Non Functional Pituitary Adenoma (NFPA)

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Agenda

- Epidemiology
- Clinical presentation
- Subtype of NFPA
- Evaluation
- Treatment
- Quality of life and long term prognosis
- Prognostic factor

Epidemiology

- Pituitary adenoma: the most common (10-20%) of intracranial tumors
- ***Non functional pituitary adenoma (NFPA):***
  - More than one-third of all pituitary adenomas.
  - The second most common type of pituitary adenomas,
  - The most frequent type of macroadenomas
  - Originated from adenohypophyseal cell
  - Without clinical presentation of hormonal hypersecretion
  - Malignant transformation: extremely rare
  - Variable prevalence based on:
    - Autopsy
    - MRI series
    - Genetic and environmental factors
    - Local access to diagnostic evaluation

Epidemiology

- ***According to recent epidemiological data:***
  - Estimated ***prevalence*** of NFPAs is 7–41.3 cases/100,000
  - Annual incidence is 0.65–2.34 cases/100,000
  - Standardized ***incidence rate*** of 1.02–2.34 cases per 100,000
  - Peak incidence between the ***fourth and eighth decade*** of life

Type of NFPA

- ***Clinically silent NFPA:***
  - Secret hormonal products, cause elevation of serum concentration
  - Don’t result clinical signs and symptoms of hormonal hypersecretion
- ***Totally silent NFPA:***
  - Basal and stimulated hormones within normal range
  - No clinical signs and symptoms attributed to hormone excess
- ***Null cell adenoma:***
  - Exceptionally rare primary adenohypophyseal tumors
  - Immuno-negative for all adeno-hypophyseal hormones and
  - Negative for all cell type specific transcription factors (TF)

Clinical presentation

- Absence of clinical manifestations of hormonal hypersecretion result in significant diagnostic delay
  - ***Neurologic manifestations***
    - Visual impairment
    - Headache
    - Pituitary apoplexy
  - ***Endocrine manifestations***
    - Hormonal deficiency
    - Hormonal excess

Visual impairment

- The most common neurological symptom (28-100% at diagnosis)
- ***Mechanism:***
  - Supra sellar extension of the adenoma and compress of the optic chiasma
- Different visual defect according of:
  - ***Degree*** and ***site*** of optic neve compression
- Usually affected both eyes
- Typical visual field defect: Bitemporal hemianopia(40%)
- Diplopia and ophtalmoplegia :
  - Para sellar expansion of the tumor (3^{rd} ,4^{th} ,5^{th} ,6^{th} cranial nerve)

Headache

- ***Second most common neurological symptoms***.
- Mainly localized in the frontal and occipital regions
- Occurs in 19-75% of pituitary tumors regardless of size
- ***Mechanisms of headache:***
  - Increased intrasellar pressure
  - Stretching of Dural membrane pain receptors
  - Activation of trigeminal pain pathways
- CSF rhinorrhea (± headache) due to erosion of the sellar floor

Pituitary apoplexy

- Sudden infarction and hemorrhage in pituitary adenoma
- Rare
- Acute and potentially life-threatening condition
- ***Presentations:***
  - Sudden severe headache, visual loss, nausea, vomiting, impaired consciousness, symptoms of meningeal irritation, and acute endocrine dysfunction
- The optimal management is challenging
- The ***role and timing*** of neurosurgical decompression is still controversial

Endocrine manifestations

- ***Hormone deficiency***:
  - More than a third of cases have one or more anterior pituitary hormone deficiencies at the time of diagnosis.
  - The prevalence of hypopituitarism at diagnosis 37-85%
  - The mechanical compression of :
    - Normal pituitary cells lead to hormone deficiencies (most commonly affected axes :GH and Gonadotropin)
    - Pituitary stalk lead to hyperprolactinemia (usually <95ng/ml)
    - Portal vessels
    - Diabetes insipidus (rare)
- ***Hormone excess:***
  - Rarely increased FSH or LH or α-subunit:
    - Ovarian hyperstimulation in young women
    - Precocious puberty or testicular enlargement in young men

Subtype of NFPA

- ***Null cell adenoma and silent Gonadotroph adenomas (SGAs):***
  - SGAs: 80% of NFPA
  - Null cell adenoma: rare , more aggressive and invasive than SGA
- ***Silent Corticotroph adenomas (15% 0f NFPA):***
  - **Totally silent:**
    - Absence of clinical features of Cushing syndrome
    - Normal circadian cortisol secretion
  - **Clinically silent:**
    - Absence of clinical features of Cushing syndrome
    - Elevated ACTH
  - Female preponderance, more frequently giant adenoma, more cavernous sinus invasion

Subtype of NFPA (cont'd)

- ***Silent Somatotroph adenoma: (2-4%):***
  - Without clinical presentation of acromrgaly
  - Preoperative normal GH and IGF-1
  - PIT-1 and GH-immunoreactive
- ***Silent Thyrotroph adenoma :***
  - More frequent than functioning thyrotroph adenoma
  - 95% macroadenoma
  - 85% extra sellar extension
- ***Silent Lactotroph adenoma:***
  - Rare
  - PRL positive in IHC
- ***Silent Plurihormonal adenoma***

Histopathological classification of NFPA

TUMOUR TYPE	TRANSCRIPTION FACTOR	HORMONE	BEHAVIOUR
Gonadotroph	SF1	β-LH, β-FSH, α-SU	—
Corticotroph	T-Pit	ACTH	High-risk
Somatotroph	Pit-1	GH	High-risk
Lactotroph	Pit-1	PRL	—
Pleurihormonal	Pit-1	GH, PRL, TSH, α-SU	High-risk
Double/Triple NFPA	Variable	Variable	—
Null-cell	None	None	—

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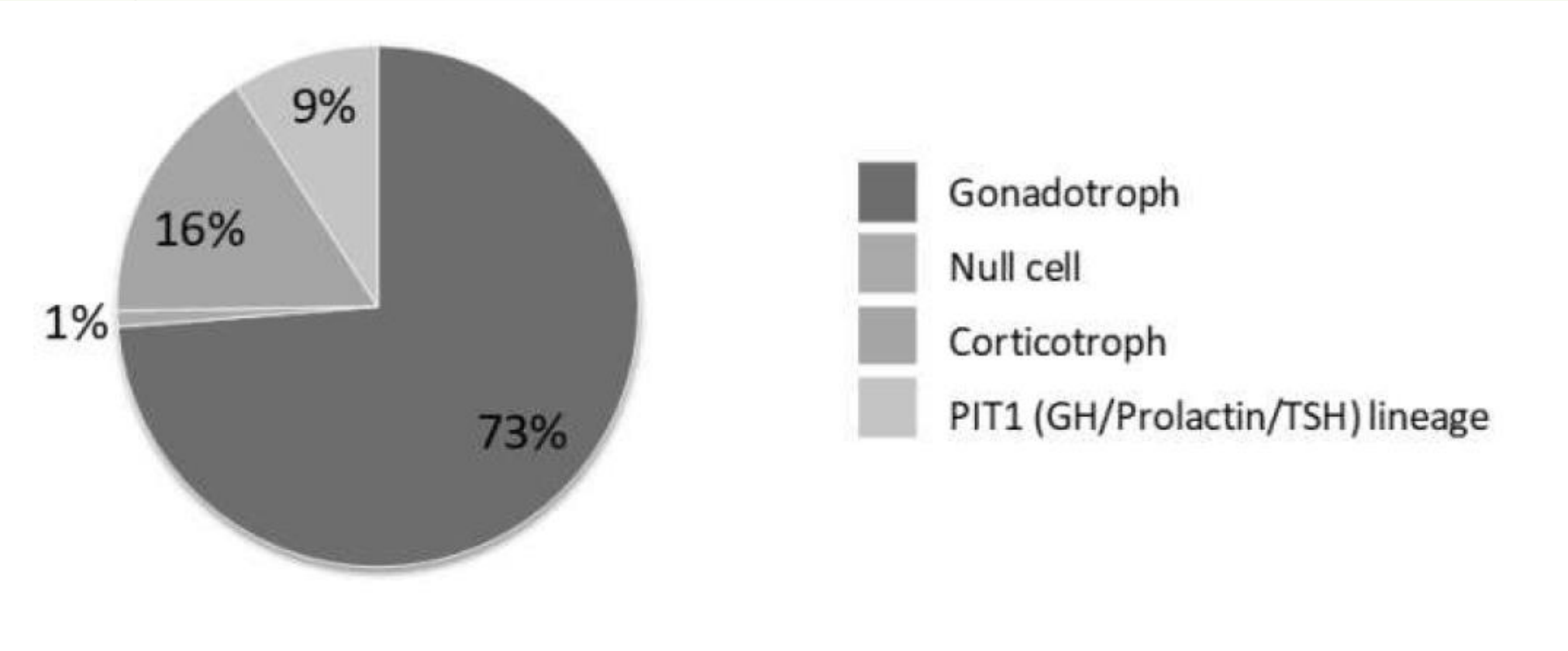
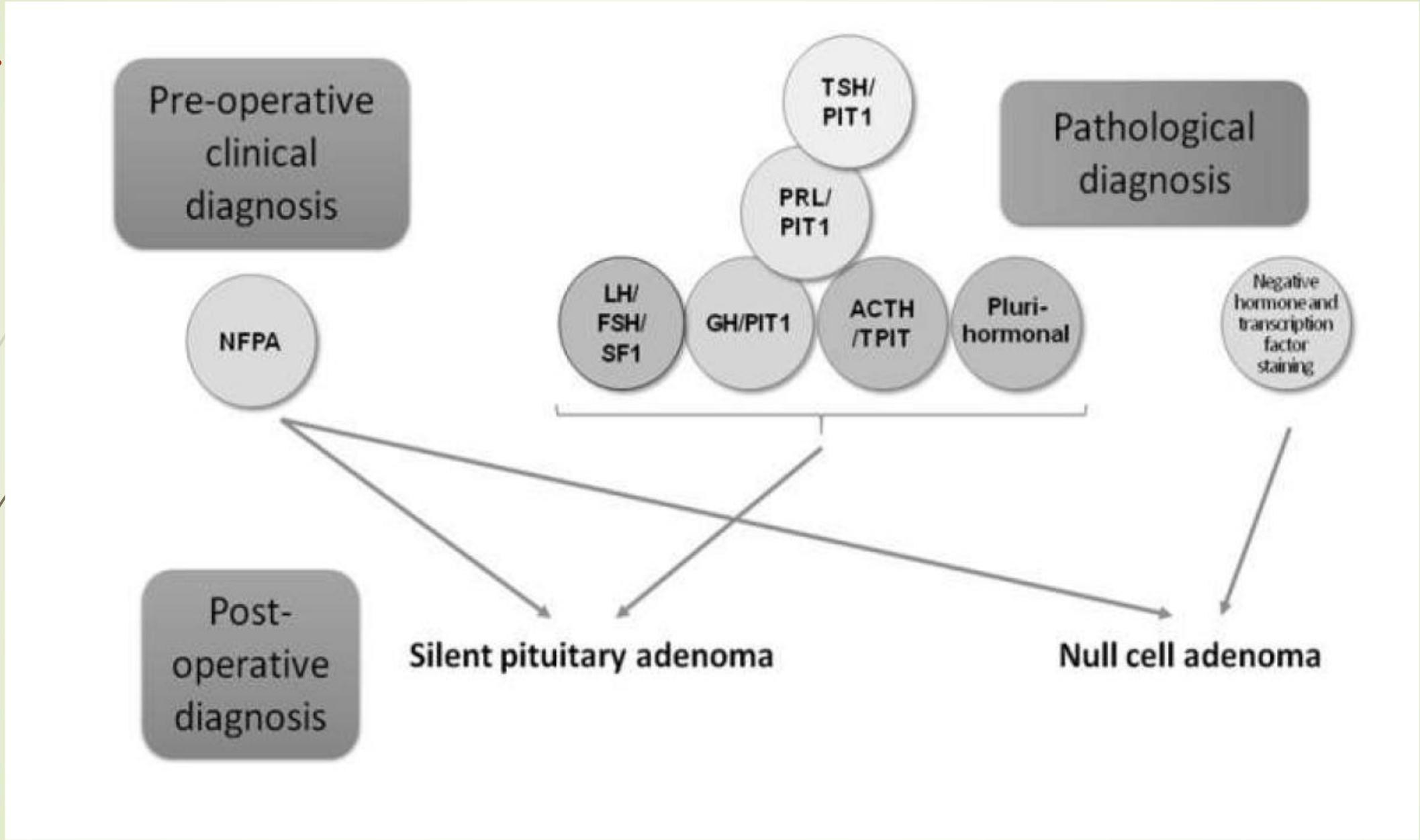
Subtype of NFPA




Pre-operative clinical diagnosis
NFPA
TSH/ PIT1
PRL/ PIT1
LH/ FSH/ SF1
GH/PIT1
ACTH /TPIT
Pluri-hormonal
Pathological diagnosis
Negative hormone and transcription factor staining
Post-operative diagnosis
Silent pituitary adenoma
Null cell adenoma

Evaluation of NFPA

- All incidentally discovered Sellar tumors without symptoms:
- Hormonal , clinical and laboratory evaluation for hyper or hypopituitarism:
  - Assessment of PRL and IGF1 in all patients
  - Cortisol excess screening : in presence of clinical symptom
  - ACTH evaluation : not routinely recommend
  - Diluted Prolactin evaluation: in macroadenoma (>3cm) and normal or slightly elevated prolactin

Evaluation of NFPA

- ***Check for pituitary hormone deficiency:***
  - In Microadenoma (<5mm): not recommended
  - In Microadenoma (6-9mm): suggested investigation of serum PRL and IGF-1
  - In Macroadenoma: suggested assessment for Cortisol, freet4,TSH, FSH,LH, testosterone, estradiol, IGF1, GH
- ***Sellar MRI***
- ***Visual field perimetry (Gold man method):***
  - In patients, tumor abuts the optic chiasma

Management of NFPA

- *Observation*
- *Surgery*
- *Medical treatment*
- *Radiotherapy*

Observation(follow up)

- Main rationale for watchful monitoring in symptomatic and asymptomatic NFPAs is probability of tumor growth over time.
- The risk of tumor growth was 10% per year, and it occurred more quickly in patients who were already hormone deficient.
- Natural history of the tumor gives insight into which tumor can be observed over time.
- No correlation was seen between ***tumor size doubling*** and ***initial tumor size***
- Of prospective randomized controlled studies, the observational approach, and its recommendations are based on ***expert opinions***.

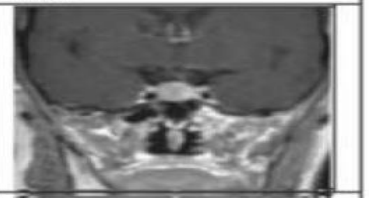
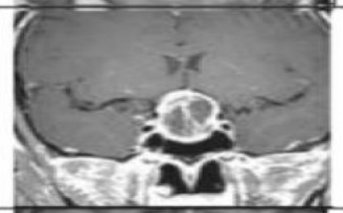
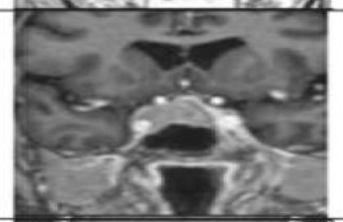
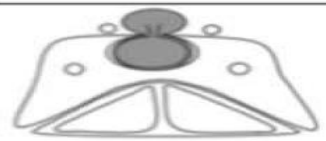
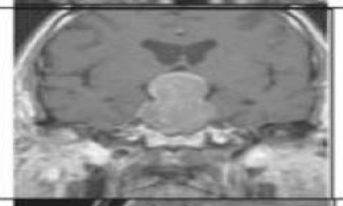
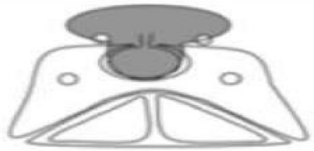
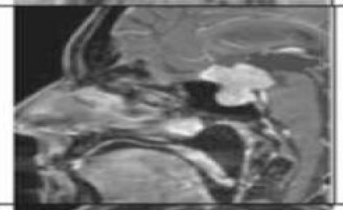
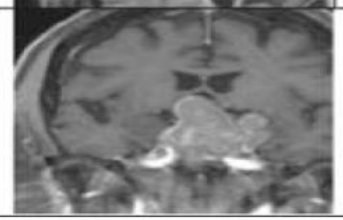
Surgery

- ***Goals in managing NFPAs :***
  - Decompress the mass effect caused by the enlarging adenoma
  - Preserving the normal pituitary gland
- ***Indication of surgery:***
- Surgery is the first choice of treatment in symptomatic NFPAs with:
  - Neurological deficit
  - Tumor affecting of optic pathway (visual loss)
  - Hormonal deficiency
  - Apoplexy with visual deficit and deteriorating level of consciousness.
  - Tumor ≥ 2cm
- ***Type of surgery:***
  - TSS (endoscopic, macroscopic)
  - Transcranial surgery

Surgery (cont'd)

- ***Prediction of surgical outcome according to:***
  - Cavernous sinus invasion (modified Knosp classification)
  - Shape grading system:
    - Spherical (I)
    - Oval (II)
    - Dumbbell (III)
    - Mushroom (IV)
    - Polylobulated (V)

- ***Surgical outcome:***
  - Total resection/resistance/recurrence
  - Improvement of visual field defect
  - Improvement of hormone deficiencies
  - DI (tumor size, age, absence or interstellar location of bright spot)

Grading	Definition	Pattern	MRI
I spherical	- round appearance - max. diameters do not differ >25%		
IIa oval, non-invasive	- oval appearance - one max. diameter differs >25% from the others - no invasion into the cavernous sinus (=Knosp grades 0-2)		
IIb oval, invasive	- oval shape as IIa, but with invasion into the cavernous sinus (= Knosp grades 3-4)		
III dumbbell	- dumbbell-like shape - Intra-/suprasellar growth mandatory (diameters don't differ >10%) - diameter at the level of the planum sphenoidale <75% of the max. diameters of the intra-/suprasellar parts (coronar and/or sagittal plane)		
IV mushroom	- mushroom-like shape - intra-/suprasellar growth mandatory - max. diameter of suprasellar part is >50% larger than that of the intrasellar part (coronar or sagittal plane)		
V octopus	- polylobulated, octopus-like shape - consists of an intrasellar part from which at least 3 parts spread into the following regions: suprasellar cistern, cavernous sinus, sphenoid sinus and/or clivus		

Medical treatment

- ***Dopamine agonist :***
  - Residual tumor Shrinkage
  - Decreased risk of recurrence or regrowth
  - Cabergoline dose:
    - Start with 0.5 mg/wk, increased 0.5 mg/wk , max:3mg/wk
- ***Somatostatin receptor ligands (SRL)***
- ***Dopastatin: chimeric compound of dopamine and SLR***
- ***Temolozomide :***
  - Oral alkylating agent
  - In aggressive and recurrent NFPA, pituitary carcinoma
- ***Peptide receptor radioneuclide therapy***

Postoperative Radiotherapy (PORT)

- Some specialized centers systematically recommend PORT :
  - for all patients, even those with apparently complete lesion resection
  - while others apply it on a case-by-case basis, considering ***the size*** and ***location of the tumor remnant***, as well as any ***hormonal deficiency*** as part of the therapeutic criteria
- ***Radiotherapy should only be considered if:***
  - Cavernous sinus involvement not amenable to surgical excision
  - Significant postoperative residual tumor

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Postoperative Radiotherapy (PORT)

- Symptomatic patients with incomplete resection or recurrence of tumor after surgery should be managed with :
  - Second surgery
  - And/or PORT
- ***Radiotherapy:***
  - Conventional
  - Stereotactic radiosurgery

Natural History of Non-Functioning Pituitary Adenomas

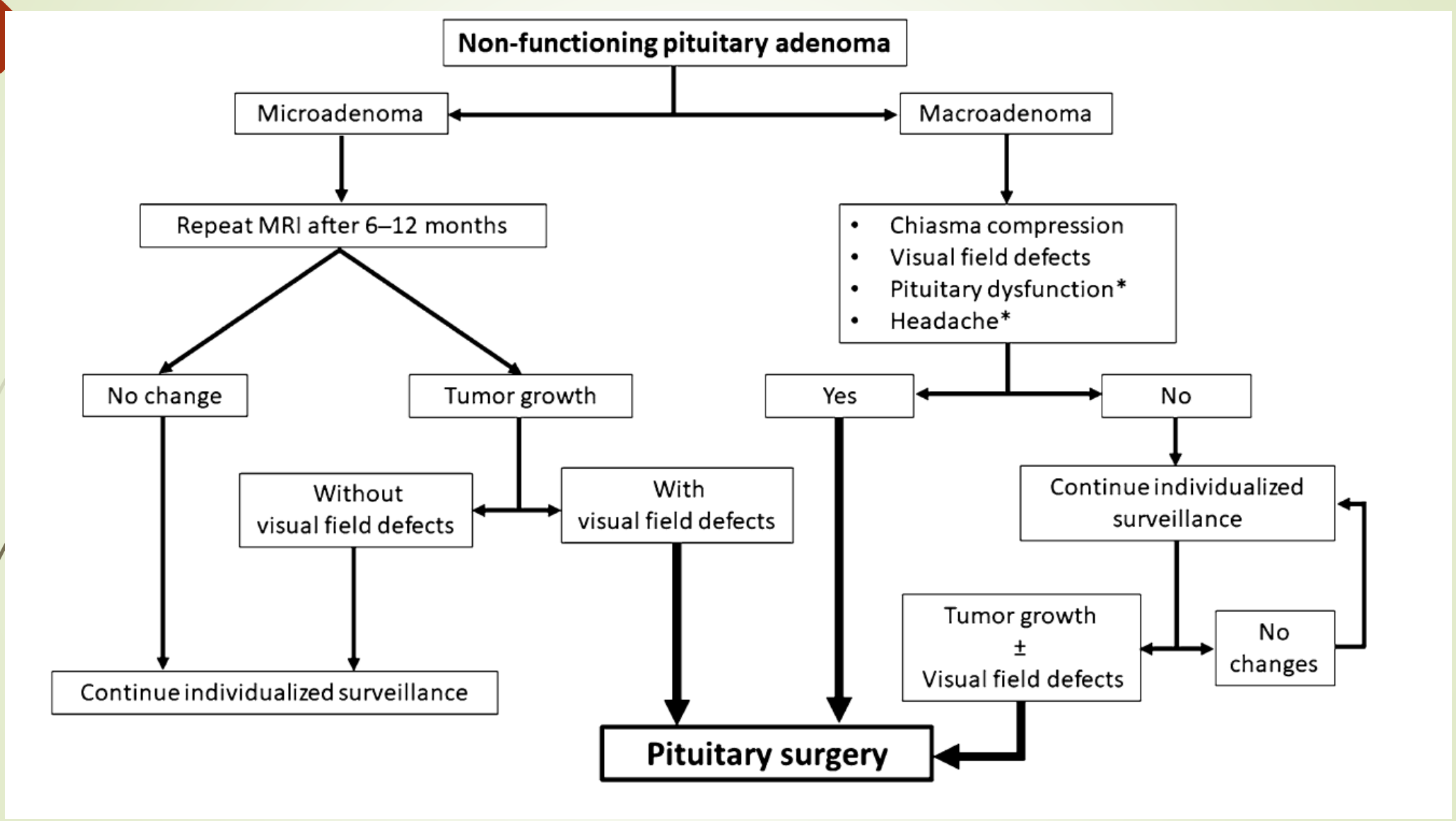
- Predicting growth behavior in NFPTs prior to pathological classification remains primarily based on ***tumor size*** and ***tumor behavior*** (aggressiveness and invasiveness)
- The current systematic review in patients with ***microadenomas*** identifies a low risk of :
  - Growth
  - New endocrinopathies
  - Surgical interventions
- Patients with normal endocrine function ***at baseline*** and no signs of tumor growth at ***a two- or three-year MRI follow-up***, could end any further assessment of pituitary function or size

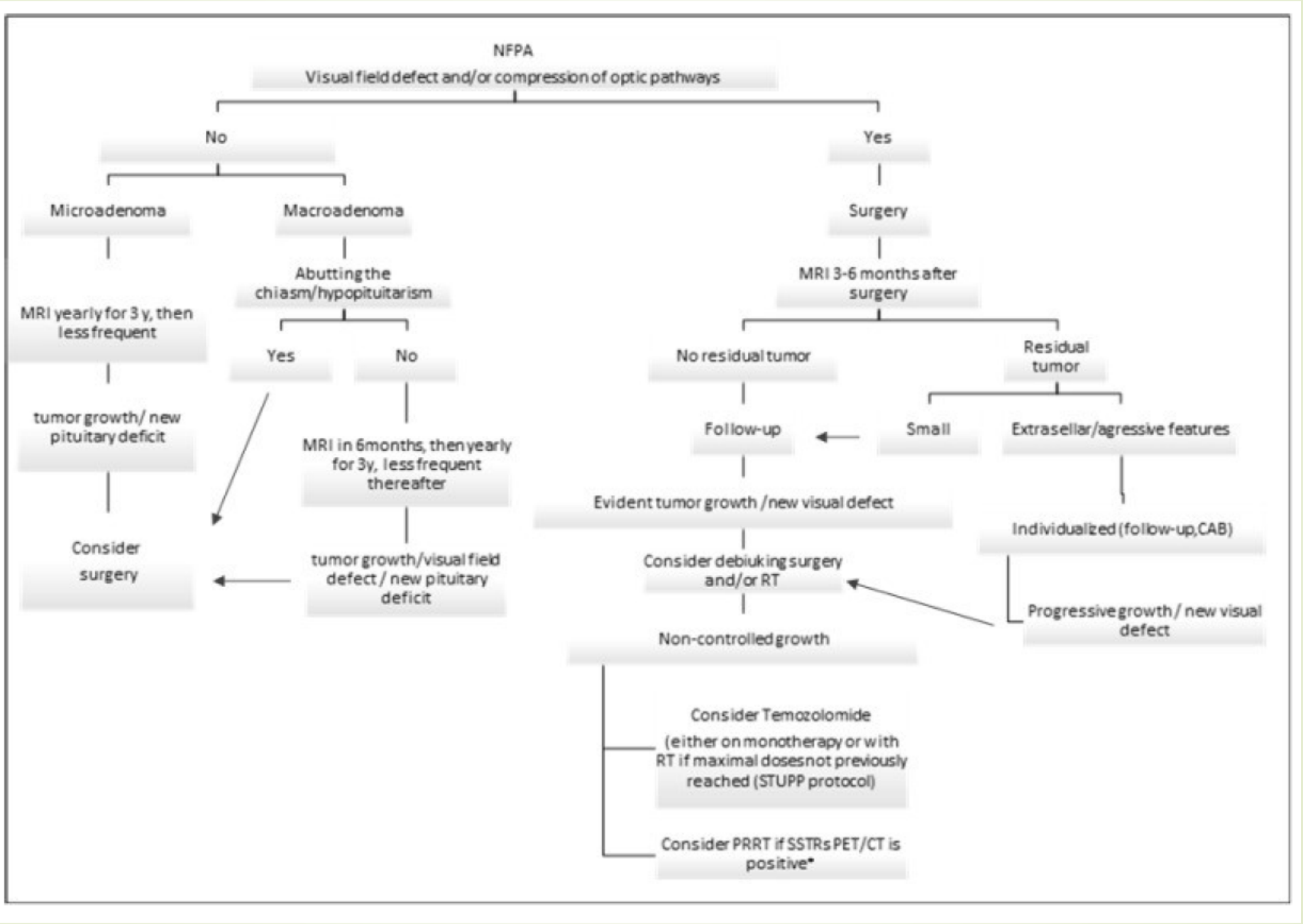
Horm Metab Res 2023; 55: 443–451

Long term mortality and morbidity

- Mortality more than general population
- ***Cause of mortality:***
  - Circulatory disease
  - Respiratory disease
  - Infectious disease
- ***Predictive factors :***
  - Older age at diagnosis
  - High dose of GC replacement therapy

Close collaboration of a multidisciplinary pituitary team is crucial


Non-functioning pituitary adenoma
Microadenoma
Macroadenoma
Repeat MRI after 6–12 months
• Chiasma compression
• Visual field defects
• Pituitary dysfunction*
• Headache*
No change
Tumor growth
Yes
No
Without visual field defects
With visual field defects
Continue individualized surveillance
Continue individualized surveillance
Tumor growth ± Visual field defects
No changes
Pituitary surgery


NFPA
Visual field defect and/or compression of optic pathways
No
Yes
Microadenoma
Macroadenoma
Surgery
MRI yearly for 3 y, then less frequent
Abutting the chiasm/hypopituitarism
MRI 3-6 months after surgery
tumor growth/ new pituitary deficit
Yes
No
No residual tumor
Residual tumor
Follow-up
Small
Extrasellar/agressive features
Consider surgery
MRI in 6months, then yearly for 3y, less frequent thereafter
Evident tumor growth /new visual defect
Individualized (follow-up,CAB)
tumor growth/visual field defect / new pituitary deficit
Consider debiuking surgery and/or RT
Progressive growth / new visual defect
Non-controlled growth
Consider Temozolomide (either on monotherapy or with RT if maximal dosesnot previously reached (STUPP protocol)
Consider PRRT if SSTRs PET/CT is positive*

Thanks for your attention