Pituitary Adenomas

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Outline

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2. Anatomical considerations
3. Pathology
4. Clinical presentation
5. Diagnostic workup
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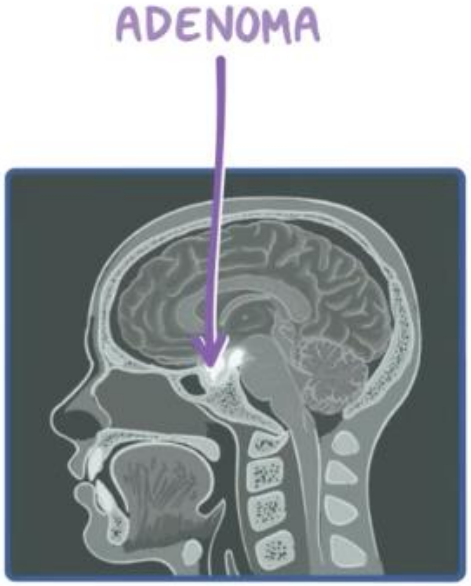
Epidemiology

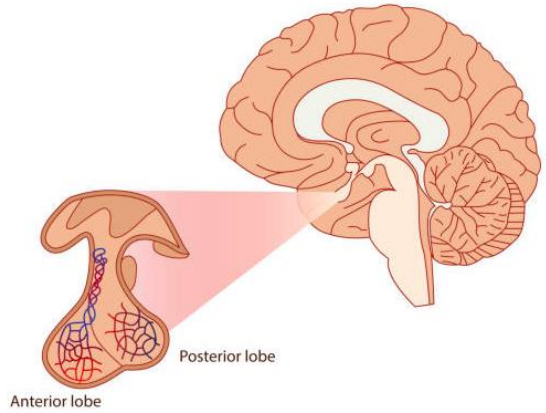
- Pituitary adenomas comprise 10-15% of CNS neoplasms
  - Median age at diagnosis is 40 years
  - They are the **most common suprasellar mass in adults** (craniopharyngiomas are more common in children)
    - Incidental adenomas are seen in around 25% of autopsies



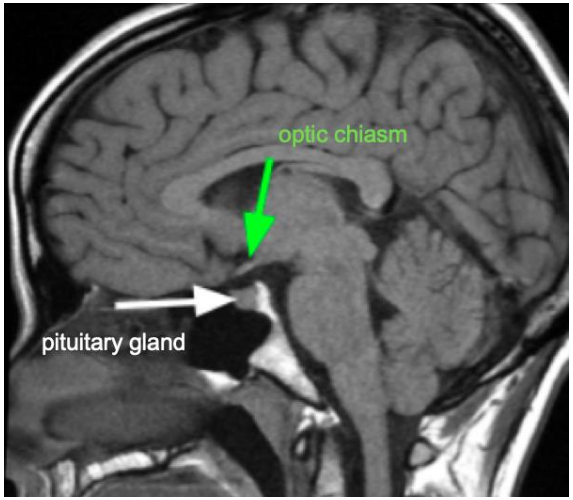
- They are sometimes categorized based on size:
  - **Microadenoma** = less than 1 cm
  - **Macroadenoma** = greater than 1 cm

Anatomical Considerations

- The pituitary gland is made up of two lobes, each of which is responsible for the regulation of different hormones
  - Anterior lobe (FLAT PiG)
    - FSH / LH / ACTH / TSH / PRL / GH
  - Posterior lobe
    - Oxytocin / ADH



- **The pituitary gland lies near the optic chiasm and cavernous sinus**
  - This has clinical presentation AND treatment implications!



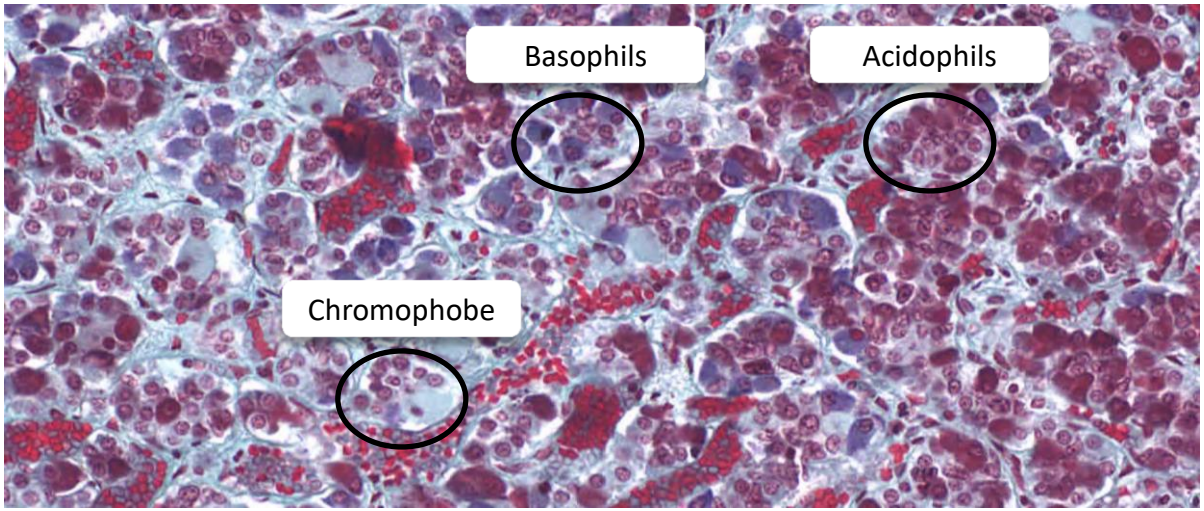
Pathology

- Masson's trichrome staining is used for easy distinction between acidophils and basophils
  - This trichome includes Weigert's Hematoxylin, Biebrich scarlet-acid fuschin solution, and Aniline blue

- Secretory function can be elucidated by histological appearance!
  - **Acidophils**: Lactotrophs (PRL-secretors) and somatotrophs (GH-secretors) stain well with acidic dyes
  - **Basophils**: Corticotrophs (ACTH-secretors), gonadotrophs (FSH-, LH-secretors), and thyrotrophs (TSH-secretors) stain well with basic dyes
  - **Chromophobes**: Cells which do not take up stain are called chromophobes, (or clear-cells); these are classically non-secretory or hormone-depleted

- Certain histologies (i.e.: **Atypical** and **Crooke cell adenomas**) are noted to be have aggressive courses

Pathology

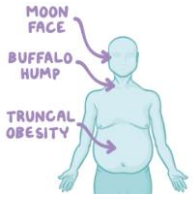


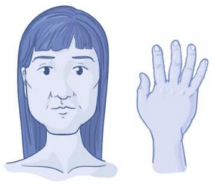
Pituitary tissue is routinely stained with PRL, ACTH, GH, TSH, LH, and FSH to more specifically characterize functional status

Subtypes and clinical presentations

Functional Tumors (70% of tumors)

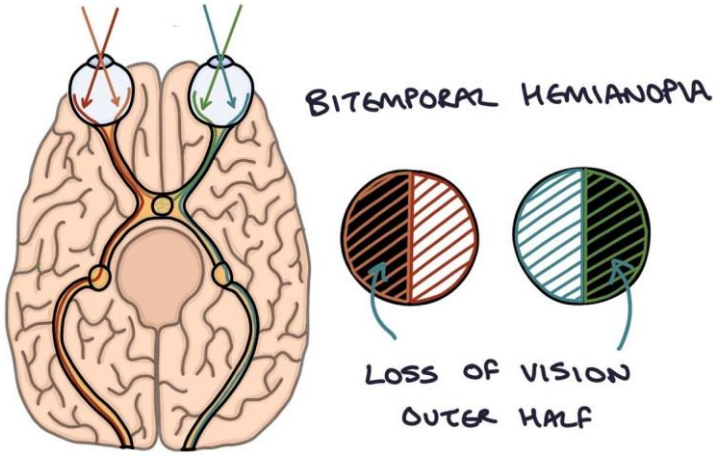
- Prolactin
  - Prolactinoma
  - About 30% of tumors
- ACTH
  - Cushing disease
  - About 15% of tumors
- GH
  - Acromegaly
  - About 25% of tumors
- TSH
  - Hyperthyroidism
  - Less than 1% of tumors



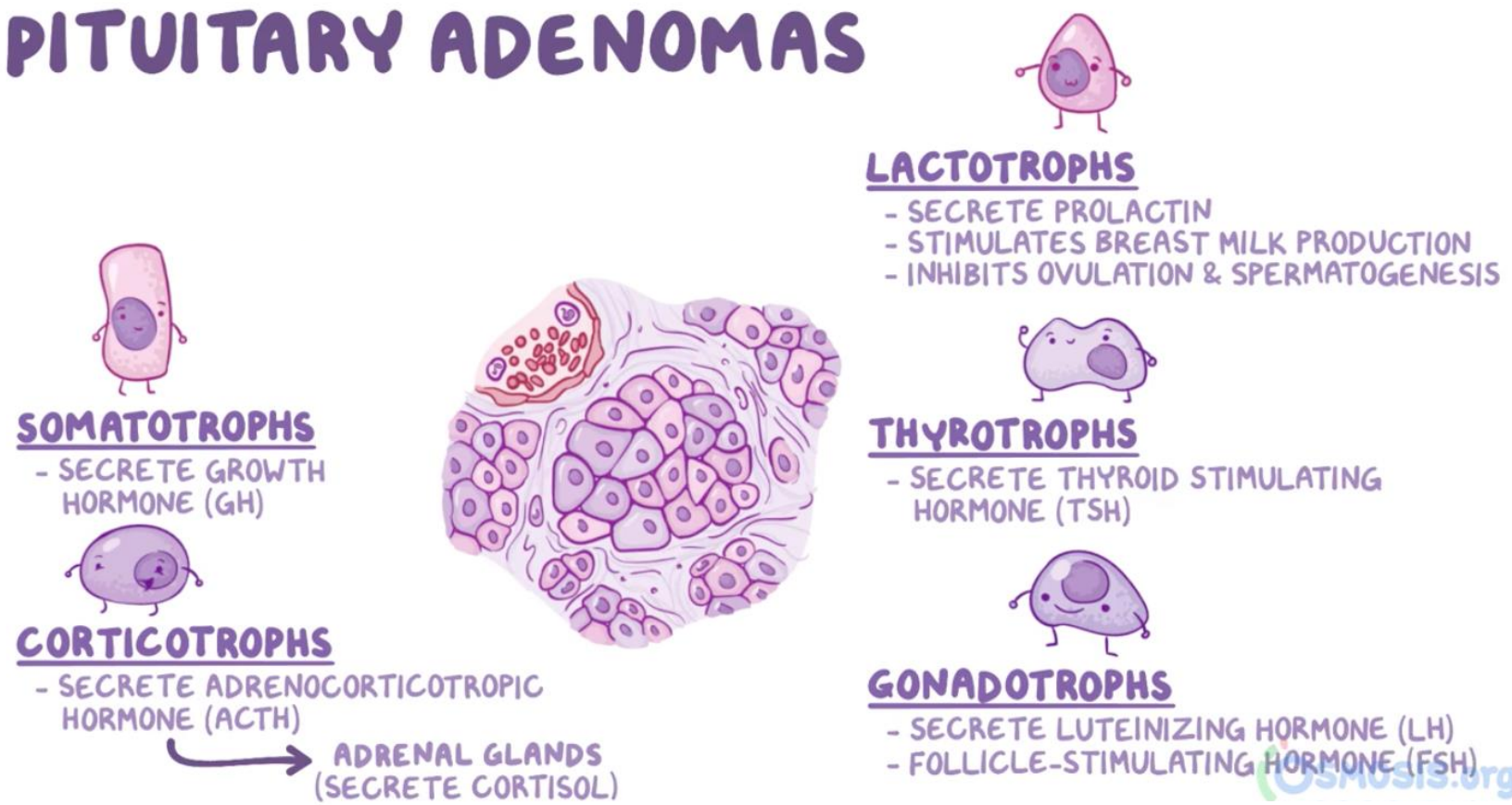


Non-Functional Tumors (30% of tumors)

- These often present incidentally or with compressive symptoms (i.e.: headaches)
- They can also present with apoplexy (sudden hemorrhage), or visual field deficits



Review of Functional Tumors

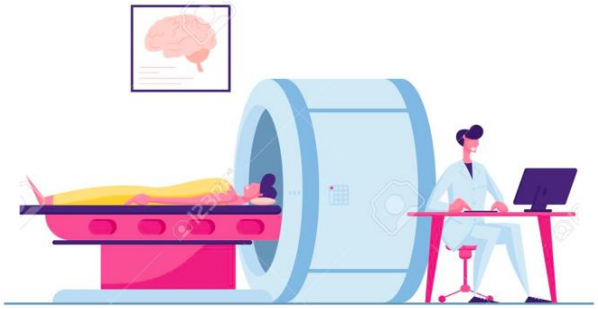


Diagnostic Workup

- **History and Physical**
  - Pay special attention to the neurologic examination with visual field testing
- **Labs**
  - Serum prolactin, IGF-1, ACTH and 24-hr urine free cortisol, T3/T4/TSH
  - CSF may be xanthochromic in cases of pituitary apoplexy

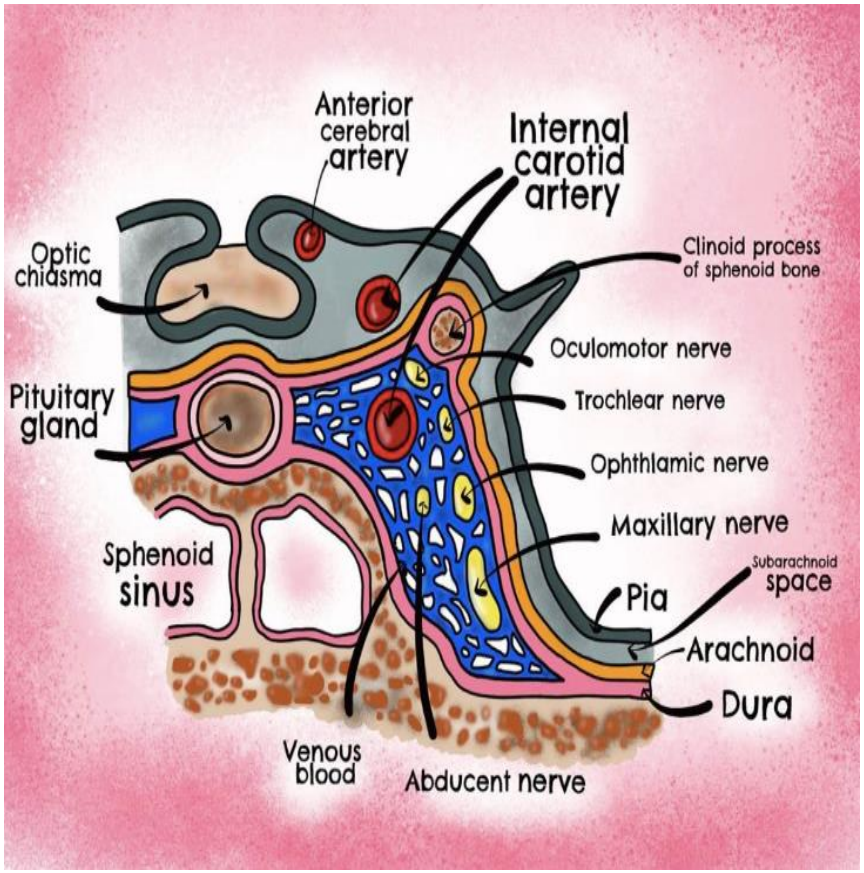
Normal serum prolactin <25 ng/mL
Microadenoma 30-100 ng/mL
Macroadenoma >100 ng/mL

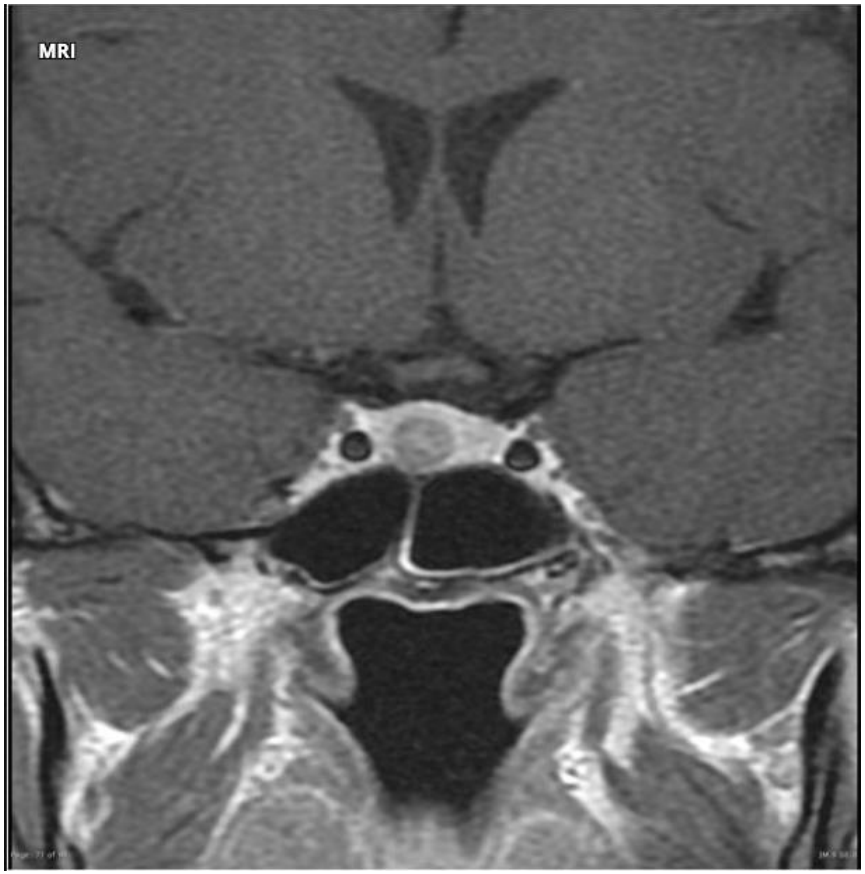
- **Imaging**
  - MRI brain
    - Note: an adenoma will have less contrast enhancement than the normal pituitary!
  - Skeletal survey (if acromegaly)



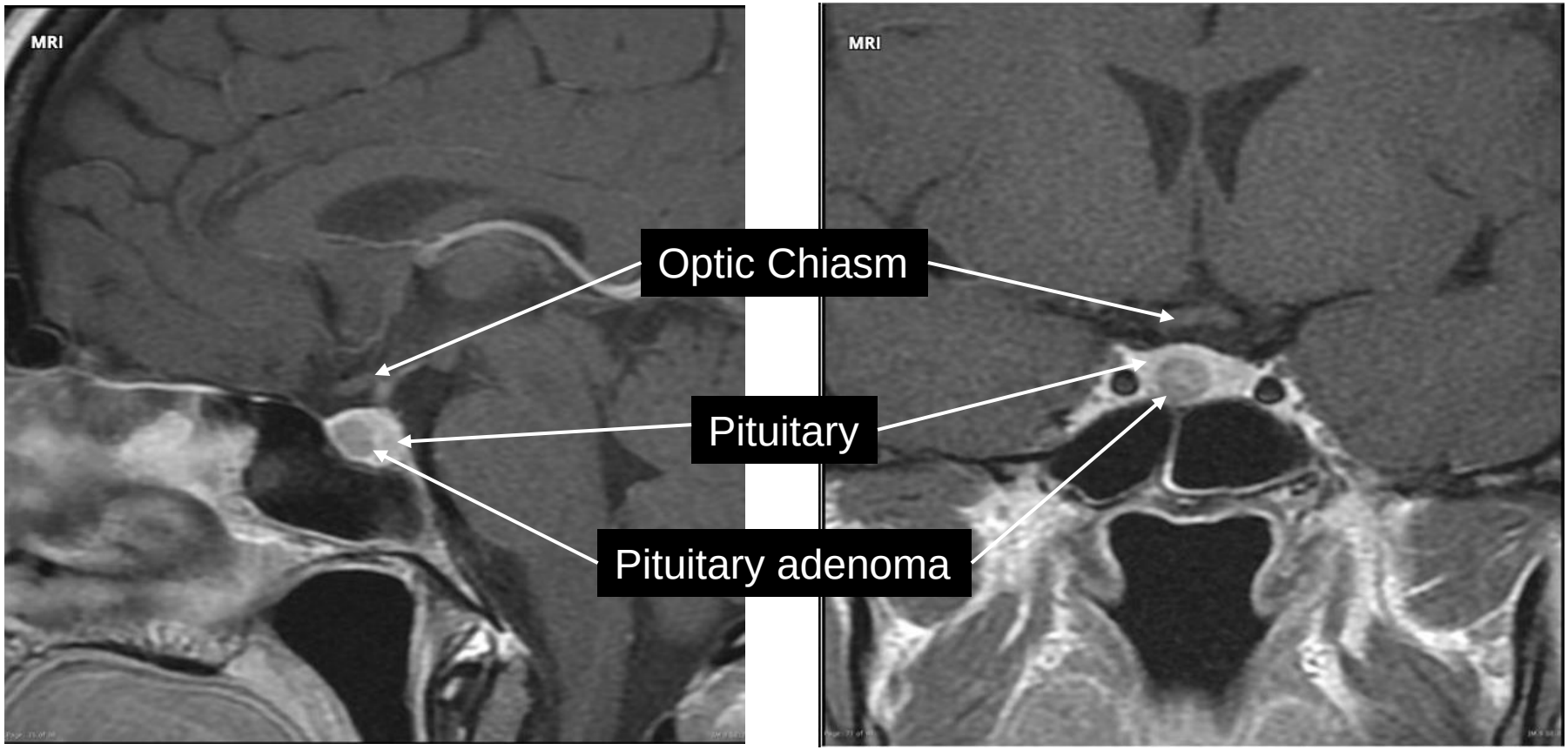
- **Procedures**
  - Given the clinical scenario, a surgery may be required for resection and/or optic chiasm compression

Review of Coronal MRI Anatomy



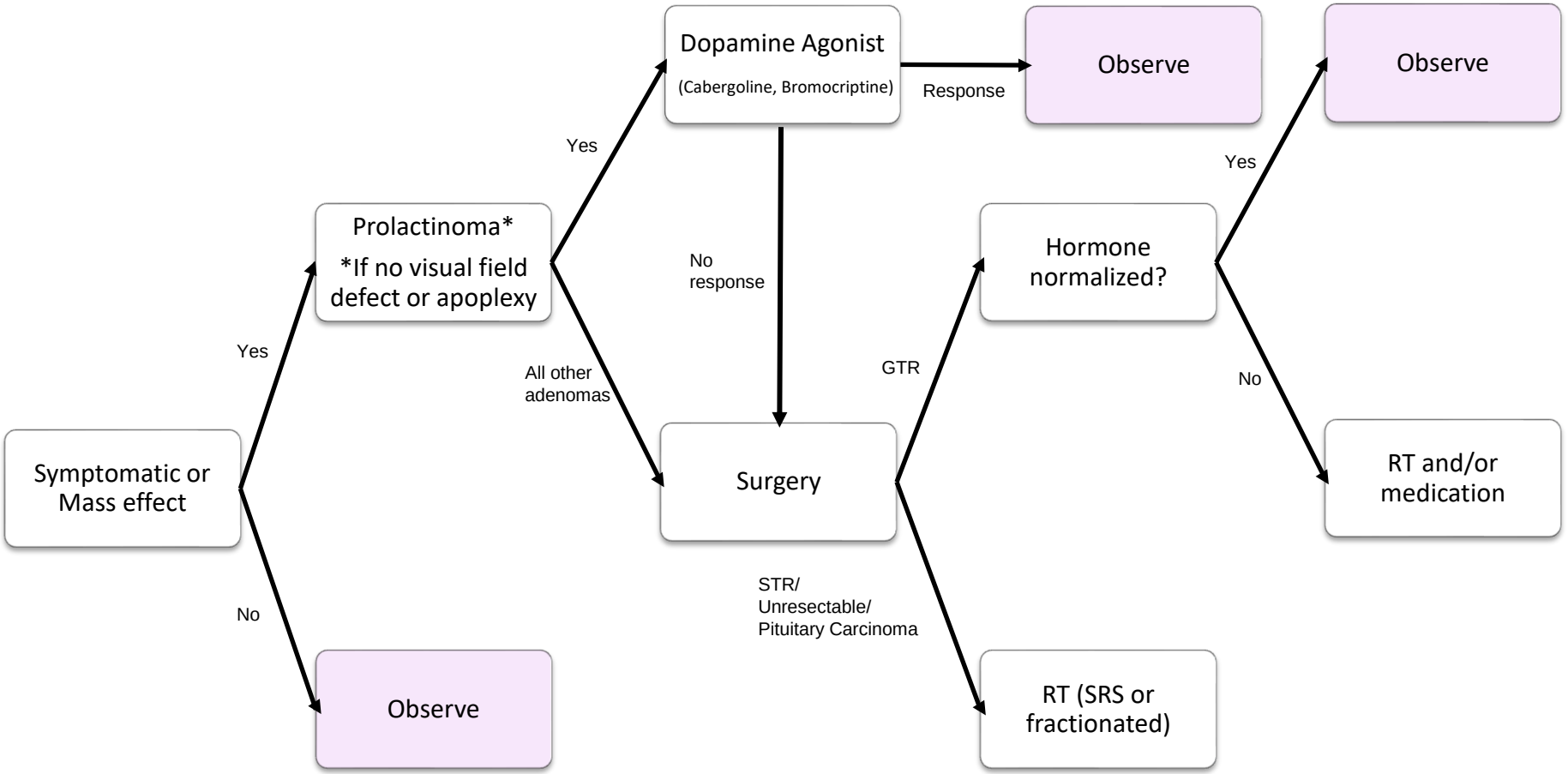


Pituitary Adenoma: T1c MRI



Note: the adenoma has less contrast enhancement than the normal pituitary!

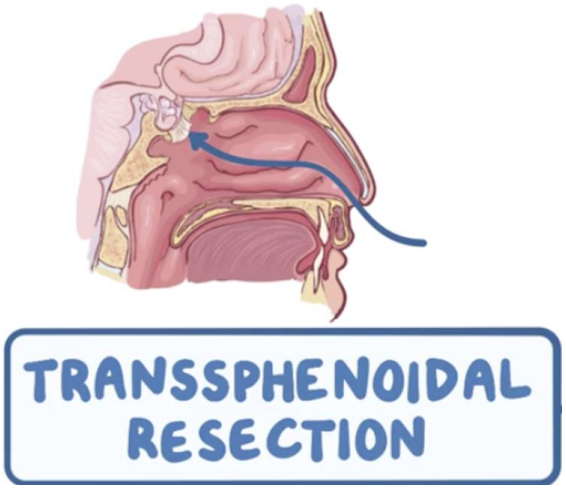
Therapeutic Management



Principles of Management: Surgery

- Surgery is first-line treatment for symptomatic adenomas apart from prolactinomas

- There are two approaches:
  - **Transsphenoidal pituitary surgery**
    - This approach is used in majority of cases
  - **Transcranial approach**
    - This approach is used for larger tumors



- Following transsphenoidal surgery:
  - Oncologic outcome varies significantly by tumor size and type
    - Recurrence at 10 years as high as 42% in ACTH adenomas, as low as 1.3% in GH adenomas
  - Hormone normalization occurs in around 70-80% patients in the short-term, falling off to 40% in the long-term

Principles of Management: Systemic Therapy

- Generally, systemic therapy is effective at hormone normalization and occurs quicker than with RT
- Different systemic therapy options are available, with varying efficacies and side effect profiles

- Systemic therapy is first line for **prolactinoma**
  - Dopamine agonists
- Systemic therapy is used at the time or recurrence and/or metastasis for **pituitary carcinoma**
  - Temozolomide

Hormone	Medical Therapy if Elevated	Medical Therapy if Deficient
Prolactin	Cabergoline / Bromocriptine	-
GH	Octreotide	Growth Hormone
ACTH	Ketoconazole	Hydrocortisone
TSH	Carbimazole / Methimazole	Levothyroxine

Principles of Management: Systemic Therapy

- Dopamine agonists (i.e.: cabergoline and bromocriptine) have side effects that sometimes lead to discontinuation of medical therapy

Effect	Bromocriptine (N = 231)	Cabergoline (N = 221)
	number (percent)	
Nausea	115 (50)	68 (31)†
Vomiting	22 (10)	10 (4)
Constipation	21 (9)	15 (7)
Headache	68 (29)	66 (30)
Dizziness or vertigo	59 (26)	55 (25)
Abdominal pain, dyspepsia, or gastritis	45 (20)	34 (15)
Fatigue or weakness	41 (18)	29 (13)
Breast pain	12 (5)	10 (4)
Depression	4 (2)	7 (3)
Hot flashes	5 (2)	7 (3)

*Cabergoline was discontinued because of headache, nausea, and vomiting in three women and because of visual disturbance, stiffness of the hands, mastalgia, and various minor disturbances in four women. Bromocriptine was discontinued in 27 women because of gastrointestinal effects in 20, dizziness in 5, mastalgia in 1, and headache in 1.

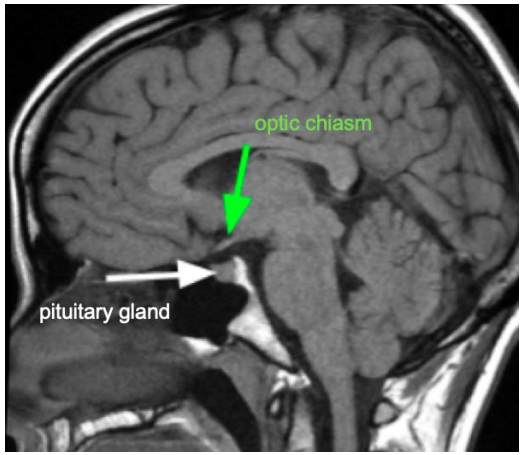
†$P<0.001$ for the comparison with the bromocriptine group.

A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. (Webster et al 1994)

Principles of Management: Radiation

- Radiation therapy is used adjuvantly in:
  - Pituitary carcinoma
  - Subtotal tumor resection
- Radiation therapy is also used for:
  - Unresectable tumors
  - Recurrent tumors
  - Tumors refractory to medical management
    - Theoretical benefit to discontinuing systemic therapy 1-2 months prior to RT, with resumption after RT completion. However, current evidence is equivocal

- Choice of radiation regimen:
  - Stereotactic radiosurgery favored for
    - Smaller tumors (< 3 cm)
  - Favor fractionated radiation for
    - Larger tumors (> 3cm)
    - Tumors < 3-5mm from the optic chiasm



- Radiation has excellent efficiency, with local control above 90%
  - Hormone normalization may take months – years

Radiation Dosing

The decision between SRS and fractionated regimens will often be decided based on the proximity and subsequent dose to the optic chiasm

Stereotactic Radiosurgery

- Non-secretory: 14 - 18 Gy
- Secretory: 18 - 35 Gy

Fractionated Radiation

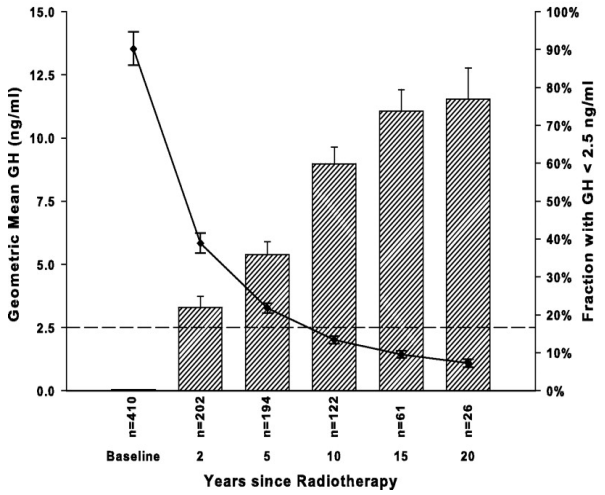
- Non-secretory: 45 Gy / 25 fx
- Secretory: 50.4 Gy / 28 fx
  54 Gy / 30 fx
- Carcinoma: 54 Gy / 30 fx
  60 Gy / 30 fx

Optic Chiasm Dose Constraint

- Single Fraction: 8-10 Gy Max
- Five Fractions: 25 Gy Max
- Conventional Fractionation: 54 Gy Max

Radiation Toxicities and Follow-Up

- Acute:
  - Fatigue
  - Headache
  - Alopecia
- Late:
  - Possible visual deficits, given proximity to optic chiasm
    - Risk is low if dose constraints are respected
  - High risk for hypopituitarism (especially hypothyroidism)
    - Almost all patients will have hormone deficiencies
- Follow-up:
  - For secretory adenomas, time-to-hormone normalization following radiation depends on the pre-irradiation hormone level as well as the type of hormone; however, this may occur on the order of years (Jenkins et al 2006)
  - Given risk of hypopituitarism, regular endocrinology follow-up with labs is important
  - MRI brain every 6 months; this can be stretched to yearly scans if imaging is stable



Percentage of all patients achieving a serum GH level less than 2.5 ng/ml (*bars*) and the mean GH level (*line*) in the years after pituitary irradiation for acromegaly (Jenkins et al 2006)

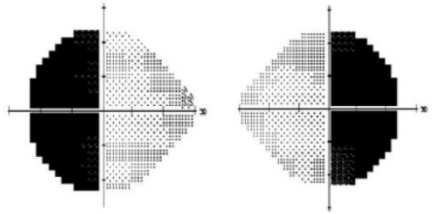
Case

History and Physical, Labs

- History
  - 19-year-old male with multiple endocrine neoplasia 1 (MEN 1) who presented with nausea, vomiting, dizziness, and headache
- Physical exam
  - Bitemporal hemianopia visual defect on exam
- Labs
  - Prolactin elevation of 2500 mcg/L (normal <200)

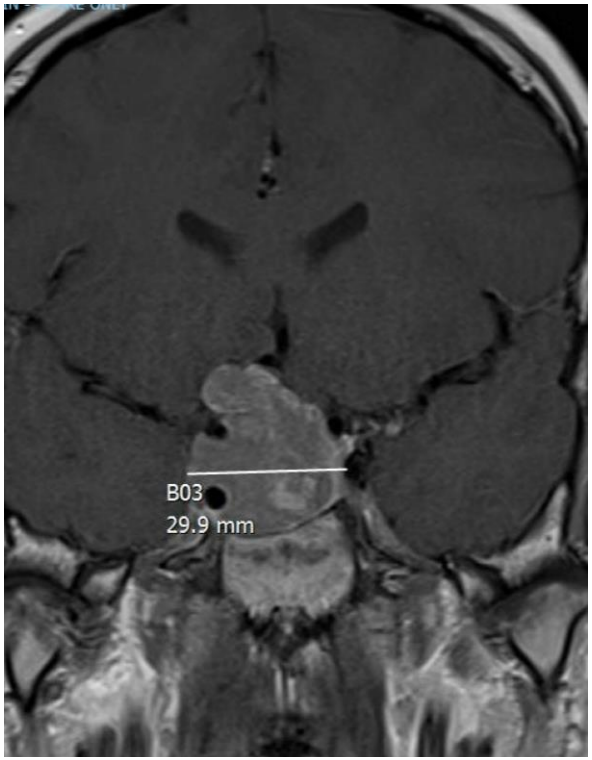
MEN 1 predisposes patients to:

- Pituitary adenoma
- Pancreatic neuroendocrine tumors
- Parathyroid adenoma

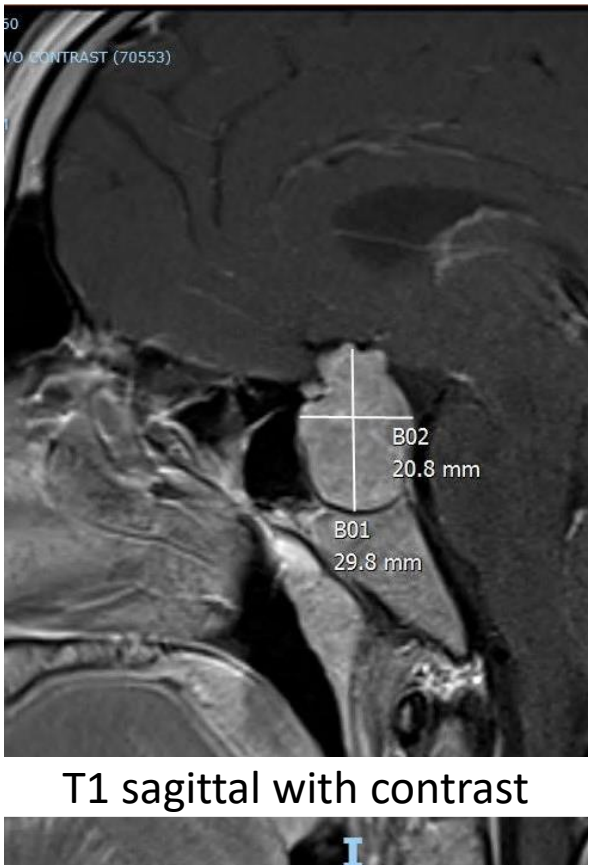


Serum prolactin level >200 mcg/L in a patient with a macroadenoma >10mm is diagnostic of a prolactinoma

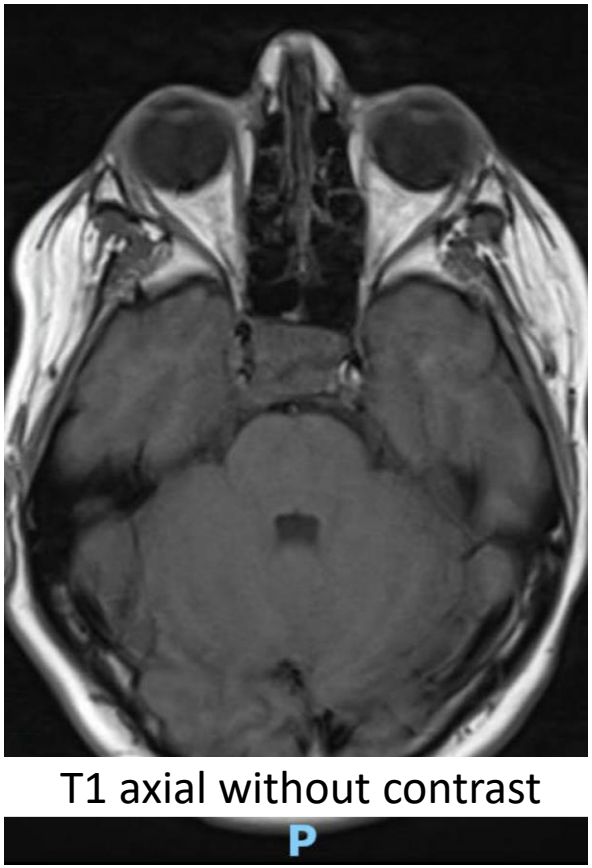
Radiologic Appearance



T1 coronal with contrast



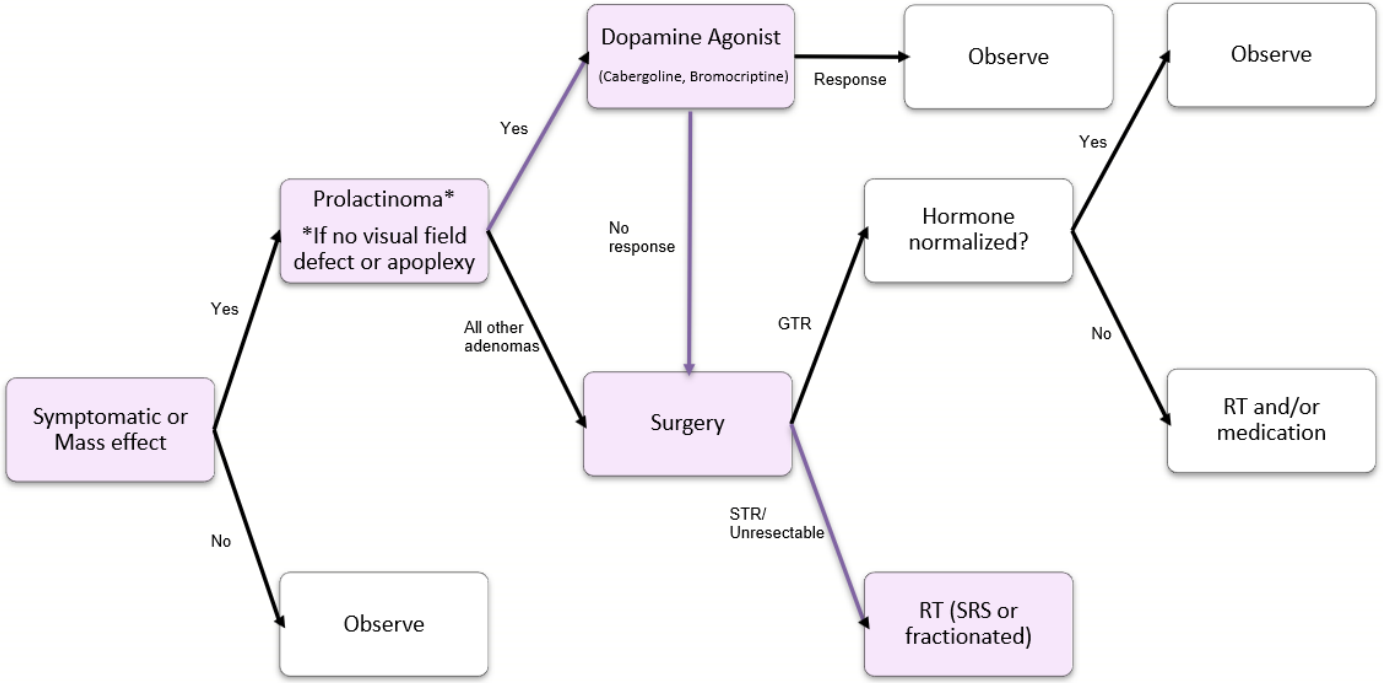
T1 sagittal with contrast



T1 axial without contrast

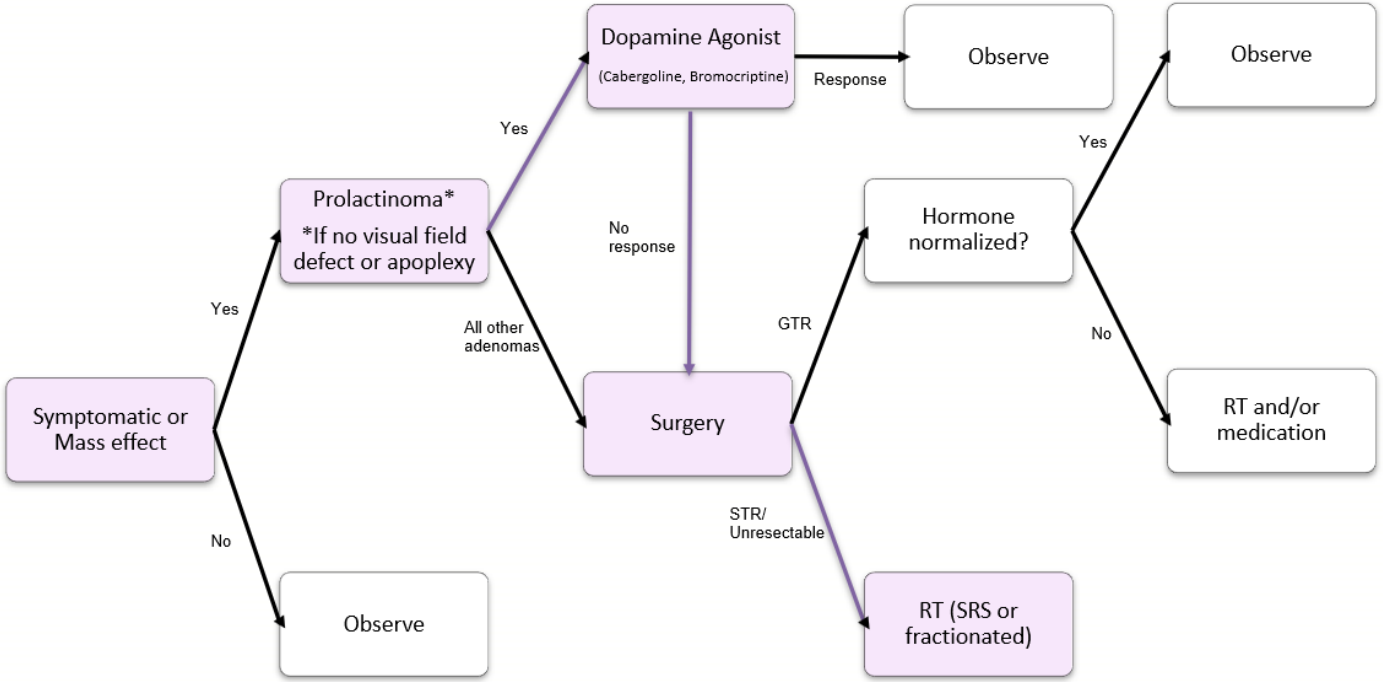
Initial Treatment

- **Medications**
  - He was started on cabergoline
  - His prolactin level initially decreased to 1700 mcg/L (normal <200)
  - He continued to have headaches and worsening vision (as well as increased prolactin levels despite cabergoline therapy), so he proceeded to surgery



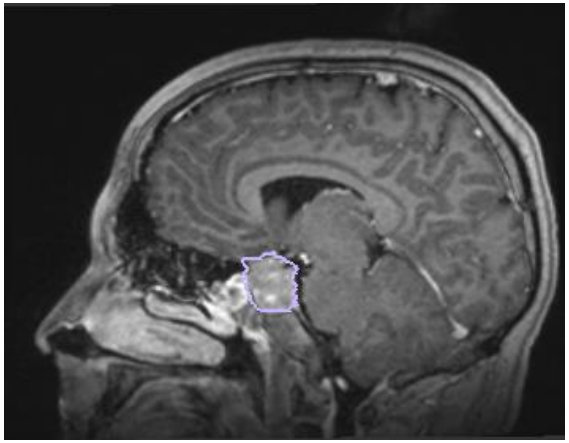
Initial Treatment

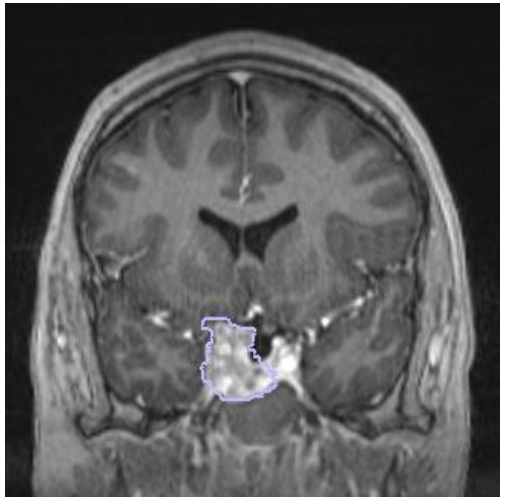
- **Surgery**
  - A subtotal resection was performed (endoscopic transsphenoidal approach)
  - Pathology returned for a lactotroph adenoma with Ki-67 of 4.7% and increased mitotic activity (associated with a more aggressive clinical course)
  - Subsequent brain MRI showed interval growth of the residual mass, so he was referred for radiotherapy

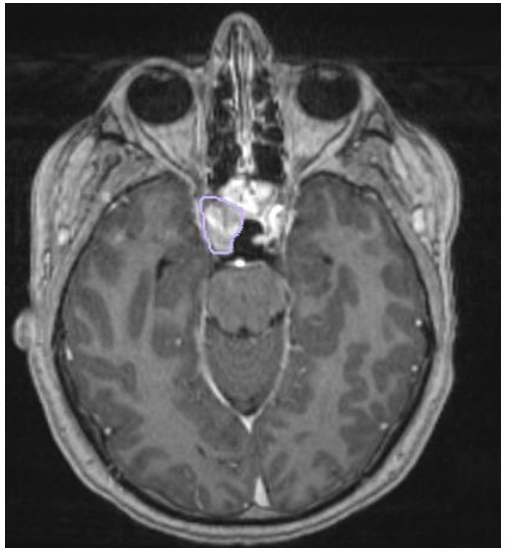


Radiation: Simulation and Treatment

- Simulation
  - CT without contrast
  - MRI with and without contrast
  - Supine with facemask
- Volumes
  - GTV: tumor seen on T1c MRI
  - CTV: 0.5 - 1 cm
  - PTV: 0.3 – 0.5 cm
- Dose
  - 50.4 Gy / 28 fx







Clinical Pearls

- Pituitary adenomas are the most common suprasellar mass in adults
- They are classified as functional and non-functional based on their secretory status

- For symptomatic tumors (apart from prolactinomas), surgery is typically first-line therapy (with radiation reserved for treatment refractory cases)
- Radiotherapy can be delivered via SRS or fractionated approaches
  - SRS Doses: 14 – 18 Gy / 1 fx for nonfunctional, 18 - 35 Gy / 1 fx for functional
  - Fractionated Doses: 45 Gy / 25 fx – 54 Gy / 30 fx

- When providing radiotherapy:
  - Special attention must be given to the optic apparatus, as this lies just superior to the treatment field
  - Regular endocrinology follow-up is key, as there is a high risk of hypopituitarism

References

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