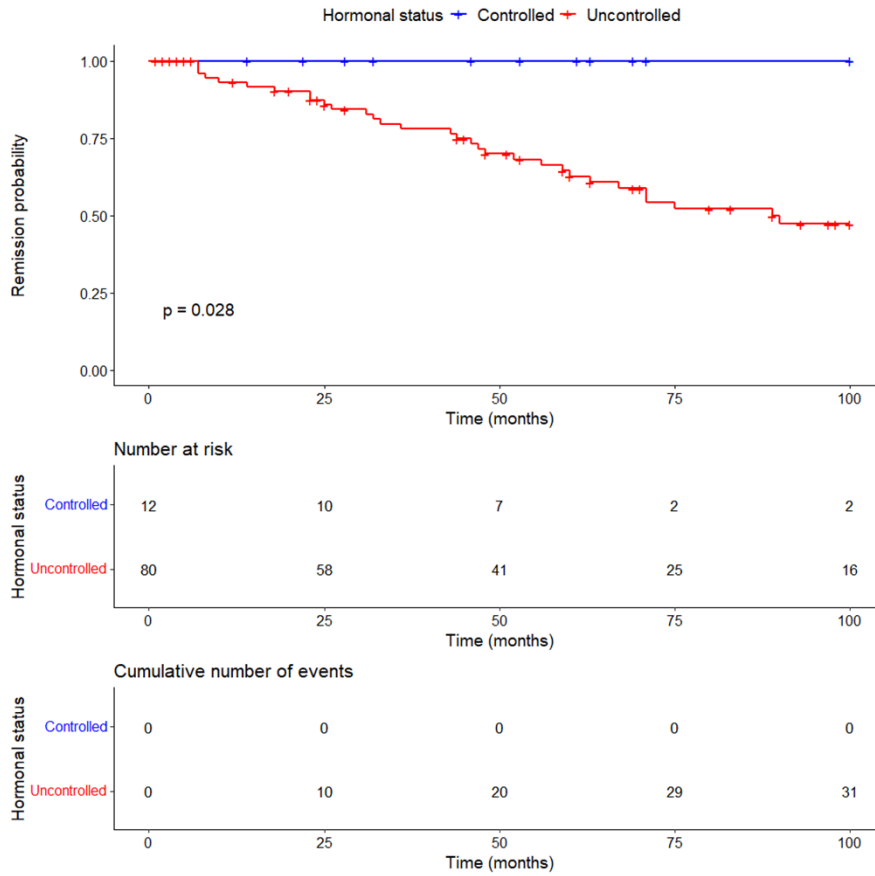
Supplementary Figure 4. Kaplan Meier curves for the probability of lasting disease remission following successful surgery (A) and of not needing additional curative treatments following surgical failure (B) based on sex. Curves were censored at 100 months in order to ensure adequate residual numerosity.



Supplementary figure 5. Patients with Cushing's disease (2) or acromegaly/TSH secreting adenoma (1) presented significantly better surgical outcomes (OR 19.9, 95%CI [5.8; 80.3] and OR 6.0, 95%CI [2.4; 16.1], respectively) than prolactinomas/non-functioning pituitary adenomas (0). Cavernous sinus invasion significantly worsened surgical outcome (OR 0.1, 95%CI [<0.1 ; 0.3]). ** $p < 0.01$.



Supplementary Figure 6. Kaplan Meier curve for the probability of lasting remission following effective surgery based on hormonal control prior to surgery (hyperfunctioning adenomas only). Curves were censored at 100 months in order to ensure adequate residual numerosity.



Supplementary Table 1. Methodological details regarding diagnosis, treatments, grading and statistical analyses.

Diagnosis
<ul style="list-style-type: none"> • In case of co-secreting adenomas including concomitant TSH or prolactin excess in addition to growth hormone excess, patients were included in the acromegaly group. • In case of a patient switching from silent corticotroph adenoma to overt Cushing’s disease during follow-up, we considered the patient in the Cushing’s disease group but with a normal hormone level at baseline.
Treatment
<ul style="list-style-type: none"> • Surgery outcome was assessed 1 year after surgery, in order to include “late” disease remissions. • If an initial medical treatment was carried out for less than 12 months prior to pituitary surgery “indication” (i.e., not to the surgery itself), it was be considered as the preoperative treatment of a patient undergoing a first line surgery; if an initial medical treatment was carried out for more than a year prior to surgical indication, surgery was considered a second line approach after primary medical therapy failure. • If a patient with persistent disease following pituitary surgery received the indication for a further curative treatment (i.e., pituitary surgery, pituitary irradiation and/or temozolomide treatment), but refused to undergo it for personal reasons, the patient was considered in the “need for further curative treatment” group to avoid bias and to correctly address a worse prognosis. • In case of preoperative medical treatment, if the hormonal control was not assessed we prudently addressed an uncontrolled secretory status. • A patient receiving a bilateral adrenalectomy as the third (or further) line of treatment was included in the study, but his/her follow-up was stopped at the time of the adrenal surgery considering it as a “persistent” Cushing’s Disease at last available follow-up. Further analyses regarding the risk of Nelson’s syndrome were not carried out.
Grading
<ul style="list-style-type: none"> • In case of Cushing’s Disease with negative magnetic resonance imaging at baseline, even if not biochemically ascertained, we assumed the absence of pituitary deficits due to the supposedly very small adenoma. • For non-functioning pituitary adenoma, the “null cell” histotype was addressed only in case of ascertained absence of staining for all pituitary hormones and at least 3 transcription factors. • In case of prolactinomas, the presence of central hypogonadism was addressed only if the pituitary deficit persisted upon biochemical control amelioration. • Headache was considered a mass effect symptom in case of suggestive clinical features and/or in case of resolution or amelioration upon tumor volume reduction.
Statistical analysis
<ul style="list-style-type: none"> • In case of first line surgery, Kaplan Meier curves and cox regression analyses for relapses and for the need of further curative treatments were started 1 year after surgery (i.e., at the time of surgery outcome evaluation). As for patients presenting ascertained persistence in the post-operative and undergoing further curative treatments within 1 year from surgery, they were considered as receiving the treatment 12 months after surgery for the purpose of statistical analysis. • Dichotomization of the age parameter was based on the median age of the group considered. • When analysing biochemical control at the last available follow-up for medically treated patients, we considered: <ul style="list-style-type: none"> ○ For persistent disease at last follow-up: the hormonal values at the last visit. ○ For patients reaching disease remission (with effective curative second line approaches or following medical treatment withdrawal): the hormonal values prior to the second line approach or to drug discontinuation.

Supplementary Table 2. Predictors of 1 year outcome with logistic regression detailed based first-line treatment: A) surgical outcome (disease remission), B) biochemical control on medical treatment. OR: odds ratio; CI: confidence interval.

A) 1-year surgical outcome			
Feature	OR	95%CI	p
Grade 2	0.90	0.37 – 2.22	0.82
Grade 3	0.48	0.18 – 1.32	0.14
Age	n.a.	n.a.	0.11
Male	0.48	0.28 – 0.81	0.01
B) 1-year hormonal control on medical treatment			
Feature	OR	95%CI	p
Grade 2	0.52	0.17 – 1.55	0.25
Grade 3	0.32	0.07 – 1.55	0.15
Age	n.a.	n.a.	0.86
Male	2.16	0.82 – 5.98	0.12