Pituitary Cases

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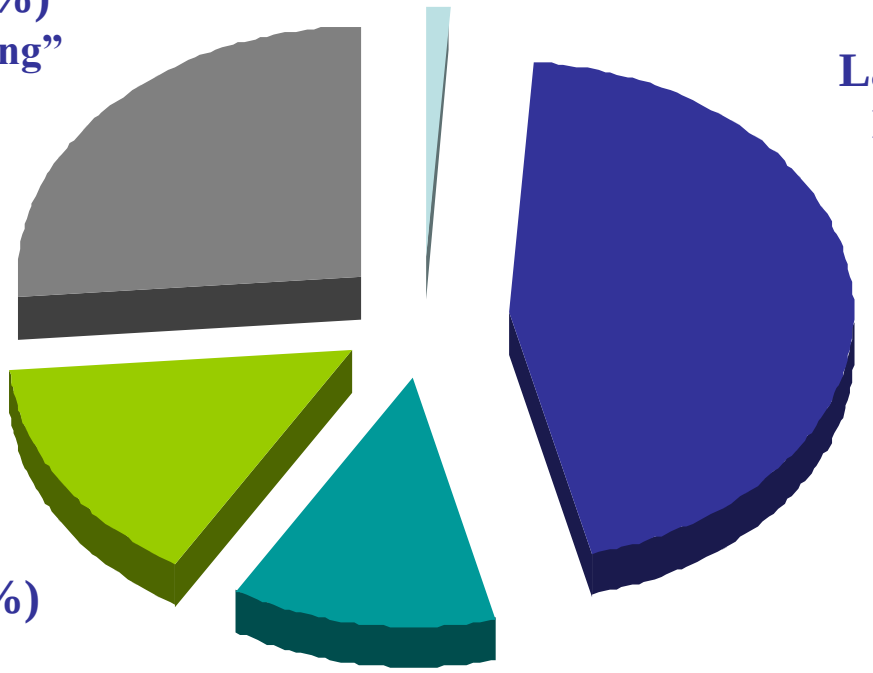
Pituitary tumor types



Thyrotroph (1%)
Hyperthyroidism

Gonadotroph (15-40%)
"Clinically nonfunctioning"
Visual field loss
Hypopituitarism

Lactotroph (40-50%)
Hyperprolactinemia

Somatotroph (10-20%)
Acromegaly

Corticotroph (10-15%)
Cushings Disease

Case

- 27-year-old woman is referred for galactorrhea and amenorrhea
- History of menarche at age 12 with regular menses until age 24
- Noticed spontaneous galactorrhea at age 25
- Prolactin found to be 42.3 ng/ml (50.0 in diltution)
- She is taking no medications

Question 1

Which test should NOT be done now?

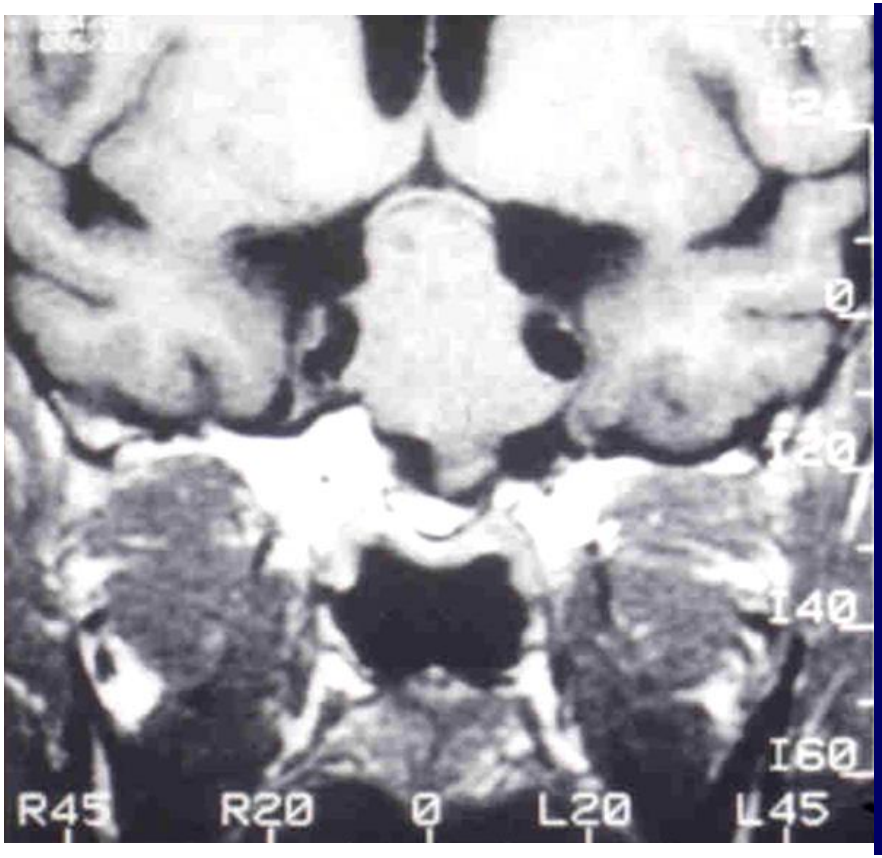
1. MRI
2. TSH
3. hCG
4. Creatinine

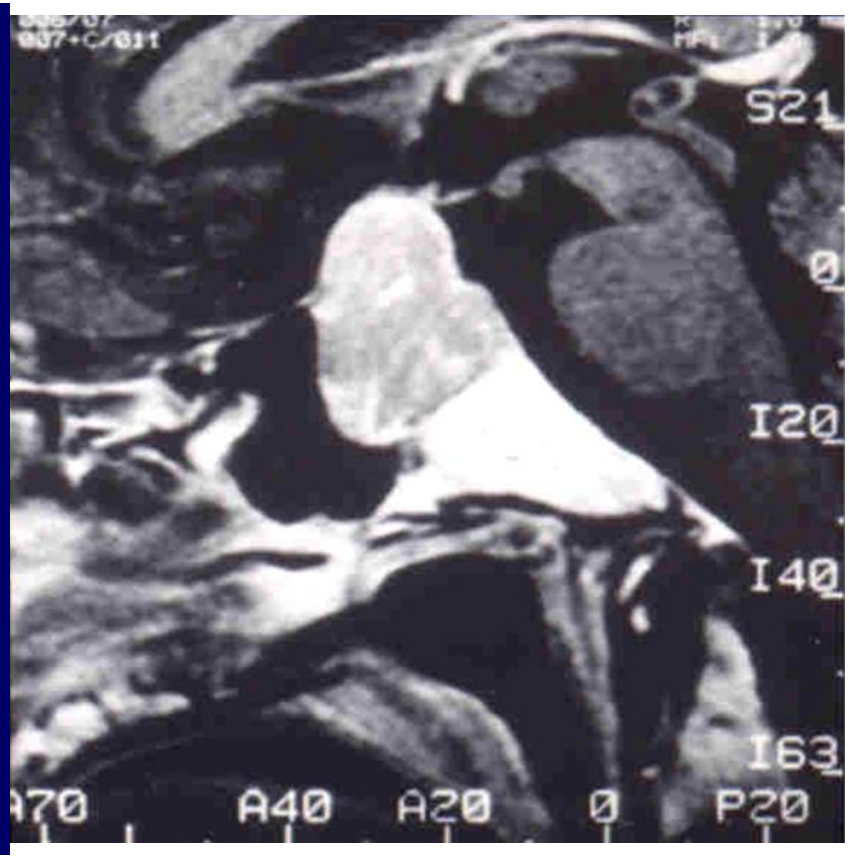
Question 2

As the blood tests were normal, which of the following should be done now?

1. Start cabergoline 0.5 mg weekly
2. Obtain MRI of pituitary/hypothalamic area
3. Start estrogen/progesterone cyclic therapy
4. Observe and repeat PRL every 6 months

The patient's MRI revealed a large macroadenoma





Question 3

What should be done next?

1. Start cabergoline 0.5 mg twice weekly
2. Measure an IGF-1
3. Evaluate for hypopituitarism
4. Obtain formal visual field assessment
5. Refer for neurosurgery

Question 3

- All patients with macroadenomas should be evaluated for hypo- and hyperpituitarism
- Patients with tumors that abut the chiasm need to have formal visual field assessments, as this will influence therapy

Question 4

She had a right superotemporal field cut.
What should be done now?

1. Start cabergoline
2. Refer to neurosurgery
3. Start replacement hormones as needed
4. Obtain the IGF-1 result

Question 4

- The IGF-1 level was 789 ng/ml- more than twice normal and 810 ng/ml on repeat
- **The patient has acromegaly**

Case

A 43-year-old man referred by his dentist for question of acromegaly

He reports:

- increased teeth spacing and jaw changes
- shoulder and hip pain
- headache
- increasing ring size and shoe size x 2 yrs
- fatigue
- poor sleep
- decreased libido

Case: Exam

HR 78 BP 144/82 WT 115.6kg HT 187cm

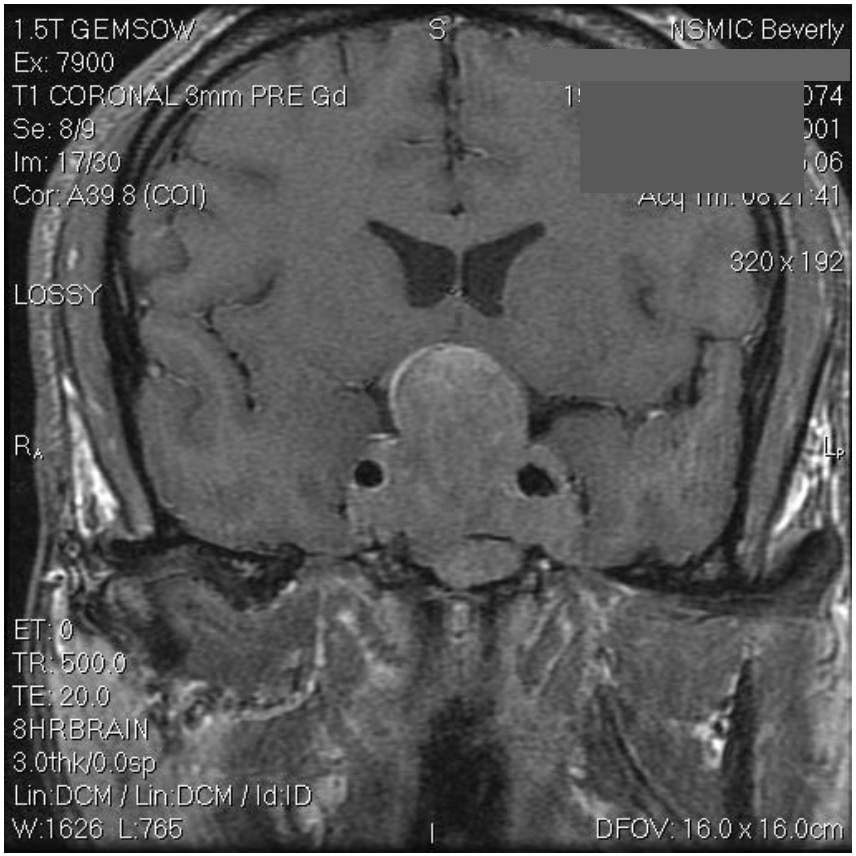
Well-virilized male

- Skin: multiple skin tags
- HEENT: large brow and jaw, increased space between teeth, large tongue, grossly abnormal visual fields
- Neck: 1cm left thyroid nodule
- Ext: thickened digits, dough-like palms
- Genital: 25ml testes

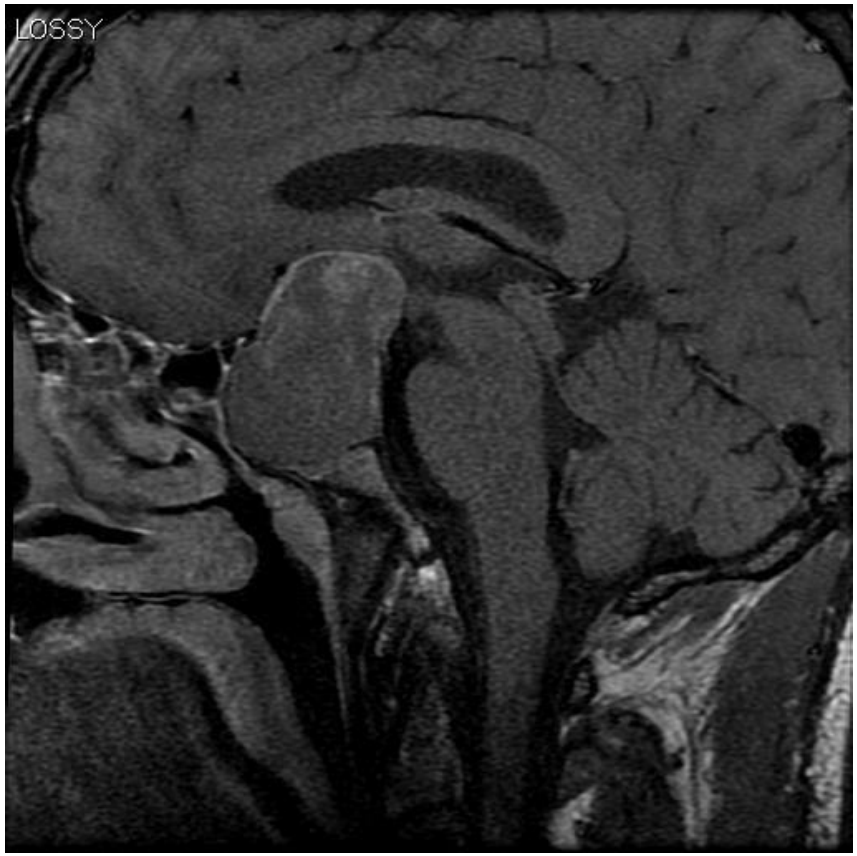
Case: Laboratory tests

- IGF 1047 ng/ml (90-360)
- GH (OGTT nadir) 14 ng/ml (2-6)
- Testosterone 102 ng/dl (175-781)
- LH 3 U/L (2-12)
- FSH 7 U/L (1-12)
- Cort stim 12 ug/dl (0 min) - 20 (60 min) (nl > 18)
- TSH .41 uU/ml) (.34-5)
- Free T4 0.8 ng/dl (.8-1.8)
- Prolactin (diluted) 33 ng/ml (3-13)
- HbgA1C 6.8 (3.8%–6.4%)
- Random glucose 158 mg/dl

Preoperative Pituitary MRI



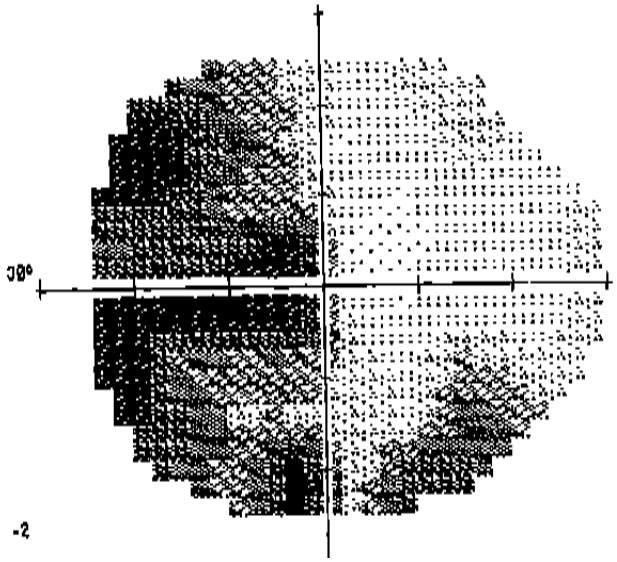
Coronal postcontrast



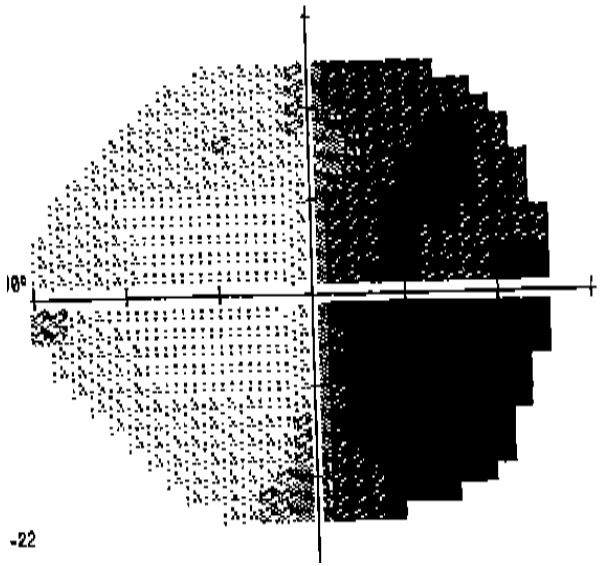
Sagittal postcontrast

Baseline Visual Fields

Bitemporal Hemianopsia



Left Eye

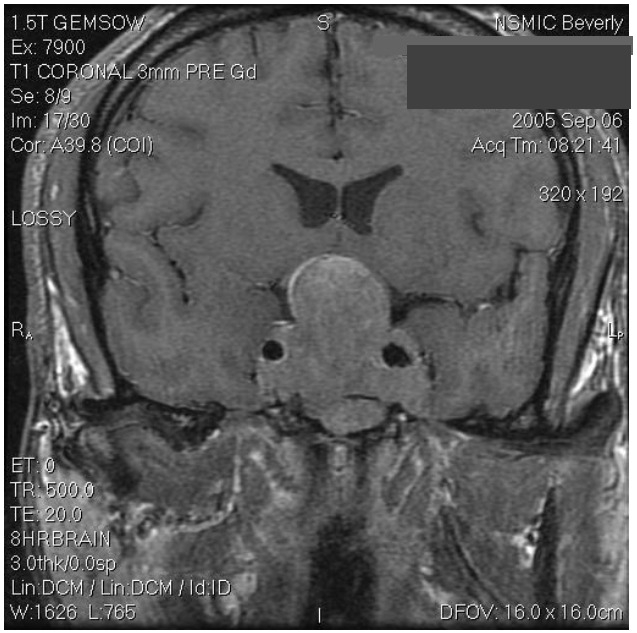


Right Eye

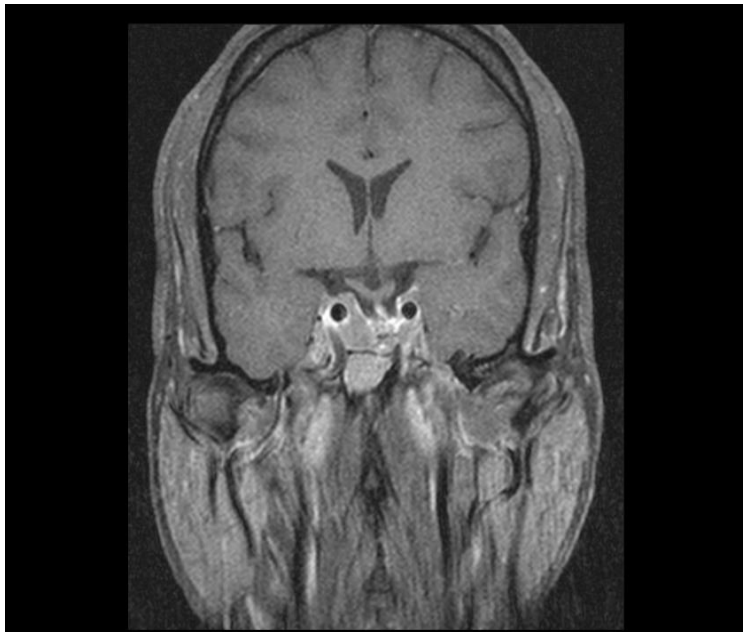
Pathology Results

- Pituitary adenoma
- Immuno-histochemical staining of tumor cells showed most cells stained for growth hormone and many for prolactin. Scattered cells positive TSH-beta
- Confirmed growth secreting adenoma

Preoperative and Postoperative Comparison



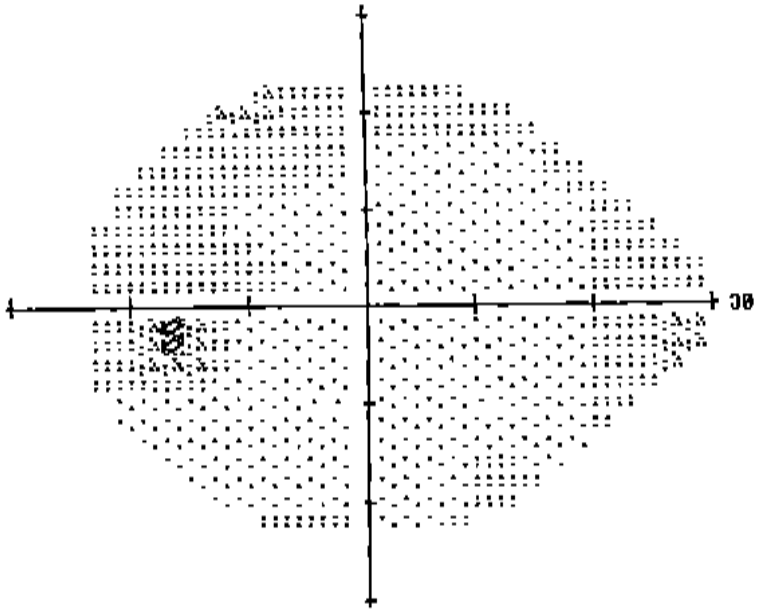
Preoperative



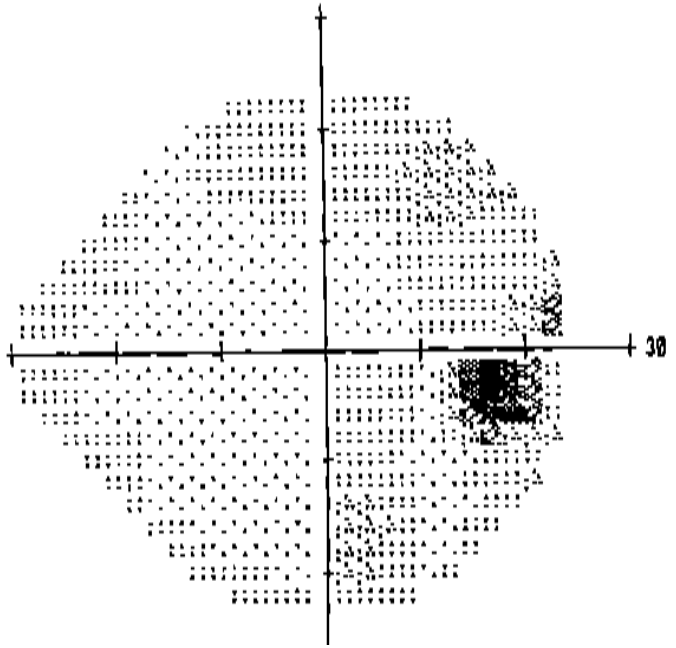
Postoperative

Postoperative Visual Fields

Normal



Left Eye



Right Eye

Serum IGF-I Concentrations Before and During TX

IGF-I (ng/mL)	Therapy
1047	**Preoperative/No TX**
862	**12 Weeks postoperative**
612	**After OCT LAR 20 x 3 months**

IGF-I normal range (90-360 ng/ml)

Acromegaly Case: Question 1

What would you suggest next as therapy for acromegaly?

A. Increase dose of OCT LAR
B. Add pegvisomant
C. Suggest radiation therapy
D. Repeat surgery
E. Add cabergoline

Cavernous sinus lesion not surgically accessible

Answer: A

Since there has been some SA response shown by improved IGF-1 and SA dose is not maximized, should increase OCT LAR as next step and if IGF-1 does not normalize, other choices could be considered.

Follow-up Serum IGF-I Levels on OCT LAR

IGF-I (ng/mL)	Therapy
1047	Preoperative/No TX
862	12 weeks Postoperative
612	20 mg OCT LAR x 3 months
411	30 mg OCT LAR x 1 months
326	30 mg OCT LAR x 3 months
291	30 mg OCT LAR x 6 months

(IGF-1 normal range = 90-360 ng/mL)

Acromegaly Case: Question 2

What would you suggest as continuing management of acromegaly?

A. **Serial follow-up of pituitary MRI**

B. **Interval re-assessment of metabolic & anterior pituitary function**

On SA follow HbgAIC since SA may inhibit insulin

C. **Monitor IGF-1 levels on a SSA- OGTT monitoring of limited usefulness in SSA treated patients.**

Carmichael JD J Clin Endocrinol Metab 2009

D. **Consider long-acting LAN SC; home-injection for convenience. SSAs are comparable in efficacy.**

E. **All of the above**

Answer: E

All of the above are important measures or considerations in the ongoing management of acromegaly in this patient

Acromegaly Case: Question 3

In this case, the IGF-1 level normalized with a SSA. What would you suggest if the IGF-1 level decreased but did not normalize?

A. **Serial follow-up of IGF-1 levels and pituitary MRI**
B. **Add cabergoline**
C. **Add pegvisomant**
D. **Consider radiation therapy**
E. **All of the above except A**

Answer: E

All of the above except for A are important measures or considerations in the ongoing management of acromegaly in this patient. Continued elevation of IGF-1 and GH levels lead to increased co-morbidities and decreased life expectancy.

Management of Acromegaly: Summary Points

- Goals are to keep IGF-I and GH levels normal; control symptoms and co-morbidities; control tumor mass
- Medical and/or radiation therapy are used in tumors not cured by surgery
- Medical therapy with a somatostatin analog is effective in controlling IGF-1/GH excess in most cases. Lower rates with very high IGF-1 levels
- Pegvisomant controls IGF-1 level in almost all patients but does not treat the underlying pituitary tumor
- Tumor shrinkage with SRLs occurs in about 30% of patients

Cushing's Case

- 43 y/o woman presented with hirsutism, wt gain, new onset hypertension
- MRI shows 10 mm lesion c/w an adenoma
- ACTH level is 90 pg/mL
- 11 pm Salivary cortisols elevated x3 done one week apart

  1, 2.0 and 1.2 mcg/dL
- 24 hr UFC 128, 164 mcg/24h
  - (353, 452 nmol/24h)
  - Nl < 70 mcg/24h

Question 1

Which should be done now?

1. Order inferior petrosal cath
2. Schedule visit to Neurosurgery
3. Obtain a high and low dose dexamethasome suppression test
4. Schedule a dex/CRH test
5. Order an adrenal CT scan

Management of CD: Typical diagnostic evaluation

- Diagnosis
  - Failed 1mg overnight dexamethasone suppression
  - Elevated UF and 11pm salivary cortisols
  - ACTH levels elevated
  - MRI <5 mm lesion
  - Inferior Petrosal Sinus Sampling (IPSS) central:peripheral ratio > 3:1 after CRH
- Treatment
  - Transsphenoidal surgery
  - Pathology: ACTH adenoma
- Outcome: hypoadrenal = remission
  - Criteria: UFC < 20 ug/24 hr; serum cortisol < 5 ug/dl
  - Post op UFC 6,11 ug/24hr
  - Fasting serum cortisol 1.5 ug/dl

“Negative” IPSS

- Make sure the test is done correctly
  - Were both IPS cannulated?
- If predictive of ectopic, and no ectopic found, should you consider pituitary exploration?

Question 2

The patient undergoes pituitary surgery and her UF cortisols on 0.5 mg of Dex are normal at 65, 40 and 35 mcg/24 hrs (normal < 70). Tumor stains for ACTH

What can you say about this patient?

1. Her UF cortisols are normal- she is cured
2. She is not cured and needs repeat surgery right away
3. She may be cured if we wait

Clinical Course

Repeat UF cortisols 3 weeks later are now markedly elevated at 125 and 130 mcg/24h. One repeat salivary cortiosl is twice normal

MRI shows a small amount of residual tissue

She continues to feel tired and has not lost weight

Question 3

What can you say about this patient?

1. Her UF cortisols are elevated but we should wait longer- she may have delayed remission
2. She is not cured and needs repeat surgery
3. She needs a petrosal cath as she never had one to make sure this is pituitary Cushing's
4. She needs medical therapy as first surgery was not curative so no point in another one

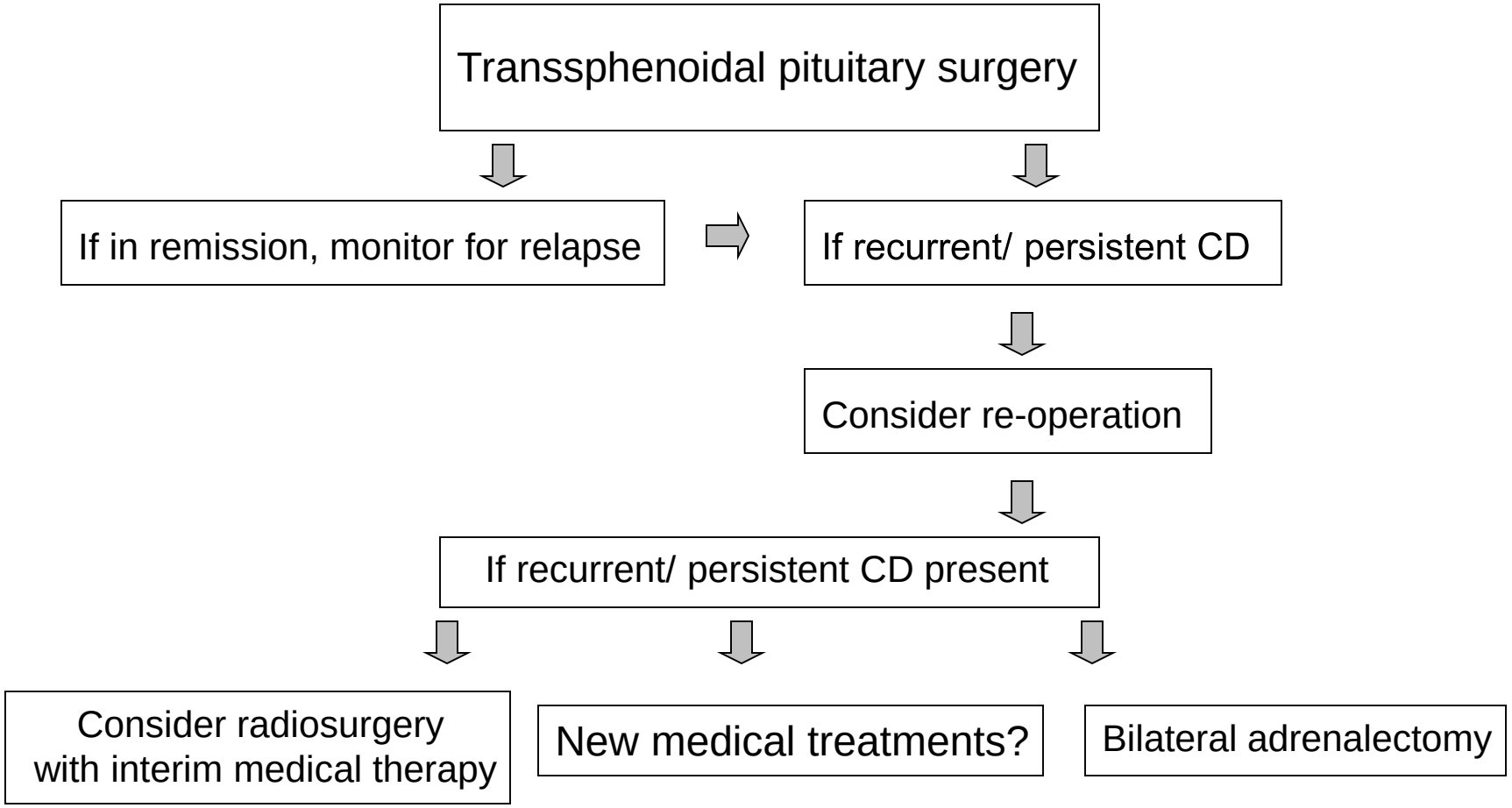
Clinical Course

No need for petrosal cath as a tumor was confirmed

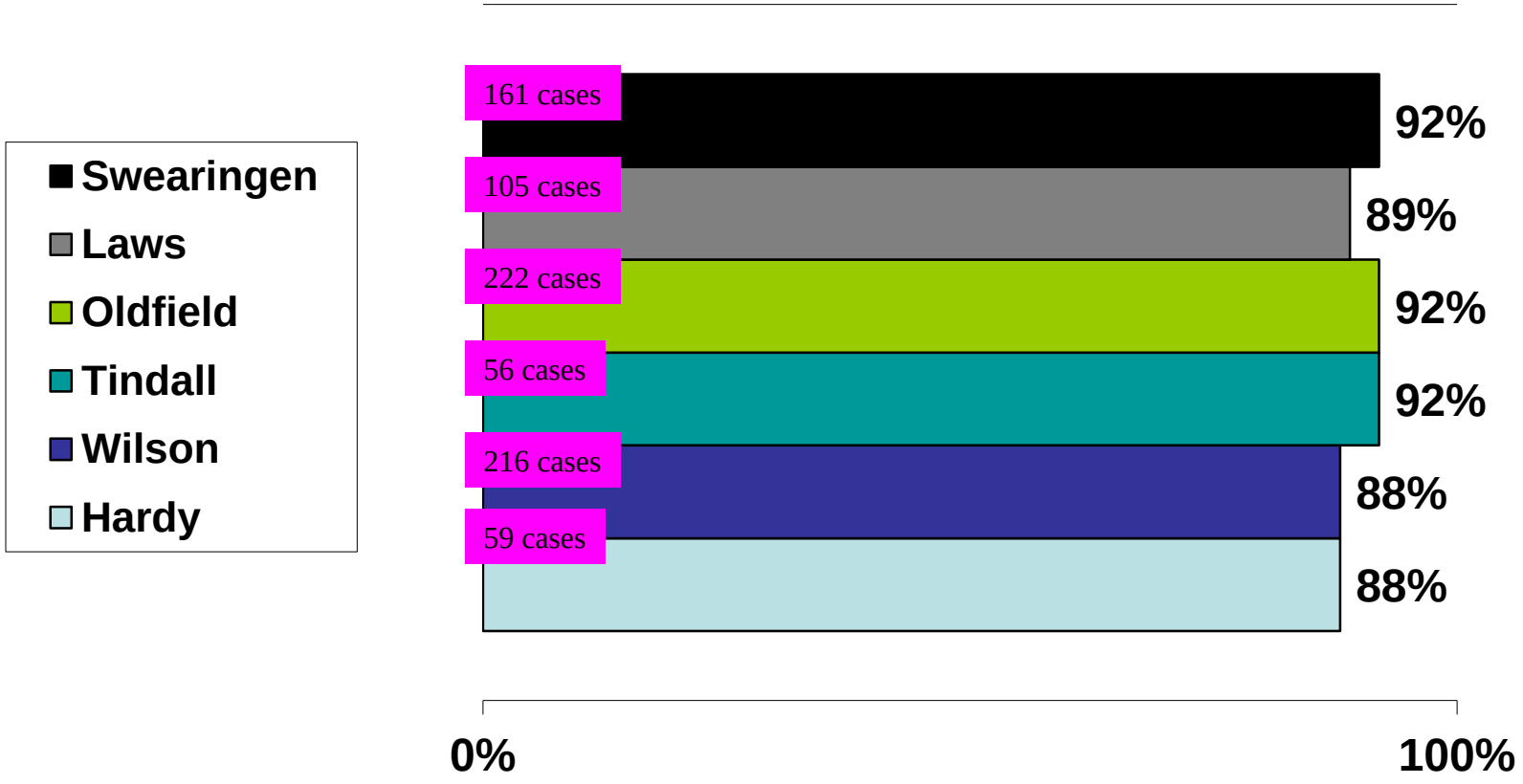
Repeat transsphenoidal surgery was done and post-op cortisols undectable

She continues to feel tired on cortisol replacement; T4 normal but has lost weight

Cushing's Disease Treatment Algorithm



Results after transsphenoidal surgery for microadenomas



Results after surgery

- No surgeon publishes bad results
- Only expert surgeons publish
- These statistics are for *intrasellar microadenomas*
- Results are from specialized centers

Patient with Cushing's Disease *before* Surgery at MGH

Patient with Cushing's Disease *after* Surgery at MGH

Management of persistent disease

- Role of early re-operation for persistent disease
  - Re-operation 7-46 d postop (Ram *J Neurosurg* 1994)
    - 12/17 (71%) resolution of hypercortisolism
  - How early is early?
  - Delayed remission (Valassi *JCEM* 2010)
    - 620 pts; three centers (MGH, Milan)
    - Progressive decline in HPA-axis testing after 5 days post-op
    - 35/620 (5.6%) delayed remission at mean 38 days (median 9 d) postop
  - Have we re-operated too early in some cases?
    - Wait until levels have plateaued before proceeding

Treatment of persistent CD after initial surgical failure

- Success rate of early re-operation
  - 15 studies (1989-2009), 192 pts overall
  - Average remission rate 54% (103/192)
    - Range 0-100%
- Increased risk of hypopituitarism (Ram *J Neurosurg* 1994)
  - 5% if selective adenomectomy
  - 50% if aggressive resection

Treatment for persistent/ recurrent Cushing's disease

- Treatment options
  - Re-operation
  - Radiation treatment
  - Bilateral adrenalectomy
  - Medical therapy

Cost of treatment

- Transsphenoidal surgery: $50,000-70,000
  - Average LOS 1-2 d
- Adrenalectomy: $75,000-100,000
  - Average LOS 4-8 days
- Proton Radiosurgery: $40,000
  - Outpatient, one day
- Medical – ongoing yearly cost, retail pharmacy
  - Cabergoline: (3.5 mg/wk) - ~$15,000/yr
  - Pasireotide: $172,603/ yr
  - Mifepristone: $271,560/ yr at 1200mg dose