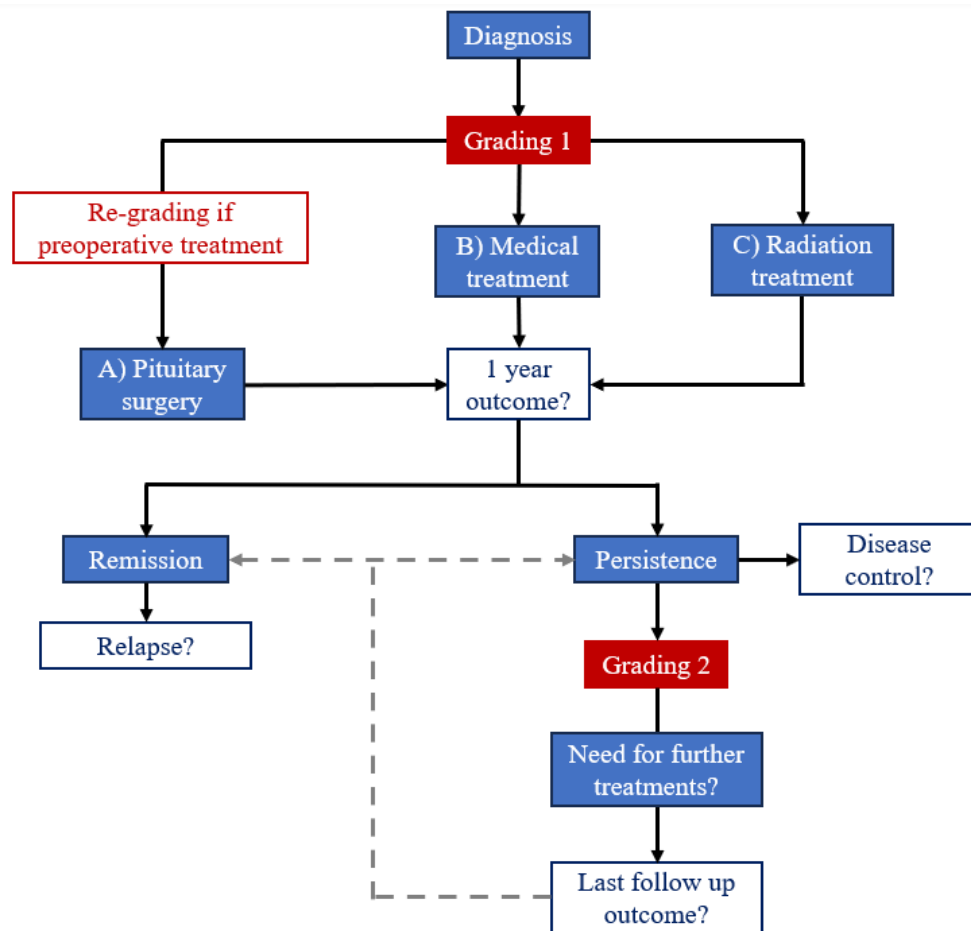


PANOMEN-3 grading score is reliable in predicting a pituitary adenoma behavior and prognosis: a single center cohort validation study

Supplementary data

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., remission or persistence) and disease control (for persisting cases) were assessed at the last follow-up.



Supplementary table 1. Criteria for diagnosis, disease remission and disease control during medical treatment. r.a.: radiologically ascertained; GH: growth hormone; OGTT: oral glucose tolerance test; IGF-1: insulin-like growth factor 1; ACTH: adrenocorticotrophic hormone; BIPSS: bilateral inferior petrous sinus sampling; UFC: urinary free cortisol; LNSC: late night salivary cortisol; DST dexamethasone suppression test; TSH; thyrotropin; α -SU: alpha subunit; THR: thyroid hormone resistance.

Adenoma type	Diagnostic criteria	Remission criteria	Biochemical disease control
Acromegaly	Histology or r.a. pituitary mass with elevated age- and sex-adjusted IGF-1 and non-suppressed GH level (> 1 ng/ml) after an OGTT	No medical treatment, normal age- and sex-adjusted IGF-1	Age- and sex-adjusted IGF-1 normalization
Cushing's Disease	Histology or ACTH dependent hypercortisolism with either concordant imaging and second line tests or with coherent BIPSS	Adrenal insufficiency or normal UFC, LNSC and 1 mg overnight DST without cortisol lowering drugs	UFC normalization
TSH secreting pituitary adenoma	Histology or central hyperthyroidism with r.a. pituitary mass, increased α -SU levels and, if indicated, exclusion of THR	No medical treatment, normal thyroid function*	Thyroid function* normalization
Prolactinoma	Histology or r.a. pituitary mass with non-stalk related hyperprolactinemia	No medical treatment, normal prolactin levels	Prolactin levels normalization
Non-functioning pituitary adenoma	Histology or r.a. pituitary mass with no hormonal excess	No radiological evidence of disease	/
** Or primary hypothyroidism/hyperthyroidism in cases with concomitant thyroid disease.			

Supplementary table 2. 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.
Treatments
<ul style="list-style-type: none"> • Surgery outcome was assessed 1 year after surgery, in order to include “late 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 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 3. Predictors of 1 year outcome with logistic regression detailed based first-line treatment: A) surgical outcome (remission), B) biochemical control on medical treatment. OR: odds ratio; CI: confidence interval.

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
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