Diagnosis and Management of Mild PHPT

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Froedtert & Medical College of Wisconsin

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Potential Conflicts of Interest (Past 12 months)

- None
- *I do have opinions*

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Topics

- PHPT
- Normocalcemic PHPT
- Pregnancy
- FHH
- Will integrate new guidelines

3

Hypercalcemia – PTH Dependent
PTH high or inappropriately normal

- Primary hyperparathyroidism
  - Sporadic (SGD, MGD, carcinoma, parathyromatosis)
  - Familial (Amy Donahue will discuss)
    - MEN1, MEN 2, MEN 3 (2b), MEN 1-like, MEN 4, HRPT2, FIH
- Familial hypocalciuric hypercalcemia (FHH)
- Autoimmune hypocalciuric hypercalcemia
- Lithium associated hypercalcemia
- Ectopic PTH – RARE!

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Typical PHPT

- Mean Ca 10.6-10.8 with nl/high PTH & nl/high Uca
- Persistent/Intermittent hypercalcemia
- Pathology;
  - adenoma ~ 80% - 90%
  - multiple gland disease 10 -20%
  - parathyroid carcinoma rare

Evaluation

3. **How should patients with PHPT be evaluated?**
   - 3.1. Biochemical: Measure adjusted total serum calcium (ionized if normocalcemic PHPT is a consideration), phosphorus, intact PTH, 25OHD, creatinine
   - 3.2. Skeletal: Three-site dual-energy X-ray absorptiometry (DXA) (lumbar spine, hip, distal 1/3 radius); imaging for vertebral fractures (vertebral fracture assessment [VFA] or vertebral X-rays); trabecular bone score (TBS) if available
   - 3.3. Renal: Estimated glomerular filtration rate (eGFR) or, preferably, creatinine clearance, 24-hour urinary calcium and for biochemical risk factors for stones; imaging for nephrolithiasis/nephrocalcinosis
   - 3.4. Nonclassical manifestations (neurocognitive, quality of life, cardiovascular): there are no data to support routine evaluation for these putative manifestations

Genetic Testing
< 30y
MGD
FH
Syndromic
Atypical adenoma/parathyroid carcinoma
Suspicion FHH

Bilezikian et al, JBMR 2022

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Lithium associated hypercalcemia

- Changes set point for PTH resulting in higher calcium to lower PTH (via CaSR)
- May have similar effect on renal CaSR resulting in hypocalciuric hypercalcemia
- Higher incidence MGD
- Lower surgical cure rate
- Usually does **NOT** resolve with stopping lithium

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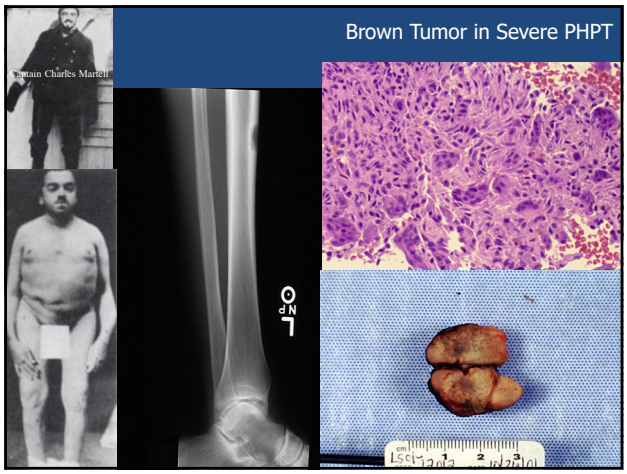
Brown Tumor in Severe PHPT

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Brown Tumor in Severe PHPT
How about the Skeleton in "Typical" PHPT?

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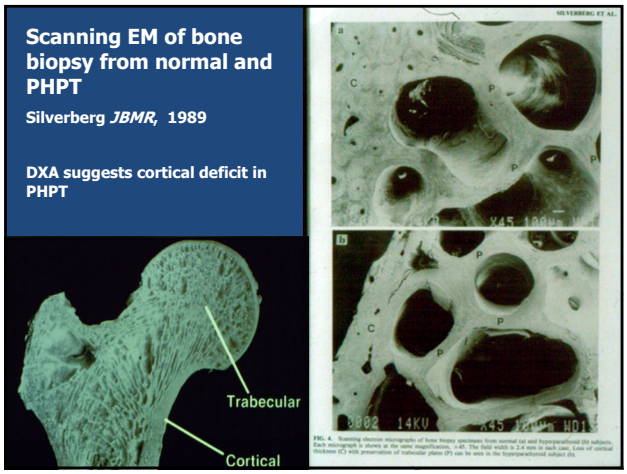
Scanning EM of bone biopsy from normal and PHPT
Silverberg JBMR, 1989
DXA suggests cortical deficit in PHPT
Trabecular
Cortical

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Fractures in PHPT

674 patients with PHPT (mean sCa 11.8 mg/dl) compared with 2021 controls. Fractures increased up to 10 years before PTx and declined after surgery. Denmark
Vestergaard *BMJ* 2000

RR of Fx before and after surgery (95% CI)

Khosla JBMR 1999
Mayo

	Site	Before Surgery	After Surgery
3.2	Vertebra	3.5 (1.3-9.7)	0.8 (0.2-2.7)
2.2	Forearm	1.9 (1.1-3.3)	0.7 (0.4-1.4)
1.4	Femur	1.5 (0.8-2.6)	1.3 (0.8-2.0)
1.3	Any site	1.8 (1.3-2.3)	1.0 (0.8-1.3)

Recent Danish population-based study found increased hip and MOF fx in PHPT compared to controls
Kanis et al, Ost Int 2023

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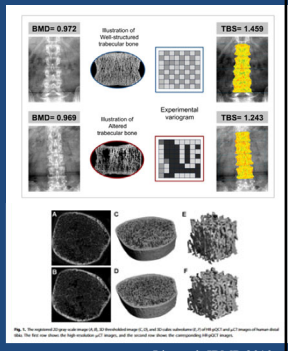
TBS/HRpQCT in PHPT

- TBS reduced PHPT (1,2)
- Low TBS assoc. with vert fx in PHPT
  - Independent of BMD (2)
- TBS improves after PTx (2)
- PHPT Abnormal HRpQCT (3)
- HRpQCT distal radius and tibia (4)
  - Microstructure improves after PTx
  - FEA estimated bone strength increases after PTx

1. Silva et al, JCEM 2013
2. Eller-Vainicher et al, Eur J Endoc 2013
3. Stein et al, JBMR 2013
4. Cusano et al, JCEM 2018



Liu et al, JBMR 2010

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PHPT Bone

- Cortical **and trabecular** defects
  - Trabecular Bone Score, HRpQCT
  - Vertebral and other fx
- Columbia prospective data
  - BMD decreases over time
- RTCs show BMD increases after PTx and stable in those without surgery 1-2 y. TBS and HRpQCT improve w/ Ptx
- Scandinavian RCT at 10 years – no difference in fx but number way to small for fx trial
  - Pretorius et al, Ann Intern Med 2022
- *I believe PTx decreases fracture risk in mild PHPT*
  - Dr. Yen will discuss in detail

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PHPT Stones

- PTx decreases stone events ("low quality evidence" (1)) over time but some still form stones (Dr. Yen will discuss)
  - *If marked hypercalciuria before surgery, I do 24 h U (Ca, Cr, Na) after surgery*
  - *If stones before surgery, I do 24 h U stone panel after surgery*

1. Ye et al, JBMR 2022

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CV PHPT

Observations

- Mortality increased in more severe PHPT. Not clear in mild PHPT (1).
- Hypertension
- LVH in some studies
- Increased carotid IMT and stiffness
- Increased aortic stiffness
- Increased cardiac calcification area
- Abnormal vascular function

RCTs

- 116 patients at 2yr .
  - No diff in BP, markers of insulin resistance, lipids etc. (2)
- 49 Patients at 2 yr.
  - Minor and borderline significant effect of surgery on echo (3)
- 50 patients at 1 year
  - Baseline echo normal and no change in either group (4)
- 130-170 patients at 10 yrs
  - No diff in survival/CV events (5)

1. Wermers et al, Am J Med 1998
2. Bollerslev et al, JCEM 2009
3. Persson et al, Clin Endoc 2011
4. Ambrogini et al, JCEM 2007
5. Pretorius et al, Ann Intern Med 2022

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CV PHPT

Observations

- Mortality increased in more

RCTs

- 116 patients at 2yr .

"Causality between PHPT and CVD mortality remains uncertain due to lack of consistent reversibility of mortality risk post-PTX" (El-Hajj Fuleihan et al, JBMR 2022)
No ***proven*** benefit of surgery on CVD/mortality *(? Adequate power)*
Dr. Yen will discuss

- Increased cardiac calcification area
- Abnormal vascular function

- 130-170 patients at 10 yrs
  - No diff in survival/CV events (5)

1. Wermers et al, Am J Med 1998
2. Bollerslev et al, JCEM 2009
3. Persson et al, Clin Endoc 2011
4. Ambrogini et al, JCEM 2007
5. Pretorius et al, Ann Intern Med 2022

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PHPT and Neuropsych

Observations

- Classical PHPT
  - Prominent psychiatric and neurological manifestations
- Observations in mild PHPT
  - anxiety, depression, decreased concentration, decreased memory, sleepiness
- Non- randomized/observational trials suggest improvement (1, 2)

RCTs

- Detroit (53 patients) PTx vs. conservative followed at least 2 yr (3)
- Pisa (50 patients) PTx vs. conservative management in mild PHPT at 1 yr (4)
- Scandinavia (191 patients) PTx vs. conservative management in mild PHPT at 1 yr (119), 2 yr (99) reported (5). 10-year data (6)
  - Very modest effects of questionable clinical significance
- Houston (18 patients) RCT PTx vs. observation in mild PHPT
  - Improved sleep and decreased sleepiness (7)

1. Espiritu et al, *JCEM* 2011
2. Kearns et al, *Clin Endoc* 2019
3. Rao et al *JCEM* 2004
4. Ambrogini et al, *JCEM* 2007
5. Bollerslev et al, *JCEM* 2007
6. Pretorius et al, *JBMR* 2021
7. Perrier et al, *Surgery* 2009

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PHPT and Neuropsych

Observations

- Classical PHPT

RCTs

- Detroit (53 patients) PTx vs.

Difference between observational and RCT could suggest selection bias/PBO.

"Randomized clinical trials (RCTs) comparing parathyroidectomy vs observation in mild PHPT showed no clear evidence for causal relationship between PHPT and neuropsychiatric symptoms" (El-Hajj Fuleihan et al, JBMR 2022)

My opinion

If significant depression/neuropsych, strongly consider surgery

Manage patient's expectations

My experience for what it's worth - 3 groups

1. ***Better and stay better***
2. ***Feel no different***
3. ***Better at 3 months but convinced PHPT back 12 months later***

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These are the patients in whom surgery is definitely recommended. Surgery is still a consideration in other patients and the guidelines are NOT intended to say the other patients should not have surgery!

Table 2. Recommendations for Surgical Management of PHPT

A. Surgery to be recommended if one of the following is present:

1. Serum calcium >1 mg/dL (0.25 mmol/L) above upper limit of normal
2. Skeletal features:
   a. Fracture by VFA or vertebral X-ray
   or
   b. BMD by T-score ≤ −2.5 at any site
   or
3. Renal features:
   a. eGFR or CrCl <60 cc/minute
   or
   b. Nephrocalcinosis or nephrolithiasis on X-ray, ultrasound, or other imaging modality
   c. Urinary calcium excretion >250 mg/day (women) or > 300 mg/day (men).*
4. Age < 50

B. Surgery to be recommended if one of the following occurs in follow-up*

1. Serum calcium consistently is measured >1 mg/dL (0.25 mmol/L) above upper limit of normal
2. Fracture
3. Kidney stone
4. Significant reduction in BMD to a T-score of ≤ −2.5).
5. Significant reduction in CrCl**

* Represents a change from prior international workshop guidelines.[1]
** For monitoring of renal function, the calculated CrCl is preferred over the estimate of eGFR.[12,17] Worsening kidney function that is thought to be clinically meaningful (e.g., a verified annual decline of 3 mL/min over several years to below 60 cc/min).
Abbreviations: CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; PHPT, primary hyperparathyroidism.

Bilezikian et al, JBMR 2022

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Summary of Panel Recommendations for Nutritional and Pharmacological Management of PHPT in those not to undergo parathyroid surgery

- BP or DMAB if needed for low BMD
- Cinacalcet if needed for hypercalcemia
- 25D > 30 ng/ml (? 20 ng/nl)
- Calcium IOM Total; 800 mg/day for women < 50 and men < 70 years old; 1000 mg/day for women > 50 and men > 70 years old.
- Annual serum calcium, renal function, 25-hydroxyvitamin D
- BMD every 1 or 2 years (? longer interval if BMD normal)
- If indicated
  - VFA or spine films
  - TBS useful
  - Renal imaging (X-ray, ultrasound, or CT) or 24-hour for calcium/creatinine

Bilezikian et al, JBMR 2022

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Case

- 62 male "normocalcemic PHPT"
  - Imaging finds compression deformity,
  - BMD T-scores
    - Spine -4.0, FN -2.9, TH -2.3
    - Calcium/D intake good
    - No stones
    - Nothing to suggest syndromic PHPT
  - FH, SH, Exam N/C
- Calcium 9.2, 9.3 mg/dl
- PTH 79, 87 pg/ml
- Phos 2.9 mg/ml
- 25D 34 ng/ml
- Ionized calcium 1.24 mmol/l
- Urinary calcium 129 mg/day
- Celiac serology/small bowel bx ok

Has surgery at famous institution

3 glands removed

Calcium 9.1, 9.3 mg/dl with PTH 70, 105 pg/ml

Goes to another famous institution

"Never had normocalcemic PHPT"

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Case

- 62 male "normocalcemic PHPT"
  - *Imaging finds compression*
- Calcium 9.2, 9.3 mg/dl
- PTH 79, 87 pg/ml

8. **How should normocalcemic PHPT be managed? Panel recommendations**
   8.1. Because of limited data, we cannot recommend guidelines for surgery in normocalcemic PHPT at this time.

  - Nothing to suggest syndromic PHPT
  - FH, SH, Exam N/C

Has surgery at famous institution

3 glands removed

Calcium 9.1, 9.3 mg/dl with PTH 70, 105 pg/ml

Goes to another famous institution

"Never had normocalcemic PHPT"

Bilezikian et al, JBMR 2022

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Definitions

- **Hypercalcemic primary hyperparathyroidism (HPHPT)**
  - Hypercalcemia or intermittent hypercalcemia with high or inappropriate PTH due to autonoumous parathyroid tissue (adenoma, multiple gland disease, cancer)
- **Secondary hyperparathyroidism (SHPT)**
  - Normal calcium with elevation in PTH that is a physiologic response
    - Eg CKD, vitamin D deficiency, GI malabsorption
- **Normocalcemic PHPT (NPHPT)**
  - Persistently (over 3-6 months minimum) normal corrected calcium and ionized calcium with persistently elevated PTH due to autonomous parathyroid tissue (adenoma, multiple gland disease, cancer)
    - Often found during evaluation of low BMD or kidney stones

SHPT and NPHPT may be very difficult to differentiate

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Normocalcemic PHPT

Course

- Some become hypercalcemic
- PTH sometimes normalizes

Assay Issues

- False elevation in PTH (1-3)
  - Heterophile ab
  - Antimurine heterophile ab
    - Muronumab CD3 immunosuppression
  - Rheumatoid arthritis

1.Cavalier et al, Clin Chim Acta 2007
2.Zanchetta et al, Ost Int 2021
3.Levin et al, Endoc Pract 2011
4.Kalaria et al, Horm Met Res 2022

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Normocalcemic PHPT

Original Article: Endocrine Care

The Diagnosis of Normocalcaemic Hyperparathyroidism is Strikingly Dissimilar Using Different Commercial Laboratory Assays

Abbott, Roche, Siemens

Authors
Tejas Kalaria[1], Jonathan Fenn[1], Anna Sanders[2], Alexandra Yates[3], Christopher Duff[3,4], Helen Ashby[2], Pervaz Mohammed[2], Clare Ford[1], Rousseau Gama[1,5]

1.Cavalier et al, Clin Chim Acta 2007
2.Zanchetta et al, Ost Int 2021
3.Levin et al, Endoc Pract 2011
4.Kalaria et al, Horm Met Res 2022

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NPHPT

- Less likely to localize (1,2)
- MGD more common
  - 45% (3)
  - Collaborative Endocrine Surgery Quality Improvement Database) 47% (4)
  - 53.5% (5)
- Persistent elevated PTH not uncommon in HPHPT (~23.5%) (6)
  - 46.5% in one study of NPHPT (5)
  - BMD only improved in those who PTH normalized (5)

1. Cunha-Bezerra et al, J Med Imag Rad Onc 2018
2. Musumeci et al, Clin Endoc 2022
3. Lim et al, Surgery 2017
4. Pandian et al, Surgery 2020
5. Sho et al, Ann Surg Onc, 2018
6. De la Plaza Llamas et al Eur Arch Oto 2017

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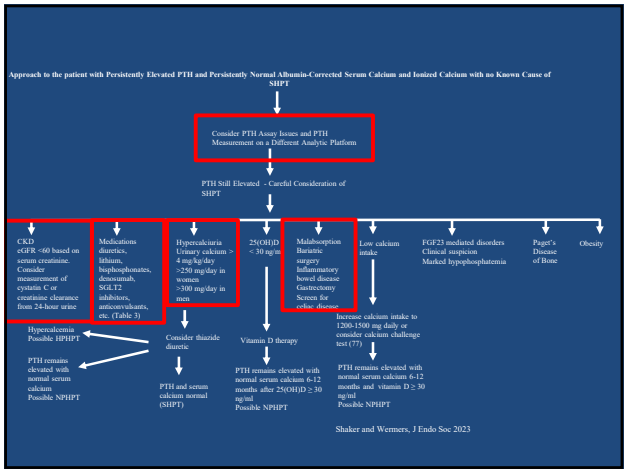

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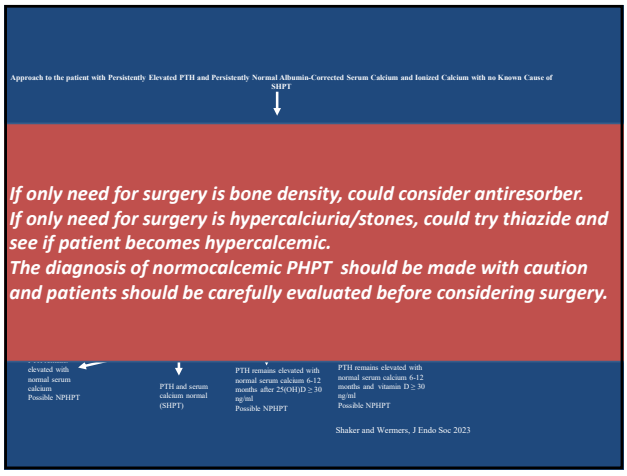

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Case

- 36 yo G1P0 24 weeks pregnant
- 4 years earlier dx PHPT
  - Calcium 10.8-11.3
  - PTH high normal
  - Urinary calcium 239 mg/day
- At that time CDC73, MEN1, CaSR genetic testing negative
- Single gland removed (170 mg)
- IOPTH 56 – 21
- Hypercalcemia persisted
- Now
  - Calcium 10.8-11.1
  - PTH 33 pg/ml
  - Urinary calcium 226 mg/day (pre-pregnancy)
- What next?
  - ? Second trimester PTx

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PHPT - Pregnancy

- **Maternal complications**
  - Nephrolithiasis
  - Bone disease
  - Pancreatitis
  - Hyperemesis gravidarum
  - Preeclampsia
  - Hypercalcemic crisis
- **Fetal complications**
  - Prematurity
  - Neonatal hypocalcemia
  - Stillbirth, Miscarriage
  - IUGR, low birth weight

Risks low if mild hypercalcemia

12. How should PHPT be managed during pregnancy?
Panel recommendations

12.1. Mild cases should be managed by maintaining good hydration and monitoring calcium levels

12.2. Bisphosphonates and denosumab should not be used

12.3. Data are very limited on use of cinacalcet

12.4. Consider surgery in the second trimester for patients with serum calcium >11.0 mg/dL and for whom surgery is not contraindicated

12.5. Preoperative imaging should be limited to ultrasound

12.6. If surgery is deferred, the neonate should be closely monitored for hypocalcemia

12.7. If surgery is deferred, PTX should be done after delivery, and before a subsequent pregnancy.

Bilezikian et al, JBMR 2022

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Back to Patient

- **What next?**
  - **Calcium to creatinine clearance ratio**
    - **0.008 (0.8%)**
    - **0.012 (1.2%) prior to initial surgery**
- **Genetic testing revealed a pathogenic variant in the AP2S1 gene - FHH3**

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Familial Hypocalciuric Hypercalcemia (FHH)

- Asymptomatic, modest, lifelong hypercalcemia
- Hypocalciuria
- PTH not suppressed (normal ~85-88%, elevated <15%)
- Magnesium highish
- Autosomal dominant
- Surgery not indicated

Genetics

- FHH1 Most families - CaSR (chromosome 3) (~2/3)
- FHH2 *(G protein alpha 11) Nesbit et al, NEJM 2013.*
- FHH3 *(Adapter Protein 2 Sigma 1) (AP2S1) Nesbit et al, Nat Genet 2013*
- Some FHH families have unknown mutation

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Autoimmune Hypocalciuric Hypercalcemia

- Acquired hypocalciuric hypercalcemia
- No FH
- No mutations FHH1, FHH2, FHH3
- Autoimmune disease
- Antibodies to CaSR

Kifor et al, JCEM 2003
Pallais et al, NEJM 2004
Makita et al, PNAS 2007
Kuo et al, Am J Kid Dis 2013
Pallais et al, JCEM 2011
Seino et al, NNGZ 2014
Song et al, Eur J Endoc 2017
Minambres et al, JCEM 2020

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FHH vs PHPT

FHH1 Mutations

- Large Data Base ~51K (1)
- Geisinger
  - 74.1/100K
  - 40.9/100K (FHH1 &hypercalcemia)
- Does not count FHH2 or FHH3

PHPT

- Kaiser Permanente (2)
- <50yo - 12-24/100K
- 50-59
  - F 80/100K
  - M 36/100K
- 60-69
  - F 131/100K
  - M 59/100K
- 70-79
  - F 196/100K
  - M 95/100K

1. Dershem et al, Am J Hum Gen 2020
2. Yeh et al, JCEM 2013

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FHH vs PHPT

FHH1 Mutations

- Large Data Base ~51K (1)
- Does not count FHH2 or FHH3

PHPT

- Kaiser Permanente (2)
- <50yo - 12-24/100K
- 60-69
  - F 131/100K
  - M 59/100K
- 70-79
  - F 196/100K
  - M 95/100K

FHH1 may be just as common as PHPT <50y

1. Dershem et al, Am J Hum Gen 2020
2. Yeh et al, JCEM 2013

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FHH

FHH vs PHPT

- 54 FHH1 and 97 PHPT surgically cured
- CCCR <0.02 picked up 53/54 FHH (0.01 missed 20% FHH)
- Problem 35% (34/97) PHPT were <0.02
  - Christensen Clin Endoc 2008

2014 Guidelines Screen for FHH

- CCCR < 0.01
  - **25D > 20 ng/ml**
  - **eGFR >60**
  - *Probably FHH*
- CCCR 0.01- 0.02
  - **25D > 20 ng/ml**
  - **eGFR >60**
  - *Might be FHH*

Eastell et al, JCEM 2014

My opinion

Sensitivity most important
Do not want to operate on FHH
Look at old calcium levels, family etc
Clues to FHH; lifelong, young age, FH, normal PTH, higher Mg
All 3 genes need to be done

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	64 F Hypercalcemia for decades Stones (UA)	50 M Hypercalcemia first noted age 40	68 F Osteoporosis (no fx) On ALN	36 yo G1P0 24 weeks pregnant Age 32 Calcium 10.8-11.3PTH high normalUrinary calcium 239 mg/day.	56 yo woman with hypercalcemia and low urinary calcium
HX	Patient/sister CaSR negative	Ref endo CaSR negative (Mayo)	3.5 gland PTX late 1980s (no records yet)	CCCR 0.012, MEN1, CaSR genetic testing negative Single gland removed (170 mg) IOPTH 56 – 21 Hypercalcemia persisted	Ref endo no variants in CASR, CDC73 (HRPT2), CDKN1B, MEN1, and RET genes
FH	Sister,Mom hypercalcemia	15Y daughter hypercalcemia	Brother and Mom recently found elevated calcium	"Negative"	?Son hypercalcemia
Calcium (mg/dl)	10.5-11.3	9.9.10.6	10-11	10.8-11.1	12.6-13
I Ca (mmol/l)		1.45			
Phos (mg/dl)	2.4	2.6	2.8	2.5,3.4	2-2.4
PTH (pg/dl)	58,76	74,37	50-86	33,45	130-160
Mag (mg/dl)	1.5	2.3	2.0		2.3
25D (ng/dl)	31	35	65	25	29
Urinary Ca mg/d	208	110,111	70	239,226	22
CCCR	0.009	0.005,0.008	0.006	0.012,0.008	0.002
Genetics	VUS ***GNA 11*** FHH2 (? correlates with Ca in family)	Pathogenic ***CaSR*** (FHH1) deletions exon 5-7	Pathogenic ***CaSR*** (FHH1)	Pathogenic***AP2S1*** (FHH3)	Pathogenic***AP2 S1*** (FHH3)

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Summary (1)

- *Diagnosis of PHPT usually clear*
- There are new guidelines for management
- *Surgery improves bone and stone disease with decreased fractures and stone events*
- *Data on neuropsych and CV in mild disease remain unclear*
- *Neuropsych - I typically advise surgery but manage expectations*
- *I favor initial surgery in most patients with DEFINITIVELY diagnosed PHPT if they are good surgical candidates*
  - *Reop may have different risk-benefit ratio*
  - *Hypopara QOL much worse than mild PHPT*

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Summary (2)

- *NPHPT dx should be made with caution after careful consideration of SHPT. I am cautious with surgery in NPHPT.*
  - *NPHPT is overdiagnosed*
- *FHH is more common than most believe*
  - *Surgery not indicated*
  - *Many of us have missed FHH*

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Thanks

Osteoporosis and Calcium Disorders Clinic

Froedtert & Medical College of Wisconsin

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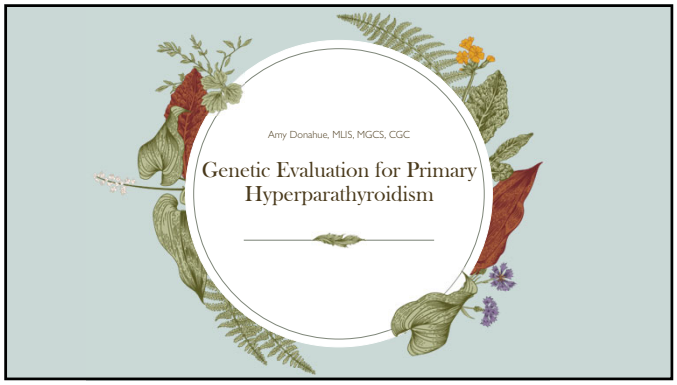

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Conflicts of Interest

- No financial conflicts
- Acknowledgement that I have my own unique experiences, values, and biases.

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2

Hereditary PHPT: Statistics

- ~10% of all PHPT has a monogenic etiology
- De Sousa et al. found "a positive testing rate of 15–26% in patients with suspected hyperparathyroidism syndromes"
  - They also proposed "Prospective studies evaluating patients by uniform testing criteria and a single standardised testing process encompassing all definitively associated genes will improve our understanding of the yield of genetic testing in the PHPT and FHH settings."
- More likely to be monogenic:
  - Younger age (males/females affected equally)
  - Multiglandular disease
  - Family history of PHPT
  - Personal and/or family history of related tumors (for syndromic causes)

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Table 1. Incidence and Prevalence of Primary Hyperparathyroidism in the World

Area	Incidence per 100,000 person-years	Prevalence per 100,000 people	
USA	48.3–50.4	Women	233
		Men	85
		Black women, 70–79 years old	1409
		White women, 70–79 years old	1110
Spain	Unspecified type of hyperparathyroidism		
Women	40.3		
Men	13.7		
Denmark	16		
Scandinavian countries		Observational studies in perimenopausal and postmenopausal women	2000–5000
Sweden		Men	730
Czech Republic	24		
Serbia		General population	300
China		Middle-aged and elderly	200
South Africa (hospital inpatients)	78		

Minisola et al, 2022

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TABLE 2 Syndromic and nonsyndromic monogenic disorders associated with hereditary hypercalcaemia/PHPT

	Estimated prevalence	Gene	Chrom. Pos	Inherit.	Variant type	Genetic testing strategy
Syndromic forms of PHPT						
Multiple endocrine neoplasia Type 1 (MEN1)	~1/30,000	MEN1	11q13.1	AD	ns, LOF, del[a]	Single gene/gene panel (MLPA)
Multiple endocrine neoplasia Type 2A (MEN2A)	~1/35,000	RET	10q11.21	AD	ns	Single gene/gene panel
Multiple endocrine neoplasia Type 4 (MEN4)	Rare (<1/million)	CDKN1B[a]	12p13.1	AD	ns, LOF	Single gene/gene panel
Hyperparathyroidism jaw tumor (HPT-JT) syndrome	Rare (<1/million)	CDC73	1q31.2	AD	ns, LOF, del[a]	Single gene/gene panel (MLPA)
Nonsyndromic forms of PHPT including FHH						
Familial isolated hyperparathyroidism (FIHP)	Uncertain	GCM2[a]	6p24.2	AD	ns	Single gene/gene panel
	-	(MEN1[a])	11q13.1	AD	ns, LOF	Single gene/gene panel (MLPA)
	-	(CDC73[a])	1q31.2	AD	ns, LOF	Single gene/gene panel (MLPA)
	-	(CASR[a])	3q13.33-q21.1	AD	ns, LOF	Single gene/gene panel
Familial hypocalciuric hypercalcemia Type 1 (FHH1)	~1/1-5,000	CASR	3q13.33-q21.1	AD	ns, LOF	Single gene/gene panel
Familial hypocalciuric hypercalcemia Type 2 (FHH2)	Rare	GNA11	19p13.3	AD	ns, IF del	Single gene/gene panel
Familial Hypocalciuric Hypercalcemia Type 3 (FHH3)	~1/15,000	AP2S1	19q13.32	AD	ns (Arg15)	Single gene/gene panel
Neonatal Severe Hyperparathyroidism (NSHPT)	Rare	CASR	3q13.33-q21.1	AR/AD	ns, LOF	Single gene/gene panel
Miscellaneous conditions associated with hypercalcaemia						
Infantile hypercalcaemia Type 1	Rare	CYP24A1	20q13.2	AR	LOF	Single gene/gene panel
Infantile hypercalcaemia Type 2	Rare	SLC34A1	5q35.3	AR	LOF	Single gene/gene panel
Hypophosphatasia	~1/100,000	TNSALP	1p36.12	AR (AD)	ns, LOF	Single gene/gene panel
Williams–Beuren Syndrome	~1/10,000	7q11.23 microdeletion	7q11.23	de novo, AD	1.5–1.8 Mb deletion	aCGH
Jansen metaphyseal chondrodysplasia (MC)	Rare	PTH1R	3p21.31	AD	ns	Single gene/gene panel

Abbreviations: aCGH, array comparative genomic hybridisation; AD, autosomal dominant; AR, autosomal recessive; chrom pos, chromosomal position; del, deletion; FHH, familial hypocalciuric hypercalcaemia; FIHP, familial isolated hyperparathyroidism; LOF, loss of function; if del, in-frame deletion; ns, missense; MLPA, multiplex ligation-dependent probe amplification; PTH, parathyroid hormone.

[a]Several monogenic disorders may result from partial or whole gene deletions, which may not be detected by single gene or gene-panel testing and may require alternate methods for detection (e.g., MLPA or aCGH), although some next generation sequencing platforms have the capability to detect these abnormalities. Loss of function (LOF) variants include nonsense mutations (i.e., resulting from an SNV introducing a premature stop codon), small insertions or deletions (indels) typically resulting in frameshift alterations, and those affected canonical splice sites resulting in aberrant transcript processing.

[b]In addition to the association with MEN4, germline variants in CDKN1B as well as other cyclin-dependent kinase inhibitor genes (e.g., CDKN1A, CDKN2B, CDKN2C) have been reported in apparently sporadic parathyroid adenomas in the absence of a relevant family history such that their role as predisposition genes for hereditary PHPT remains uncertain.

[c]FIHP represent a heterogeneous disorder whose incidence is uncertain. Approximately 15%–20% of FIHP kindreds are reported to harbour GCM2 mutations, although these variants are reported to be associated with low disease penetrance. Kindreds with FIHP have also been identified to harbour MEN1 and CDC73 mutations but distinguishing FIHP from the wider PHPT clinical syndromes is difficult as PHPT is frequently the first manifestation of disease, and for practical purposes such kindreds should be followed up as per the guidelines for MEN1 and HPT-JT, respectively. Although a small number of kindreds with apparent FIHP have been reported with heterozygous or homozygous inactivating CASR mutations, most individuals/kindreds with inactivating CASR mutations will have a biochemical phenotype consistent with FHH, which is not improved with parathyroid surgery.

Newey et al. 2022

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5

Hereditary PHPT: Testing

Endocrine (and other) tumor syndromes	• CDC73 • CDKN1B • MEN1 • RET
Familial Isolated HPT	• CASR • CDC73 • GCM2 • MEN1
Familial Hypocalciuric Hypercalcemia	• AP2S1 • CASR • GNA11

6

Hereditary PHPT: Testing

- Panel testing
  - Available through multiple genetic testing laboratories
- MCW&F genetic counseling team currently uses 1 laboratory
  - In-network w/ most insurance, lower cost at baseline
    - Most patients cost is <$100
  - Free family member testing for 150 days (currently)
  - Fastest turnaround time (2-3 weeks)

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Hereditary PHPT: Genetic Counseling Appt

- Family history
  - Known tumor/cancer/calcium/parathyroid history
    - I do not ask ethnicity/ancestry
  - Doesn't typically change testing strategy
  - Informs risk discussion and post-test interpretation
  - Opportunity for rapport building & provides context for test discussion
- Anticipatory guidance
  - Surveillance
  - Surgery
  - Cascade testing of family members
    - Neonatal severe hyperparathyroidism risk (*CASR*)
- Testing
  - Result types (positive/diagnostic, negative/normal, variants of uncertain significance)
  - Logistics (costs, turnaround time, results disclosure, sample collection)

8

Forward thinking

- Research opportunities
- New gene discoveries (check back in a year or 2!)
- Polygenic risk
  - Soto-Pedre E, Newey PJ, Srinivasan S, Siddiqui MK, Palmer CNA, Leese GP. Identification of 4 New Loci Associated With Primary Hyperparathyroidism (PHPT) and a Polygenic Risk Score for PHPT. J Clin Endocrinol Metab. 2022 Nov 25;107(12):3302-3308. doi: 10.1210/clinem/dgac527. PMID: 36102151; PMCID: PMC9693767.
- Pharmacogenetics
  - Jeong S, Kim IW, Oh KH, Han N, Joo KW, Kim HJ, Oh JM. Pharmacogenetic analysis of cinacalcet response in secondary hyperparathyroidism patients. Drug Des Devel Ther. 2016 Jul 8;10:2211-25. doi: 10.2147/DDDT.S103370. PMID: 27468225; PMCID: PMC4944925.

9

9


Thank you
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Newey PJ, Hannan FM, Wilson A, Thakker RV. Genetics of monogenic disorders of calcium and bone metabolism. Clin Endocrinol (Oxf). 2022 Oct;97(4):483-501. doi: 10.1111/cen.14644. Epub 2021 Dec 21. PMID: 34935164.
De Sousa SMC, Carroll RW, Henderson A, Burgess J, Clifton-Bligh RJ. A contemporary clinical approach to genetic testing for heritable hyperparathyroidism syndromes. Endocrine. 2022 Jan;75(1):23-32. doi: 10.1007/s12020-021-02927-3. Epub 2021 Nov 13. PMID: 34773560.
11

11

ENDOCRINE SURGERY
MEDICAL COLLEGE OF WISCONSIN

Outcomes After Parathyroidectomy for Primary Hyperparathyroidism

Tina Yen, MD, MS
Professor of Surgery
Medical College of Wisconsin 2023 Endocrine Surgery and Neuroendocrine Tumor Symposium
Renaissance Milwaukee West Hotel, Wauwatosa, WI
March 31, 2023

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Outline

- Reasons and guidelines for surgery
- Outcomes with observation
- Outcomes after surgery

BMD Fractures	Kidney stone Hypercalciuria Renal function	Neurocognitive Neuropsychiatric QOL	CV events CV mortality Hypertension Aortic stiffness

- I have no disclosures.

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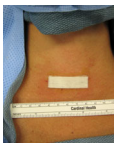
Surgery is recommended for all patients with classical symptoms and manifestations

- *"bones, stones, abdominal moans and psychic groans"*
- Nephrolithiasis, nephrocalcinosis
- Overt bone disease
  - Osteitis Fibrosa Cystica
  - Non-traumatic/fragility fractures
- Pancreatitis
- Significant hypercalcemia (> 12 mg/dL)
  - Mental status changes
- Parathyroidectomy
  - ↑ Bone density
  - ↓ Fracture rates
  - ↓ Kidney stone rates
  - ↑ Cognitive function
  - ↓ Cardiovascular and premature death rates



Bilezikian JP. JCEM 2014
Silverberg SJ. N Eng J Med 1999
Udelsman R. JCEM 2009
Wilhelm SM. JAMA Surg 2016

3

Guidelines for surgery in asymptomatic pHPT

Summary statement from the 5th International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism

- Serum calcium > 1.0 mg/dL above upper limit of normal
- Skeletal
  - Osteoporosis: T-score < - 2.5 at any site*
  - Vertebral fracture (X-ray, CT, MRI, VFA)
- Renal
  - eGFR < 60 mL/min
  - 24-hour urinary calcium >300 mg/d (male) or >250 mg/d (female)
  - Nephrolithiasis or nephrocalcinosis by X-ray, US, CT
- Age < 50 years
- Medical surveillance is not possible or desired

Bilezikian JP. J Bone Miner Res 2022

* Z-score < 2.5 in premenopausal women and men < 50 years

4

AAES 2016 guidelines for parathyroidectomy

- All symptomatic patients
- Most asymptomatic patients
  - Fourth International Workshop Guidelines
  - Neurocognitive and/or neuropsychiatric symptoms attributable to pHPT (low quality evidence)

Weak recommendations with low to moderate-quality evidence

- Patients with cardiovascular disease who might benefit from mitigation of potential cardiovascular sequelae other than hypertension
- Non-traditional symptoms
  - Muscle weakness, functional capacity, abnormal sleep patterns
- Non-traditional features
  - Gastroesophageal reflux and fibromyalgia symptoms

Wilhelm SM. JAMA Surg 2016

5

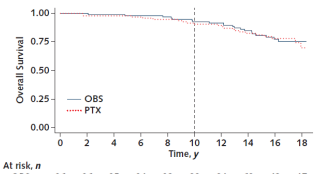
Scandinavian Investigation of Primary HPT

Randomized control trial for mild pHPT

8 Scandinavian centers: Oct 1998 - June 2005

191 patients

At mean F/U of 15.3 years: no difference in mortality



At risk, *n*										
OBS	96	96	95	94	93	88	84	68	43	17
PTX	95	93	93	92	90	87	80	68	42	15

Pretorius M. Ann Int Med 2022

6

Table 3. Morbidity Events During 10 Years of Follow-up*

Event	PTX (n = 95)	OBS (n = 96)	Hazard Ratio (95% CI)
Peripheral fracture	15 (15.8)	17 (17.7)	0.75 (0.37-1.50)
Cardiovascular events	10 (10.5)	10 (10.4)	0.81 (0.33-1.99)
Coronary artery disease	4 (4.2)	6 (6.3)	-
Arrhythmia	3 (3.2)	4 (4.2)	-
Pulmonary embolism	2 (2.1)	0	-
Heart failure	1 (1.1)	0	-
Cancer	13 (13.7)	7 (7.4)	1.78 (0.71-4.48)
Breast	6 (6.3)	1 (1.1)	-
Hematologic	1 (1.1)	3 (3.1)	-
Gastrointestinal	1 (1.1)	1 (1.1)	-
Skin	1 (1.1)	1 (1.1)	-
Lung	1 (1.1)	1 (1.1)	-
Prostate	1 (1.1)	0	-
Gynecologic	2 (2.1)	0	-
Cerebrovascular events (all ischemic)	5 (5.2)	5 (5.2)	0.73 (0.20-2.65)
Kidney stones	2 (2.1)	5 (5.2)	0.34 (0.06-1.82)

Vertebral fracture assessment (n=127): 16 new fractures in 14 patients (7 per group)

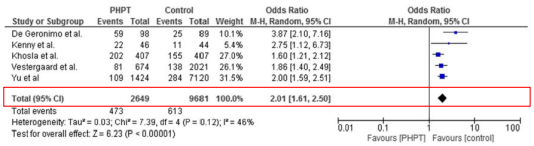
Parathyroidectomy does not appear to reduce morbidity and mortality in patients with mild pHPT

Pretorius M. Ann Int Med 2022

7

pHPT patients have worse bone health

- Increased bone remodeling activity
- Lower BMD, particularly in cortical bone (forearm and hip)
- Increased risk of fracture
  - Meta-analysis through December 2019 (Ejlsmark-Svensson)
  - 12 studies: 5233 pHPT and 13,154 controls



Axelsson K. JAMA Netw Open 2022
Christiansen P. Bone 1997
Ejlsmark-Svensson H. Osteoporos Int 2021
Khosla S. J Bone Miner Res 1999
Rolighed L. European Endocrinol 2014
Silverberg SJ. J Bone Miner Res 1989
Vestergaard P. World J Surg 2003

8

pHPT associated with increased risk of fracture

Fracture	OR (95% CI)	No. studies	I2 (heterogeneity)
Any	2.01 (1.61-2.50)	5	46%
Forearm	2.36 (1.64-3.38)	4	0
Vertebral	3.00 (1.41-6.37)	9	88%
Vertebral and mild pHPT	4.22 (2.20-8.12)	4	57%
Vertebral and postmenopausal women	8.07 (4.79-13.59)	3	0%

No increased risk of hip fracture (3 cohort studies)

Patients with pHPT have an increased risk of any fracture, forearm and vertebral fractures

Ejlsmark-Svensson H. Osteoporos Int 2021

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Beneficial effects of surgery on bone health

Bone mineral density increases

3 RCTs in asymptomatic patients Total cohort, follow-up	Significant improvement after surgery
Rao DS. JCEM 2004 N=53, 2 years	Femoral neck; total hip
Bollerslev J. JCEM 2007 N=191, 2 years	Lumbar spine; femoral neck (borderline effect)
Ambrogini E. JCEM 2007 N=50, 1 year	Lumbar spine; total hip

- Normocalcemic pHPT and normohormonal pHPT: limited data
- No consistent factors predict response

Bone geometry and microarchitecture improves

Caron NR. World J Surg 2009 | Kaji H. JCEM 2008 | Lundstam K J Bone Miner Res 2017 | Sharma J. World J Surg 2014
Dy BM. Surgery 2012 | Koumakis E. JCEM 2013 | Rolighed L. Eur Endocrinol 2014 | Vestergaard P. World J Surg 2003
Hangge PT. Am J Surg 2022 | Lee D. Surgery 2019 | Rubin MR. JCEM 2008

10

Fracture risk may decline after surgery

- No randomized control studies with fracture as primary endpoint
- Danish cohort study (Vestergaard)
  - 3213 pHPT patients (1980 - 1999)
  - 1934 (60%) underwent surgery
  - Median F/U 6.1 years: 31% decreased risk of fracture

Fracture	HR (95% CI)
All	0.69 (0.56-0.84)
Upper arm	0.44 (0.27-0.72)
Femur	0.50 (0.37-0.68)
Hip	0.44 (0.32-0.62)
Spine	1.46 (0.62-3.44)

Adjusted for age, gender and prior fracture history

Vestergaard P. J Int Med 2004
Vestergaard P. BMJ 2003

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Fracture risk may decline after surgery

- Kaiser Permanente retrospective cohort study (1995-2010)
- 6272 pHPT (calcium>10.5; PTH>65)
- 1402 (22%) underwent surgery
- Median F/U 4.5 years, surgery associated with:
  - 64% reduction in absolute risk for hip fracture
  - 24% reduction in absolute risk for any fracture
  - Reduction seen in patients with osteoporosis and osteopenia
  - Reduction seen regardless of whether surgery criteria met

Adjusted for age, race/ethnicity and comorbidity

Yeh MW. Ann Int Med 2016

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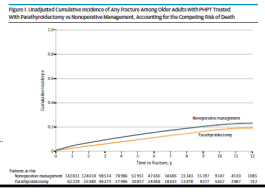
VA longitudinal cohort study

- VA Corporate Data Warehouse
- 210,206 pHPT patients (2006 - 2017)
- 30% (n=63,136) underwent surgery within 1 year of diagnosis
- Fractures determined by modified claims-based algorithm
- F/U 58.5 months (surgery) and 52.5 months (observation)
- Unadjusted incidence of fracture:

	Surgery	Non-operative
Any fracture	10.2%	13.7%
Hip fracture	2.9%	4.2%



Seib CD. JAMA Intern Med 2022

13

Fracture risk reduction with surgery

Adjusted Absolute Risk Reduction of Fracture Associated with Surgery

Time point (year)	Adjusted ARR, % (95% CI) Any fracture	Adjusted ARR, % (95% CI) Hip fracture
1	0.67% (0.52-0.82)	0.18% (0.11-0.26)
2	1.2% (1.0-1.4)	0.36% (0.26-0.46)
5	2.8% (2.5-3.1)	0.98% (0.81-1.2)
10	5.1% (4.6-5.5)	2.3% (2.0-2.6)

Inverse probability weighted and adjusted for many factors

Benefits not limited to those with higher risk of fracture

Surgery associated with lower probability of any fracture (HR 0.84 [0.82-0.85]) and hip fracture (HR 0.83 [0.80-0.85]) when accounting for competing risk of death

Seib CD. JAMA Intern Med 2022

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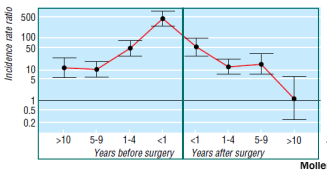
Nephrolithiasis and pHPT

- Nephrolithiasis occurs in 15 - 20% of patients with pHPT
- Prevalence of silent (radiographic) stone disease is unknown
- Denmark study (1979 - 1997): Mollerup
  - 674 pHPT patients who underwent curative parathyroidectomy matched 1:3 to controls by age and gender



pHPT group:

↑ stone risk 10 years before surgery
Normalized >10 years after surgery

Mollerup CL. BMJ 2002
Silverberg SJ. Am J Med 1990
Suh JM. AJR Am J Roentgenol 2008
Walker MD. Nat Rev Endocrinol 2018

15

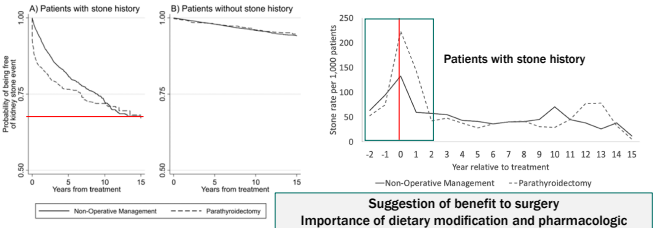
Surgery reduces stone formation but small risk of stone formation remains

- Denmark study (Mollerup)
  - Risk remained higher than normal population until more than 10 years after surgery
- VA longitudinal cohort study using VA Corporate Data Warehouse (Seib)
  - 44,978 pHPT patients with > 2 years follow-up (2000 - 2018)
  - 12% had history of nephrolithiasis
  - 11.7% underwent surgery within 2 years of diagnosis
  - Stone event: ER/inpatient admission with stone diagnosis
    Any urinary stone procedure
  - Mean F/U of 5.1 years: 20.5% with history of stones experienced at least 1 recurrence
    Cumulative unadjusted incidence: 30.5% (surgery) vs 18% (observation)

Charles PY. Urolithiasis 2021
Deaconson TF. Surgery 1987
Hedback G. Eur J Clin Invest 2001
Huang SY. Surgery 2022
Mollerup CL. BMJ 2002
Seib CD. JCEM 2022

16

Higher risk of stone events after surgery although risk declines over time



Suggestion of benefit to surgery
Importance of dietary modification and pharmacologic therapy to prevent recurrent stone formation

Seib CD. JCEM 2022

17

Hypercalciuria improves but persists after surgery

VA study (Seib)
- Surgery group had average decrease in 24-hour urinary calcium levels of 105 mg (vs. increase of 6.1 mg in non-operative group)

Palmieri study
- 95 pHPT and normal eGFR (2008 - 2012); 74% hypercalciuric at baseline
- F/U 2 years post-op: 32% persistent hypercalciuria
- Preop hypercalciuria and MGD were associated with persistent hypercalciuria

Shariq study
- 110 pHPT who underwent surgery (2007 - 2017)
- 28 baseline hypercalciuria: 21% persistent hypercalciuria post-op
- No predictors of normocalciuria

PTH-independent primary or acquired defect in renal tubular calcium reabsorption unmasked after surgery

Charles PY. Urolithiasis 2021
Nilsson IL. Surgery 2017
Palmieri S. JCEM 2015
Shariq OA. Surgery 2020
Seib CD. JCEM 2022

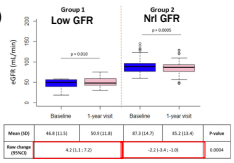
18

Surgery may slow decline in renal function

RCTs demonstrate no improvement in GFR at 1-2 years post-op

Frey prospective cohort (France; 2016 - 2021)

- 246 pHPT who underwent surgery
- 27 (11%) with GFR<60 mL/min
- 12 months post-op in low GFR group:
  - Improvement in raw change in GFR
  - 48% improved CKD stage; 22% had GFR≥60



Mean (SD)	44.8 (11.5)	50.9 (11.8)	87.3 (14.7)	85.2 (13.4)	P-value
Raw change (95%CI)	4.2 (1.1 - 7.2)		-2.2 (-5.4 - 1.0)		0.0004

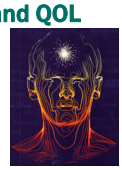
Tassone study (Italy; 1995 - 2012)

- 109 pHPT with underwent surgery
- 14 with GFR<60: no change after surgery (52.6 to 50.2; p=0.5)
- 95 with GFR≥60: decrease after surgery (86.8 to 81.6; p<0.0002)

Bollerslev J. JCEM 2007
Frey S. Surgery 2023
Hedback G. Eur J Clin Invest 2001
Liang CC. J Endocrinol 2021
Rao DS. JCEM 2004
Tassone F. JCEM 2015

19

Neurocognitive/neuropsychiatric symptoms and QOL



- Many patients report non-specific symptoms
  - Low energy level
  - Depressed mood/irritability/anxiety
  - Memory/concentration/cognitive problems
  - Sleep disturbance
  - Musculoskeletal aches, pain, weakness
  - Perception of poor general health-related quality of life
- Patients with pHPT have more non-specific neuropsychological complaints than controls
  - No correlation between serum calcium level and degree of symptoms
- Modest beneficial effect of surgery on QOL and psychological functioning
- 5th International Workshop: These manifestations should not be used, by themselves, to recommend surgery.

Coker LH. Ann Surg 2005
Livschitz JL. JAMA Surg 2022
Pasieka JL. World J Surg 1998
Pasieka JL. Surgery 2009
Perrier N. Surgery 2005
Silverberg SJ. JCEM 2009
Walker MD. J Clin Densitom 2015
Walker MD. Nat Rev Endocrinol 2018

20

Randomized control trials reveal inconsistent results

Study	Detroit (Henry Ford) **Rao DS. JCEM 2004**	Denmark/Sweden/Norway **Bollerslev J. JCEM 2007** **Pretorius M. J Bone Min Res 2021**	Italy (University of Pisa) **Ambrogini E. JCEM 2007**
N (years)	53 patients (1994-1997)	191 patients (1999-2005)	50 patients (2002-2005)
Instruments	SF-36 SCL-90	SF-36 CPRS	SF-36 SCL-90R
Timepoints	q6 months At least 24 months	2, 5 and 10 years	12 months

Outcomes slightly favored surgery
Differences are modest, inconsistent across studies and of uncertain clinical significance

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Quality of life improves after surgery

- Systematic review: literature published 6/1998 - 2/15/2021
- 31 studies in 14 countries with median F/U 1-year follow-up (1 - 10 years)
- 3298 patients with pHPT: 2975 (90%) surgery and 323 observed
- Controls: 5445 age- and sex-matched participants
  386 patients with benign thyroid disease
- QOL instruments: SF-36, disease-specific tool (PAS), others
- Patients with pHPT have more symptoms than controls
- 87% (27/31) studies: improvement in long-term QOL after surgery
- 4 studies with mixed results

Livschitz JL. JAMA Surg 2022
Amstrup AK. Eur J Endocrinol 2011
Bollerslev J. JCEM 2007
Pretorius M. J Bone Miner Res 2021
Rao DS. JCEM 2004

22

Improved and sustained QOL after surgery

1550 patients assessed in 18 studies with SF-36

Domain	% of studies
Vitality	94%
Mental health	89%
Social function	72%
Bodily pain	72%
Role limitation (emotional)	67%
Mental component score	64%
Physical component score	57%
Role limitation (physical)	56%
Physical function	50%

587 patients assessed in 9 studies with PAS

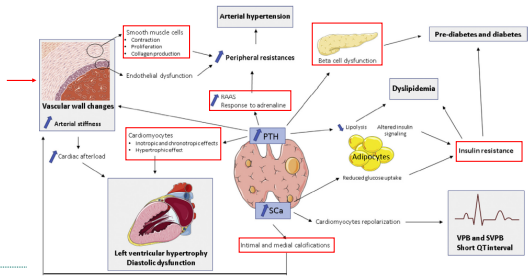
Domain	% of studies
Tired	100%
Mood swings	89%
Forgetful	89%
Weakness	88%
"Blue" (depressed)	78%
Headache	75%
Thirsty	75%
Irritable	72%
Joint pain	62%
Pruritus	50%
Difficulty getting out of care	25%

Mental health components more likely to improve with surgery
Screen with validated QOL tool: guide discussion and frame expectations

Livschitz JL. JAMA Surg 2022

23

Effects of pHPT on the heart, vessels, and cardiovascular risk factors



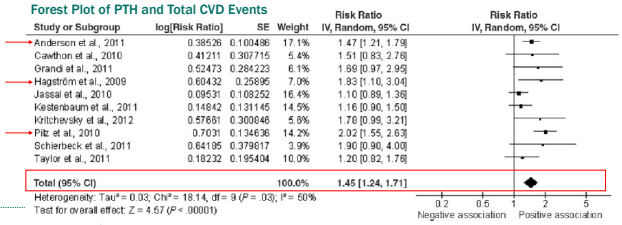
Antonopoulou V. J Surg Res 2020
Frey S. Nutr Metab Cardiovasc Dis 2021
Rashid G. Eur J Clin Invest 2008
Walker MD. J Endocrinol Invest 2008

24

Higher PTH associated with increased risk of total, fatal and non-fatal cardiovascular events

Systematic review and meta-analysis (1947 - 10/2012)
12 prospective studies with 2-14 year follow-up (most >6 years)
10: total CVD events; 7 fatal CVD events; 3 non-fatal CVD events

Forest Plot of PTH and Total CVD Events



van Ballegooijen AM. Am Heart J 2013

25

Surgery and mortality

Severe or moderately severe classical pHPT:
Increased CV mortality and morbidity positively impacted by surgery

Milder disease: limited and conflicting data
- Review (Frey): unclear CV mortality benefit of surgery
- Scandinavian RCT (Pretorius): no difference in mortality or CV events
- Sweden cohort study (2006 - 2017; Axelsson)
  - 16,374 pHPT
  - Matched with 10 controls
    - Sex, birth year, county
  - F/U through 12/31/2017

Adjusted for age, sex, year, comorbidity and previous CV event

Outcome	HR (95% CI)
Any CV event (MI or CVA)	0.87 (0.75-1.00)
Acute MI	0.87 (0.70-1.08)
Ischemic stroke	0.92 (0.76-1.12)
Overall death	0.64 (0.58-0.71)
Cardiovascular-related death	0.71 (0.59-0.85)

Frey S. Nutr Metab Cardiovasc Dis 2021
Hedback G. World J Surg 1991
Nilsson IL. J Bone Miner Res 2002
Pretorius M. Ann Int Med 2022
Silverberg SJ. JCEM 2009
van Ballegooijen AJ. Am Heart J 2013
Vestergaard P. World J Surg 2003
Yu N. Clin Endocrinol 2010

26

VA longitudinal cohort study

210,206 pHPT patients (2006 - 2017); 30% surgery within 1 year of diagnosis

Major adverse cardiovascular event (MACE):
- Non-fatal MI or CVA
- Inpatient hospitalization for unstable angina, CHF, cardiac arrest, cardiogenic shock
- Procedure/surgery for CAD

Secondary outcomes: CVD-related hospitalization
CV hospitalization-associated death

Unadjusted incidences and competing risk regression results

Outcome	Surgery	Non-operative	HR (95% CI)
MACE	10%	11.5%	0.99 (0.97-1.01)
CVD-related hospitalization	12.1%	13.7%	0.95 (0.93-0.96)
CV hospitalization-associated mortality	1.4%	2.0%	0.85 (0.81-0.89)

Seib CD. Ann Surg. Epub August 26, 2022

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Adjusted absolute risk reduction and numbers needed to treat

Outcome	Time point	aARR (95% CI)	NNT
MACE	2 yrs	0.35% (0.16-0.54)	288
	5 yrs	0.84% (0.55-1.13)	119
	10 yrs	1.66% (1.26-2.06)	60
CVD-related hospitalization	2 yrs	0.63% (0.41-0.84)	159
	5 yrs	1.42% (1.10-1.74)	70
	10 yrs	2.48% (2.07-2.89)	40
CV hospitalization-associated mortality	2 yrs	0.11% (0.06-0.17)	884
	5 yrs	0.46% (0.34-0.57)	220
	10 yrs	1.37% (1.17-1.57)	73

Absolute risk reductions are modest after surgery and most likely to be meaningful for patients with long life expectancy

Seib CD. Ann Surg. Epub August 26, 2022

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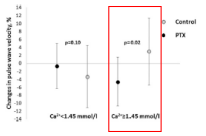
Effect of surgery on HTN

- 40-65% of patients with pHPT have hypertension
- Conflicting data whether surgery improves HTN, particular for mild pHPT
- Most indicate that HTN is not reversible with surgery
- Denmark RCT (2017 - 2018; Ejlsmark-Svennson):
  - 79 pHPT
  - Short-term assessment at 3 months:
    - Office and ambulatory 24-hour BP
    - Pulse wave velocity (PWV), measure of aortic stiffness
    - Augmentation index
    - Fasting plasma cholesterol
  - No differences except lower cholesterol levels in surgery arm (p=0.04)
  - 28 patients with baseline ionized calcium levels ≥ 1.45 mmol/L:
    - Decrease in PWV in the surgery arm

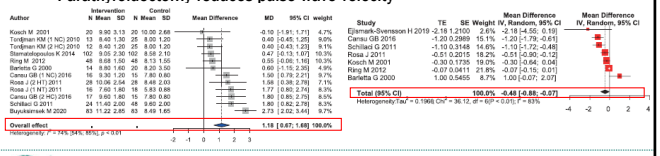


Beysel S. BMC Cardiovasc Disord 2019
Elsmark-Svennson H. JCEM 2019
Frey S. Nutr Metab Cardiovasc Dis 2021
Rydberg E. Int J Cardiol 2010

29

Effect of mild pHPT and parathyroidectomy on aortic stiffness

- Meta-analysis through October 2020: 9 studies and 1 RCT
- 433 mild pHPT; 171 (39%) underwent surgery; 407 controls
- Aortic stiffness (pulse wave velocity) is increased in those with mild pHPT compared with controls
- Parathyroidectomy reduces pulse wave velocity



Bernardi S. JCEM 2021
Ejlsmark-Svennson H. JCEM 2019

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Review of impact of surgery on CV risk

Classic pHPT:
- Positive impact on cardiovascular morbidity and mortality
- Possible improvement in hypertension
- Improvement in markers of glucose homeostasis
- Marginal effect on dyslipidemia

Conflicting data:
- Vascular function (aortic stiffness and endothelial dysfunction)
- Left ventricular hypertrophy
- Diastolic dysfunction

Mild pHPT: conflicting and limited data

Surgery is not currently recommended for patients with mild pHPT solely on the basis of cardiovascular risk reduction

Frey S. Nutr Metab Cardiovasc Dis 2021 Wilhelm SM. JAMA Surg 2016
Walker MD. Nat Rev Endocrinol 2018

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Outcomes after surgery for milder pHPT

⬆BMD
⬇Fractures

⬇Kidney stone
⬇Hypercalciuria
? Renal function

⬆QOL
Mental>
Physical

CV events
CV mortality
Hypertension
Aortic stiffness

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Future studies

- Fracture risk reduction
  - Types of fractures
- Silent (radiographic) stone disease

- Stone formation and hypercalciuria
  - Pathogenesis and persistence after surgery

- Renal function
- Health-related QOL studies with longer follow-up and validated instruments

- All cardiovascular outcomes
  - Mortality, MACE
  - Hypertension, particularly nocturnal hypertension
  - Cardiac morphology and function
  - Glucose homeostasis and lipid profiles

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MCW Endocrine Surgery

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Surgical Approaches for Primary Hyperparathyroidism

Medical College of Wisconsin 2023 Endocrine Surgery
& Neuroendocrine Tumor Symposium

March 31, 2023

Patrick T. Hangge, MD
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1

Disclosures

Patrick T. Hangge
Nothing to Disclose

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2

Surgical Approaches for Primary Hyperparathyroidism

1. Parathyroid Anatomy
2. Preoperative Localization
3. Choice of Procedure
   - Bilateral Exploration
   - Focused/Minimally Invasive Parathyroidectomy
4. Parathyroidectomy Approach
5. Intraoperative Preparation/Assessment
   - ioPTH monitoring
   - Ex vivo aspiration of parathyroid gland with ioPTH
   - Radioguided localization
   - Near-infrared autofluorescence and angiography
   - Bilateral jugular vein sampling
6. Postoperative Care

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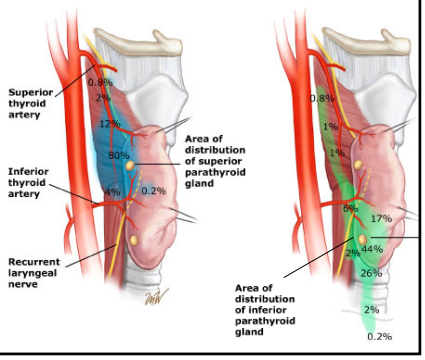
Parathyroid Anatomy

- Most common cause of failed parathyroidectomy or persistence is missed gland
- 3-7 mm, 30-50 mg
- Within 1 cm of recurrent laryngeal neve (RLN) and inferior thyroid artery
  - Superior = *posterior*
  - Inferior = *anterior*
- Bilateral symmetry
  - Superior = 80%
  - Inferior = 70%
- 15% ectopic
- 2-15% supernumerary



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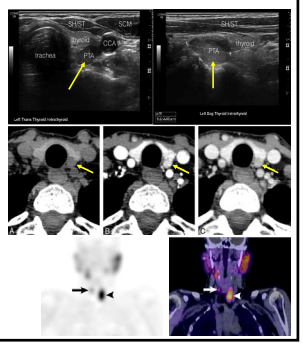
Preoperative Localization

- Useful to identify
  - candidates for minimally invasive approach
  - concurrent thyroid pathology
  - a target for reoperative parathyroidectomy
  - ectopic glands
- Surgical tool, not for diagnosis
- Studies vary by surgeon/institution:
  - Ultrasound
  - Sestamibi scintigraphy
  - 4D-CT
  - Selective venous sampling (SVS)
  - MRI
- Typical MCW preoperative protocol: US, 4D-CT
  - Reoperations: + Sestamibi (MRI and SVS if needed)



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Imaging Modality	Sensitivity	Positive Predictive Value	Advantages	Disadvantages
Ultrasound	64-91%	83-96%		
Sestamibi-SPECT	70-81%	91-95%		
4D-CT	83-95%	88-99%		

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Example Patient - Presentation

69M, several year history hypercalcemia, silent nephrolithiasis on imaging

- Ca: 10.8
- iCa: 1.39
- PTH: 89.5
- 25-OH Vit D: 44
- 24hr UCa: 516.2
- DEXA: normal

No personal or family history of endocrinopathies

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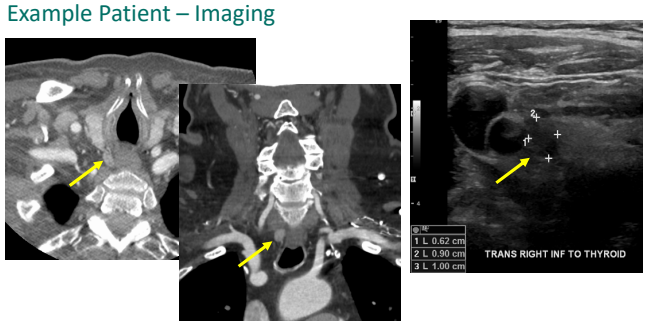
Example Patient – Imaging



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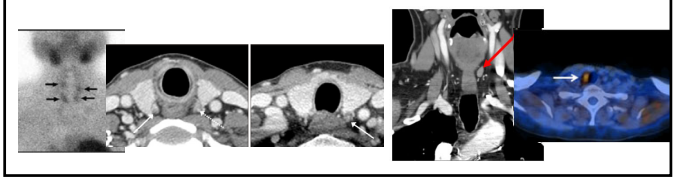
Choice of Procedure

Bilateral Cervical Exploration vs. Focused/Minimally Invasive Parathyroidectomy

- Ultimate goal = cure

- Bilateral cervical exploration for known or suspected MGD
- Focused/Minimally invasive approach for localized single adenoma



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When to perform a bilateral exploration

Initial exploration
- Negative localization or evidence of multigland disease on imaging
- Intraoperative parathyroid hormone monitoring (ioPTH) unavailable
- Multiple Endocrine Neoplasia Type 1 (MEN1)
  - Consider for other familial syndromes of HPT
- Thyroid disease needing resection
- Lithium-induced HPT

Conversion from unilateral exploration
- Failure to localize abnormal parathyroid gland
- Identification of more than one abnormal gland
- Inability to obtain adequate drop in ioPTH

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When to perform a minimally invasive parathyroidectomy

Ideal Candidates
- Single parathyroid adenoma by imaging
- No evidence of thyroid disease requiring operation
- No family history of MEN syndromes

Excellent outcomes comparable to bilateral exploration
- Smaller incision
- Less extensive dissection

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Bilateral exploration (BE) vs. minimally invasive parathyroidectomy (MIP) in the literature


Ann Surg Oncol (2017) 24:1924–1934
DOI 10.1245/s10434-016-5694-1

Annals of SURGICAL ONCOLOGY

ORIGINAL ARTICLE – ENDOCRINE TUMORS

Focused Versus Bilateral Parathyroid Exploration for Primary Hyperparathyroidism: A Systematic Review and Meta-analysis

Marcel Jiuk, MB BCh[1], Emer O'Connell, MB BCh[1], Donal P. O'Leary, MB BCh, MRCS, PhD[2], Aaron Liew, MB BCh, MRCPI, MRCS (Glasg), PhD[3,4], and Henry P. Redmond, MCh, FRCSI, FACS[1]

[1]Department of Academic Surgery, Cork University Hospital (CUH), Cork, Ireland; [2]National University of Ireland Galway (NUIG), Portiuncula University Hospital and Galway University Hospital, Saolta University Health Care Group, Galway, Ireland; [3]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK

- 19 comparative studies, 12,000+ patients
- Similar:
  - Recurrence (BE 0.8% vs. MIP 1.3%)
  - Persistence (BE 2.4% vs. MIP 2.3%)
  - Reoperative rate (BE 1.3% vs. MIP 2.2%)
- Lower complication rates for MIP
  - Overall: BE 17.1% vs. MIP 3.7%

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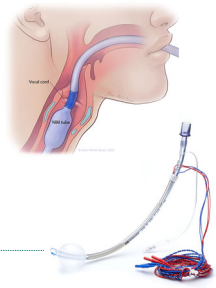
Intraoperative Preparation

Routine anesthesia at MCW

- General endotracheal anesthesia
- Intraoperative nerve monitoring with NIM tube
- Placement of esophageal temperature probe

Patient preparation

- Neck hyperextension
- Ensure adequate IV access after arms tucked
  - Preferred: bilateral 20-gauge antecubital IV
  - Consider arterial line, existing central line access, foot IV



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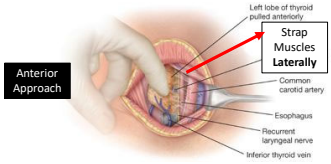
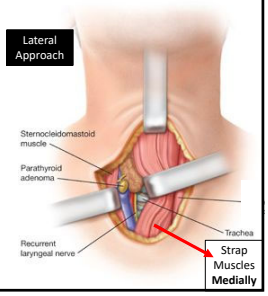
Parathyroidectomy Approach

- Anterior cervical
- Lateral cervical (Backdoor)
- Endoscopic or robotic
  - Cervical
  - Remote access (axillary, thoracic, breast, transoral)





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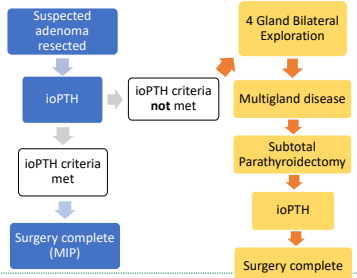
Parathyroidectomy – Basic Principles

Pre-incisional baseline ioPTH

1. 3-5 cm collar incision
2. Divide platysma, raise subplatysmal flaps
3. Separate strap muscles (midline or lateral approach)
4. Mobilize thyroid as needed to identify parathyroid adenoma
5. Protect and preserve RLN



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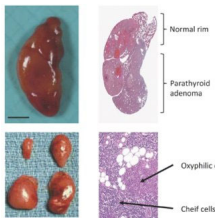
Parathyroidectomy Terminology

Minimally invasive parathyroidectomy
- Typically single adenoma removed

Subtotal parathyroidectomy
- 3 or 3 ½ gland parathyroidectomy
- Remnant from most normal appearing gland, easiest location to access on reoperation

Total parathyroidectomy
- All parathyroid tissue removed

Total parathyroidectomy with autotransplant
- Remnant reimplanted into muscle (forearm or neck)



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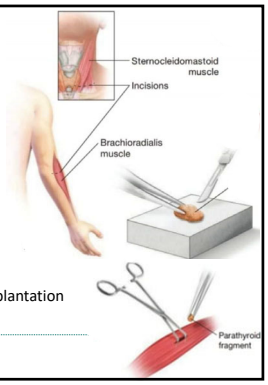
Further Considerations

Total parathyroidectomy with autotransplantation
- Less common in primary HPT
- May be an approach in MEN-1 patients

Autotransplantation into muscle of forearm or neck
- Planned **or** if comprised remnant
- Forearm recommended in hereditary PHPT
  - More accessible for localization and/or control of recurrent disease

Cryopreservation of parathyroid tissue for future reimplantation



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Intraoperative Assessment Tools

- ioPTH monitoring
- Ex vivo aspiration of parathyroid gland with ioPTH
- Radioguided localization and/or ex vivo confirmation
- Near-infrared autofluorescence and angiography
- Bilateral jugular venous sampling

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Intraoperative PTH Monitoring

- ioPTH during MIP associated with higher cure and lower reoperations
- Exploits the short half-life of PTH (3-5 minutes)
- Various ioPTH protocols
  - Baseline "pre-incision" PTH or "Time 0" PTH after adenoma removal
  - Serial PTH at 5, 10, 15, 20 minutes

Protocol			Percentage of false results		
Baseline	Time	PTH decline	FP	FN	
Highest	5	≥50%	0.6	11	
Highest	10	≥50%	0.4-0.9	2.3-2.6	← Miami/>50%
Highest	10	≥50% and within normal	0.4	24	← Dual
Highest	10	≥50% and below pre-incision	0.6	6	
Highest	20	≥50% and/or within normal and/or ≥7.5 ng/L lower than T10	0	16.2	
Pre-incision	10	≥50%	0.3-0.4	7.3-16	
Pre-excision	10	≥50%	0.6	15	
None	15	Low normal (≤35 pg/mL)	0	35	

Abbreviations: FP, False positive; FN, False negative.

Shawky 2017

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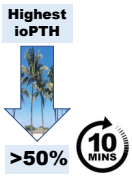
Commonly used ioPTH protocols

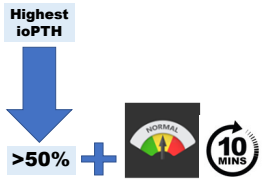
Miami/>50% PTH Drop Criterion

>50% drop from highest PTH (baseline/time 0) by 10 minutes



Dual Criteria Protocol

>50% drop from highest PTH (baseline/time 0) **and** into normal range by 10 minutes



Both with excellent rates of predicting 6 month eucalcemia: **96-98%**

Stricter criteria may ↑ false negative rates of bilateral exploration, but ↓ operative failures

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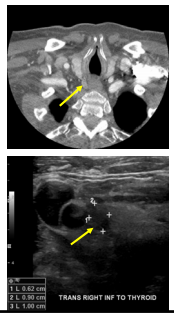
Example Patient: Intraoperative Findings

69M, several year history hypercalcemia, silent nephrolithiasis on imaging

- Ca: 10.8
- iCa: 1.39
- PTH: 89.5
- 25-OH Vit D: 44
- 24hr UCa: 516.2
- DEXA: normal



Intraoperative Findings

- Right thyroid lobe medialized
- Fullness posterior to gland identified
- Right superior parathyroid adenoma isolated, removed:
  - 20 x 12 x 8 mm, 950 mg
  - Ex vivo aspiration > 5000 pg/mL
- **Baseline PTH 117 pg/mL**
  - Time 0: PTH 79
  - Time 5: PTH 50
  - **Time 10: PTH 38**
  - Time 15: PTH 32
- Consistent with biochemical cure

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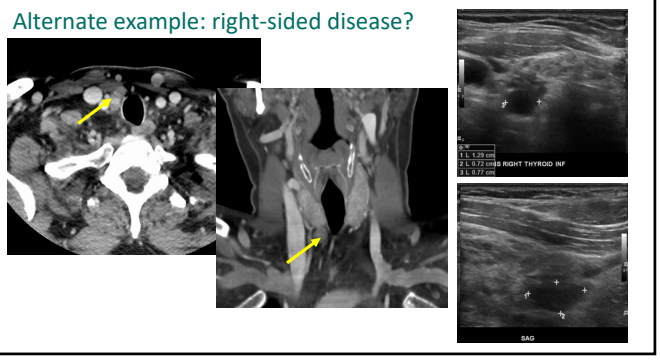
Alternate example: right-sided disease?



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Alternate example: Intraoperative Findings

Intraoperative Findings

- Right inferior gland enlarged, removed
  - 14 x 8 x 6 mm, 380 mg
  - Ex vivo aspiration > 5000 pg/mL
- Baseline PTH 70 pg/mL
  - **Time 0: PTH 74**
  - Time 5: PTH 48
  - **Time 10: PTH 43**
  - Time 15: PTH 37
- Failure to reach intraoperative biochemical cure of >50% drop
- Bilateral exploration
  - Left superior: minimally enlarged
  - Left inferior: normal
  - Right superior: minimally enlarged
- Both superior glands resected
- Left inferior gland: *in situ*
- New time 0: PTH 27 pg/mL
  - Time 5: PTH 24
  - **Time 10: PTH 21**
  - Time 15: PTH 19
- Consistent with biochemical cure

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Ex Vivo Aspiration

1. Suspected abnormal parathyroid gland removed
2. Parathyroid tissue aspirated with multiple passes of 3mL syringe (prefilled with 1mL NS) using 22-gauge needle
3. Additional 1mL NS aspirated
4. Centrifuge for 90 sec = "cell button"
5. ioPTH performed

Aspirate ioPTH level 1.5x greater than baseline serum ioPTH
= 98.1% sensitivity, 100% specificity for confirmation of parathyroid tissue

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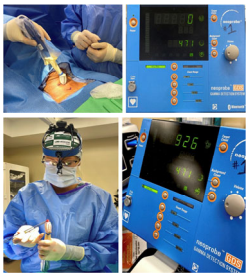
Radioguided Parathyroidectomy

Sestamibi uptake as surrogate for hyperfunctioning parathyroid

Protocol (Herb Chen et al.)

1. IV technetium-99m labeled sestamibi in preop
2. Handheld gamma probe on thyroid for background
3. Parathyroid adenoma removed
4. Ex vivo counts of ≥20% background confirms parathyroid tissue
5. ioPTH to confirm biochemical cure

*Increased radioactivity in operative field can assist with in vivo localization (not routine)



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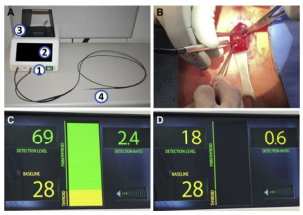
Near-Infrared Autofluoresence and Indocyanine Angiography

- Autofluorescence of 820 – 830 nm
- 2-11x than surrounding tissues
- Useful during parathyroid and thyroid surgery
- Indocyanine green (ICG) can assess in vivo parathyroid tissue perfusion



Solórzano et al. 2021

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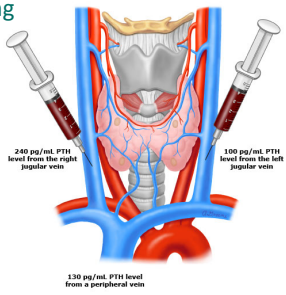
Bilateral Jugular Vein Sampling

Lateralization defined as ≥10% difference in PTH levels



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Postoperative Care

- Many patients can go home same day
  - Extent of dissection, co-morbidities can influence overnight observation
- All receive postop calcium carbonate (Tums)
  - MIP: 1000 mg BID
  - Subtotal: 2500 mg TID
- POD#1 labs: iCa, Ca, PTH
- Calcitriol 0.25 - 0.5 mcg BID added for low PTH (<5.0 pg/mL)
- Clinic visit within 1 week: repeat labs, wean as able
- Labs at 6 months, then yearly

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Summary

- Parathyroidectomy can provide some challenges
  - Wide variability in anatomy
  - Limitations of localization studies
  - Risk/benefit balance
- Ultimately pathophysiology dictates surgery performed
- Intraoperative assessment tools vary by institution/surgeon
- Goal is to restore calcium homeostasis & improve long-term sequalae of hypercalcemia with minimal perioperative complications
  - Importance of specialized surgeons and institutions

MCW Surgery
knowledge changing life

29

Thank you

MCW Surgery
knowledge changing life

30

Resources

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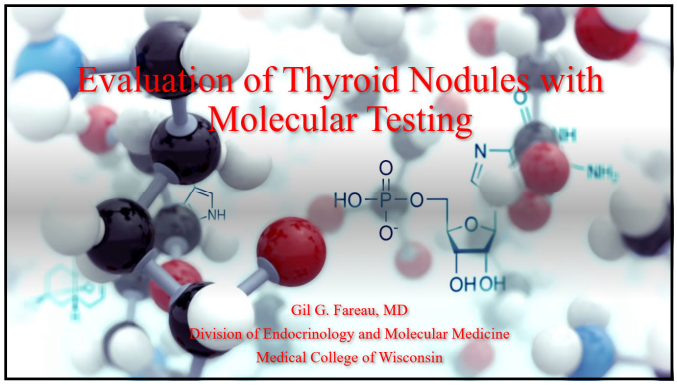

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Disclosures

- I have no financial or commercial interests to disclose

2

Thyroid nodules

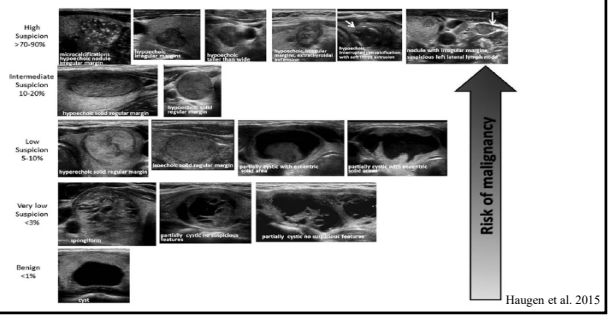
- Between 3 to 5% of adults will have a palpable thyroid nodule
- Approximately 20% will have a visible nodule on imaging
  - Over 50% of women over the age of 60 years
- Between 5-10% of thyroid nodules are malignant

- Early treatment typically favors better outcomes
- How do we effectively identify the relatively small percentage of patients with cancer and avoid over treatment of benign changes?

Haugen et al. 2015

3

American Thyroid Association: ultrasound



Haugen et al. 2015

4

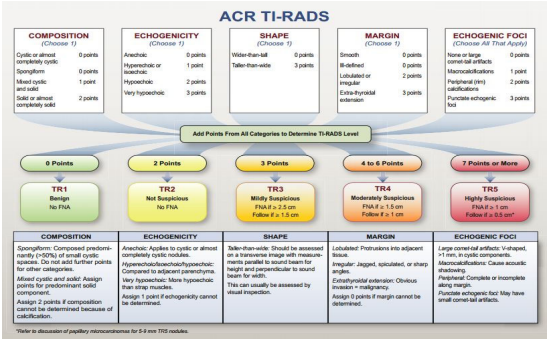
American Thyroid Association: ultrasound

Category	US Pattern	Malignancy Risk	Action
Benign	Purely Cystic (no solid component)	< 1%	No FNA
Very low risk	Spongiform or complex cyst with no fx*	< 3%	FNA >2cm (observe?)
Low risk	Iso/hyperechoic with no fx Complex cyst with eccentric mural no fx*	5-10%	FNA > 1.5cm
Intermediate risk	Solid hypoechoic with no fx*	10-20%	FNA >1cm
High risk	Solid hypoechoic with one or more fx*	70-90%	FNA >1cm

fx* (suspicious features): irregular margins, microcalcifications, extrathyroidal extension, taller than wide

Haugen et al. 2015

5



https://www.acr.org/Clinical-Resources/

6

American College of Radiology

Category	Points	Interpretation	Action
TR1	0	Benign	No FNA
TR2	2	Not suspicious	No FNA
TR3	3	Mild suspicion	FNA >2.5 cm
TR4	4-6	Moderate suspicion	FNA >1.5 cm
TR5	>7	High suspicion	FNA >1.0 cm

https://www.acr.org/Clinical-Resources/

7

The Bethesda Criteria

Diagnostic Terminology and Morphologic Criteria for Cytologic Diagnosis of Thyroid Lesions:
A Synopsis of the National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science Conference

Zubair W. Baloch, M.D., Ph.D.,[1*] Virginia A. LiVolsi, M.D.,[1,2] Syl L. Asa, M.D., Ph.D.,[3] Juan Rosai, M.D.,[4] Maria J. Merino, M.D.,[5] Gregory Randolph, M.D.,[6] Philippe Vielh, M.D., Ph.D.,[7] Richard M. DeMay, M.D.,[8] Mary K. Sidawy, M.D.,[9] and William J. Frable, M.D.[10]

Diagn. Cytopathol. 2008; 36: 425-437

8

Bethesda Classification. Baloch et al. 2008

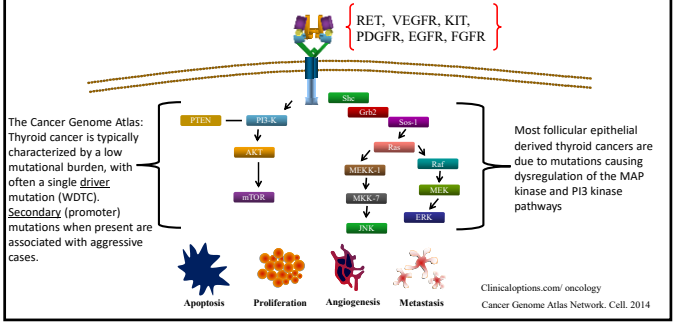
NCI classification	Alternate term	Risk of Malignancy
Nondiagnostic (I)	Unsatisfactory	1-4%
Benign (II)		0-3%
Atypia of undetermined significance (III)	Follicular lesion of unknown significance	5-15%
Follicular Neoplasm (IV)	Suspicious for follicular neoplasam	15-30%
Suspicious for malignancy (V)		60-75%
Malignant (VI)		97-99%

20-25%

Diagn. Cytopathol. 2008; 36: 425-437
Acta Cytol. 2012;56(4):333–339

9

Tyrosine Kinase Receptors



The Cancer Genome Atlas: Thyroid cancer is typically characterized by a low mutational burden, with often a single driver mutation (WDTC). Secondary (promoter) mutations when present are associated with aggressive cases.

Most follicular epithelial derived thyroid cancers are due to mutations causing dysregulation of the MAP kinase and PI3 kinase pathways

Clinicaloptions.com/ oncology

Cancer Genome Atlas Network. Cell. 2014

10

Papillary Thyroid Carcinoma

- BRAFv600E
  - 45-50% of all PTC
  - Up to 70% of classic variant
  - Up to 90% of tall cell variant
- RET fusion
  - 10% (primarily diffuse sclerosing and solid PTC)
- NTRK 1/3 fusion
  - 5%
- Alk fusion
  - 1% (up to 13% in diffuse sclerosing)
- TERT: 10% (more aggressive presentation)
- Various other:
  - EIF1AX, PTEN, MEN1, NF1

Cancer Genome Atlas Network. Cell. 2014
Rajab et al. Cancers. 2022

11

Follicular variant papillary thyroid carcinoma

- Infiltrative unencapsulated
  - Clinical behavior like classic variant PTC
  - Pattern of genetic alteration also like classic variant PTC (ie "BRAF-like" mutations)
- Invasive encapsulated
  - Clinical behavior like FTC
  - Similar genetics to FTC (40-70% with RAS mutation)
    - BRAF k601e
    - PPARG fusion
    - THADA
- Non-invasive encapsulated
  - Indolent, premalignant lesion
  - Recategorized as NIFTP
    - Similar mutation to follicular lesions ("RAS like")

Cancer Genome Atlas Network. Cell. 2014
Rajab et al. Cancers. 2022

12

Follicular Thyroid Carcinoma

- RAS
  - N/K/H RAS mutations in 40-50%
- PAX8:PPARG
  - Up to 35%
- PI3k
  - Up to 10%
- PTEN, DICER1, EIFA1X
  - Less common
- TERT
  - Up to 17% (more aggressive presentation)

Nikiforov Nat Rev Endocrinol. 2011
Liu, et al GENES 2016
Mourra J Clin Endocrinol Metab 2011

13

Oncocytic Thyroid Carcinoma

- Hurthle cell thyroid carcinoma
  - Variably categorized as a variant of FTC
  - Genetically distinct malignancy
- Three primary types of genetic aberration:
  - Mitochondrial complex 1 DNA alterations
  - somatic nuclear DNA mutations (DAXX, EIFA1X, NF1)
  - chromosomal alterations (duplications [chrom 7, 5, 12])

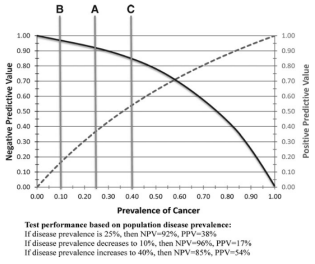
Ganly et al. Cancer Cell. 2018

14

Disease Prevalence and Test Characteristics

	Disease Present	Disease Absent	
Test +'ve	True positive (TP)	False positive (FP)	**PPV:** TP/TP+FP
Test – 've	False negative (FN)	True negative (TN)	**NPV:** TN/TN+FN
	Sens: TP/TP+FN	**Spec:** TN/FP+TN	

The estimated thyroid cancer prevalence determines how various tests perform in "ruling in" (PPV) or "ruling out" (NPV) the presence of malignancy in a thyroid nodule.



Ferris et al. Thyroid 2015

15

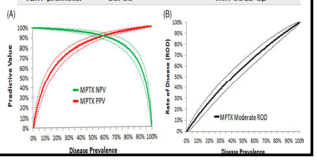
ThyGenNEXT/ThyraMIR

- ThyGenNEXT
  - Next generation sequencing
    - DNA and RNA
- ThyraMIR
  - Thyroid microRNA classifier
    - non-coding RNA
    - post-transcriptional regulation of gene expression

	Bethesda III	Bethesda IV
Sens	97%	86%
Spec	93%	88%
NPV	97%	93%
PPV	85%	60%

Lupo MA et al. Diagn Cytopathol 2020

Expanded mutation panel (ThyGeNEXT)		microRNA risk classifier(ThyraMIR)
DNA variant	Fusions (n) and mRNA	microRNA
BRAF[a]	*BRAF* (3)[a]	miR-31-5p
ALK	*ALK* (2)	miR-29b-1-5p
GNAS	*NTRK* (8)	miR-138-1-3p
HRAS	*PPARg* (5)	miR-139-5p
KRAS	*RET* (1-4)[a]	miR-146b-5p
NRAS	*THADA* (5)	miR-155
PIK3CA	*NKX2.1*	miR-204-5p
PTEN	*PAX8*	miR-222-3p
RET[a]	*TBP*	miR-375
TERT promoter[b]	*USP33*	miR-551b-3p



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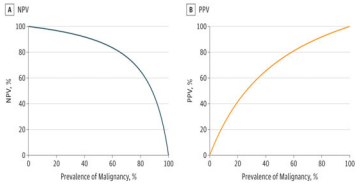
Afirma GSC/XA

- Genomic sequencing classifier (GSC)
  - Upgrade of previous gene expression classifier (GEC)
    - next-generation whole transcriptome analysis (negative vs suspicious result)
- Xpression atlas (XA)
  - Reflex RNA sequencing for suspicious
  - 593 genes (905 variants and 235 fusions)

	Bethesda III	Bethesda IV
Sens	93%	88%
Spec	71%	64%
NPV	97%	95%
PPV	51%	42%



Meta analysis of 13 post validation studies (Beth III/IV)
Sens: 97% Spec: 88% NPV: 99%* PPV:65%

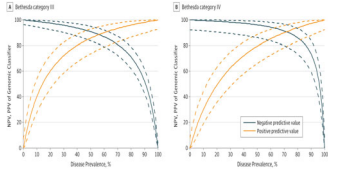
Patel et al. JAMA Surg 2018
Nasr et al. JCEM 2022

17

ThyroSeq v3

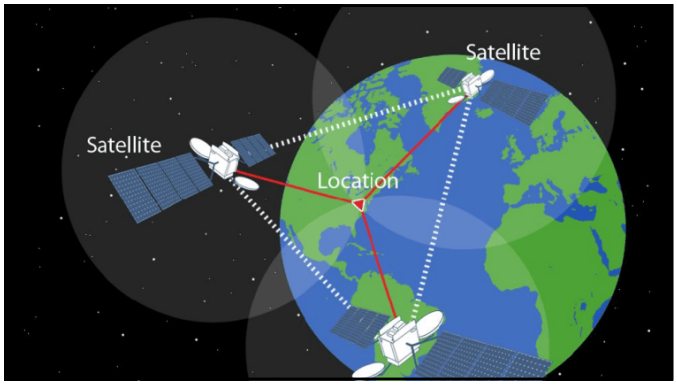
- Next generation sequencing
  - Analyzes DNA and RNA of 112 thyroid related genes
    - >12000 mutation variants, >150 fusions, copy number alterations, gene expression alterations
    - Genomic classifier score based upon identified genetic alterations
    - Positive or negative test result

	Bethesda III	Bethesda IV
Sens	91%	97%
Spec	85%	75%
NPV	97%	98%
PPV	64%	68%



Steward DL, Nikifurov YE, et al. JAMA Oncol 2019

18



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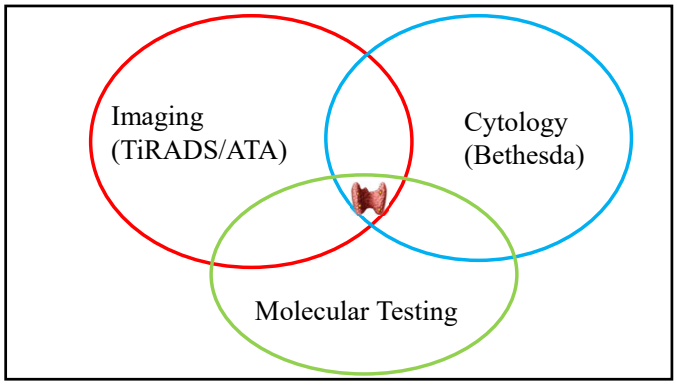
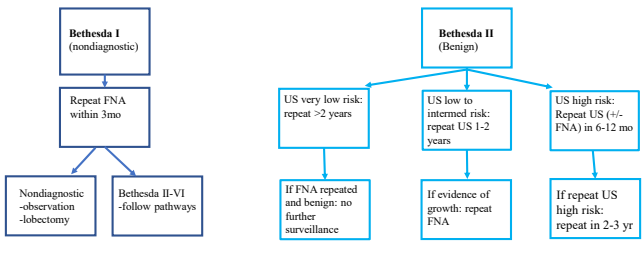


20

American Head and Neck Society Endocrine Section:
Bethesda I and II thyroid nodules



Head & Neck, Volume: 41, Issue: 4, Pages: 843-856 December 2018

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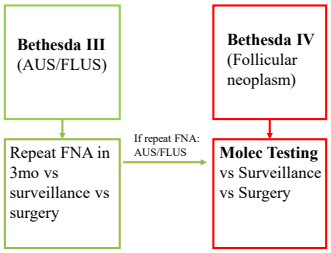
American Head and Neck Society Endocrine Section: Bethesda III and IV thyroid nodules



Head & Neck, Volume: 41, Issue: 4, Pages: 843-856 December 2018

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American Head and Neck Society Endocrine Section: Bethesda V and VI thyroid nodules

Head & Neck, Volume: 41, Issue: 4, Pages: 843-856 December 2018

23

ATA: MT and Surgery

Ferris et al. Thyroid 2015

Bethesda cytologic category	*Ancillary testing*		*Estimated[a] risk of malignancy; range (median)*	*Recommendation*
III (AUS/FLUS)	None		6–48% (14%)	Repeat FNA, ancillary testing, or diagnostic lobectomy
	GEC[b] (reported prevalence 24%)	Suspicious	38%	Diagnostic lobectomy
		Benign	5%	Active surveillance
	7-gene MT[c] (reported prevalence 14%)	Positive	88%	Oncologic thyroidectomy
		Negative	6%	Active surveillance or diagnostic lobectomy
IV (FN/FL)	None		14–34% (25%)	Ancillary testing or diagnostic lobectomy
	GEC[b] (reported prevalence 25%)	Suspicious	37%	Diagnostic lobectomy
		Benign	6%	Active surveillance
	7-gene MT[c] (reported prevalence 27%)	Positive	87%	Oncologic thyroidectomy
		Negative	14%	Diagnostic lobectomy
	ThyroSeq2.0 panel[d] (reported prevalence 27%)	Positive	87%	Oncologic thyroidectomy
		Negative	5%	Observation
V (SMC)	None		53–87% (70%)	Ancillary testing or oncologic thyroidectomy
	GEC[b] (reported prevalence 62%)	Suspicious	76%	Oncologic thyroidectomy
		Benign	15%	Diagnostic lobectomy
	7-gene MT[c] (reported prevalence 54%)	Positive	95%	Oncologic thyroidectomy
		Negative	28%	Diagnostic lobectomy

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Final Thoughts

- Initial evaluation
  - Clinical assessment
  - Comprehensive imaging with appropriate decision to biopsy
  - Thoughtful use of molecular testing (MT)
- Likely to see a more expanded use of molecular profiling
  - Increased access/Lower cost of service
- MT to help inform surgical choices
  - Improving PPV and NPV in current tests
- MT to guide additional treatment
  - Use of radioactive iodine
  - Intensity/frequency of monitoring
  - Selection of systemic therapies for advanced cases

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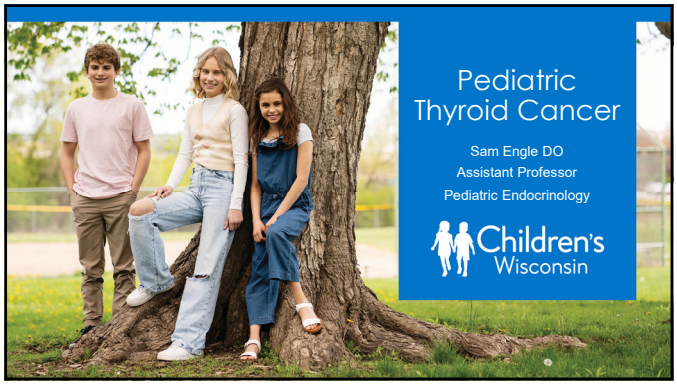

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No Financial Disclosures

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Outline

- Primary focus
  - Papillary thyroid cancer (PTC)
  - Follicular thyroid cancer (FTC)
- Identifying differences in diagnosis and management of pediatric thyroid cancer vs adult-onset thyroid cancer
  - Evaluation of nodules
  - Malignancy rates
  - Role of molecular analysis

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3

Pediatric Thyroid Cancer: Demographics

SEER Database (1975-2016)	Age	Sex	Race
• 4343 Pediatric thyroid cases	• 0-9: 5% • 10-14: 21% • 15-19: 74%	• Female: 81% • Male 19%	• White: 81% • Black: 5% • Other: 11%

4

Does Age Matter?

- Pediatric Population
  - WHO < 19 years old
    - < 9 children, 10-9 adolescents
  - ATA < 18 years
  - AAP < 21 years
- No consensus age re: pediatric thyroid malignancies
  - Different molecular characteristics
  - Hormonal influence
  - Radiation exposure

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Key Points Pediatric Thyroid Cancer

- Pediatric present with more advanced disease
- 0.5-5% of pediatric population with nodule→19-25% malignancy rate
- Higher recurrence rate
- Overall incidence increasing all subtypes~ 1% (PTC, FTC, MTC)
- **Mortality rate low < 2%**
- Regardless of subtype, worse outcome if metastasis to bone, lung, or brain
- One of the most common secondary malignancies in childhood cancer survivors

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6

PTC
- ~90%
- FNA more diagnostic
- More advanced (lymph nodes)
- Treatment approach varies in adults vs peds

FTC
- ~10%
- FNA insufficient for diagnosis
- Less advanced (can spread hematogenously)
- Similar evaluation and treatment in adults and peds

Monitoring similar in pediatrics

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7

THYROID
Volume 25, Number 7, 2015

Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer

The American Thyroid Association Guidelines Task Force on Pediatric Thyroid Cancer

Gary L. Francis,[1,*] Steven G. Waguespack,[2,*] Andrew J. Bauer,[3,4,*] Peter Angelos,[5] Salvatore Benvenga,[6] Janete M. Cerutti,[7] Catherine A. Dinauer,[8] Jill Hamilton,[9] Ian D. Hay,[10] Markus Luster,[11,12] Marguerite T. Parisi,[13] Marianna Rachmiel,[14,15] Geoffrey B. Thompson,[16] and Shunichi Yamashita[17]

8

Goals of DTC Therapy ATA 2015

- Maintain low disease specific mortality currently experienced by children with DTC
- Reduced potential complications from therapy

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9

To FNA or Not

- In pediatrics size not the only cut-off
  - Lower threshold to proceed with further diagnostic work-up
- Ectopic thymus can appear hypoechoic, linear, with punctate foci (can mimic PTC)

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10

ATA guidelines vs TI-RADS for FNA

- ATA guideline for FNA
  - Solid or part solid nodule > 1 cm regardless of imaging features
  - **All nodules < 1 cm* with suspicious features or risk factor**
    - Microcalcification
    - Hypoechoic
    - Irregular margins
    - Hyper vascular with abnormal lymph nodes
- TIRADS
  - Composition
  - Echogenicity
  - Shape
  - Margin
  - Echogenic Foci

* If technically feasible

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11

ATA vs TIRADS

- University of Utah, 2010-2020, 77 pediatric cases who had FNA
- ATA vs TIRADS in malignant cases n=18
  - TIRADS: Ignore 1 lesion, 4 follow-up, 13 FNA
  - ATA: FNA all cases (100%)
- ATA vs TIRADS in benign cases n=42
  - TIRADS: Ignore 17, 8 follow-up, 17 FNA (40.5%)
  - ATA: Ignore 1, 2 follow-up, 39 FNA (93%)

Dunya G, Dance L, Grimmer JF. Comparing ATA guidelines vs TI-RADS for evaluation of pediatric thyroid lesions. *Int J Pediatr Otorhinolaryngol*. 2023;164:111411. doi:10.1016/j.ijporl.2022.111411

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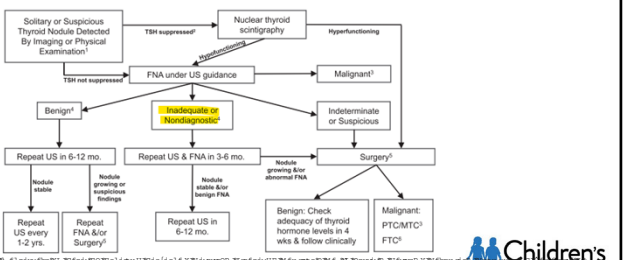
12

Initial Eval Pediatric Thyroid Nodule



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Bethesda System

I. NONDIAGNOSTIC OR UNSATISFACTORY

II. BENIGN

III. ATYPIA OF UNDETERMINED SIGNIFICANCE *or* FOLLICULAR LESION OF UNDETERMINED SIGNIFICANCE

IV. FOLLICULAR NEOPLASM *or* SUSPICIOUS FOR A FOLLICULAR NEOPLASM

V. SUSPICIOUS FOR MALIGNANCY

VI. MALIGNANT

14

Interpreting FNA

THYROID
Volume 29, Number 8, 2019
© Mary Ann Liebert, Inc.
DOI: 10.1089/thy.2018.0728

Differences in Thyroid Nodule Cytology and Malignancy Risk Between Children and Adults

Christine E. Cherella,[1] Trevor E. Angell,[2] Danielle M. Richman,[3] Mary C. Frates,[3] Carol B. Benson,[3] Francis D. Moore,[4] Justine A. Barletta,[5] Monica Hollowell,[6] Jessica R. Smith,[1] Erik K. Alexander,[2] Edmund S. Cibas,[5] and Ari J. Wassner[1]

15

Difference in Cytology and Malignancy Risk Ped vs Adult

- Greater number of cystic nodules in Peds (27% vs 11%)
- Nondiagnostic cytology 12% in peds vs 6% in adults
  - Increased rate if nodule > 50% cystic
- Malignancy rate 19% in peds vs 12% adult (p=0.0002)
  - Malignancy rate higher in **nondiagnostic, AUS, and SNF**
  - No difference in SUSP or malignant cytology
- Ped nodules more likely to be resected than adults in nondiagnostic, benign, and AUS

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Cytology continued

- For AUS surveillance w/o surgery may be recommended in adults but NOT in kids
  - Cohort that had repeat FNA did have improved classification (28% benign)
- Distribution of subtypes similar in peds and adults
- Poorly differentiated and anaplastic thyroid carcinomas not seen in peds
- **Malignancy rate 2-2.5 times higher in pediatric AUS or SFN nodules with equivalent cytology**

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Imaging

- Comprehensive Neck US
  - ± Neck CT or MRI
  - Chest XR or CT if substantial cervical lymph node

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18

Surgery in PTC

- Most cases of PTC total thyroidectomy recommended
  - High incidence of bilateral/multifocal disease
- Unclear evidence who benefits from prophylactic central neck dissection
  - Limited data improves DFS
- Recommended CND if clinical evidence of extrathyroidal invasion
- Lateral neck dissection recommended if FNA confirmed metastasis

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TABLE 6. AMERICAN THYROID ASSOCIATION PEDIATRIC [illegible] AND POSTOPERATIVE MANAGEMENT IN CHILDREN WITH PAPILLARY THYROID CARCINOMA

ATA pediatric risk level[a]	Definition	Initial postoperative staging[b]	TSH goal[c]	Surveillance of patients with no evidence of disease[d]
Low	Disease grossly confined to the thyroid with N0/Nx disease or patients with incidental N1a disease (microscopic metastasis to a small number of central neck lymph nodes)	Tg[e]	0.5–1.0 mIU/L	US at 6 months postoperatively and then annually × 5 years Tg[e] on LT_4 every 3–6 months for 2 years and then annually
Intermediate	Extensive N1a or minimal N1b disease	TSH-stimulated Tg[e] and diagnostic ^{123}I scan in most patients (see Fig. 2)	0.1–0.5 mIU/L	US at 6 months postoperatively, every 6–12 months for 5 years, and then less frequently Tg[e] on LT_4 every 3–6 months for 3 years and then annually Consider TSH-stimulated Tg[e] ± diagnostic ^{123}I scan in 1–2 years in patients treated with ^{131}I
High	Regionally extensive disease (extensive N1b) or locally invasive disease (T4 tumors), with or without distant metastasis	TSH-stimulated Tg[e] and diagnostic ^{123}I scan in all patients (see Fig. 2)	<0.1 mIU/L	US at 6 months postoperatively, every 6–12 months for 5 years, and then less frequently Tg[e] on LT_4 every 3–6 months for 3 years and then annually TSH-stimulated Tg[e] ± diagnostic ^{123}I scan in 1–2 years in patients treated with ^{131}I

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Molecular Profile PTC

- Limited data
- BRAF V600E point mutations less common in peds
  - Especially under 15
- BRAF **fusions** seen in peds
  - Higher prevalence in younger PTC cases (<10)
  - More aggressive disease and higher RAI requirement
- RET/PTC and NTRK **fusions MOST** common in peds
  - More common Caucasian < 15 yo
- Decreased rate of fusions with advancing age (20 yo)

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Molecular Profile FTC

- RAS and PAX8/PPARG fusion seen in adults
  - Very little data in peds
- PTEN association
  - FTC in 25% of carriers
  - Germline testing for PTEN mutation recommended
- DICER1
  - Frequency 25-53%
  - Macrofollicular subtype FTC

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Targeted Therapy?

- ATA does not recommend molecular testing on cytology.. yet
- Metastatic symptomatic cancers not controlled with localized therapy or RAI refractory
- Evolving topic
- Approved agents but not standard of care

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Summary

- Thyroid cancer in pediatrics is **different** than adults
  - More aggressive presentation→ favorable mortality
  - Molecular difference
- Pediatric nodule imaging **does not use size** criteria solely
- Aim to **reduce harm** from intervention (RAI/Surgery)
- TIRADS **not validated** in pediatrics
- Molecular profiling **early** stages

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Update on WHO Classification of Thyroid Tumors

Tamara Giorgadze, MD, PhD
Professor of Pathology
Medical College of Wisconsin

1

Disclosure

- I have no commercial interests

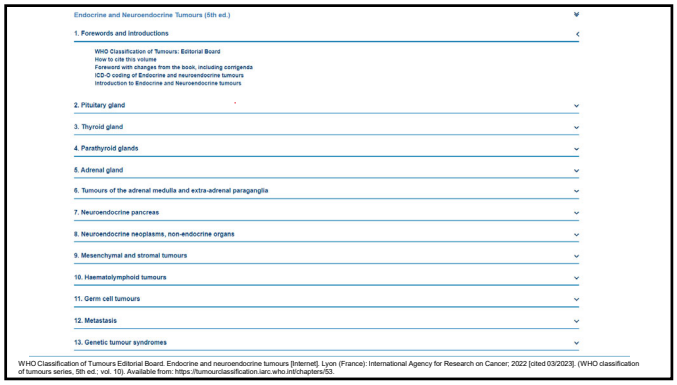
2

WHO Classification of Endocrine and Neuroendocrine Tumors (5th edition)

- Carl Linnaeus approach - hierarchical taxonomic classification
- 4 taxonomic ranks:
  - Category
  - Family (class)
  - Type
  - Subtype
  - Cell of origin, pathologic or molecular features, biological behavior
- Newly recognized tumor types, subtypes, and a grading system

Carl von Linné
By Alexander Roslin,1775
(oil on canvas)

3



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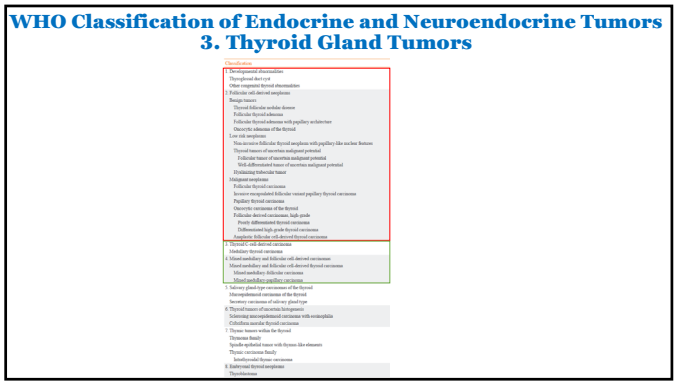

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3.1. Developmental abnormalities

1. Thyroglossal duct cyst
2. Other congenital thyroid abnormalities (Thyroid dysgenesis)
- Agenesis, hemiagenesis, ectopic thyroid, hypoplasia
- Dyshormonogenetic goiter

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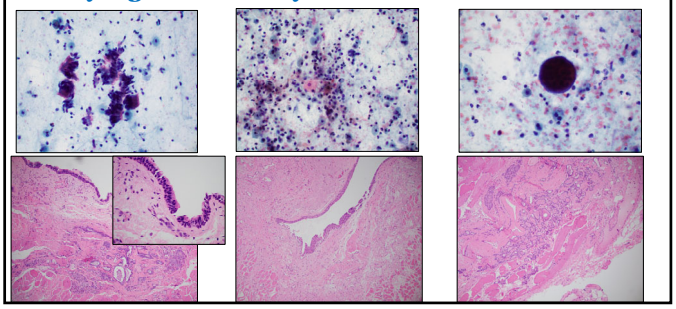
3.1. Developmental abnormalities

Thyroglossal duct cyst



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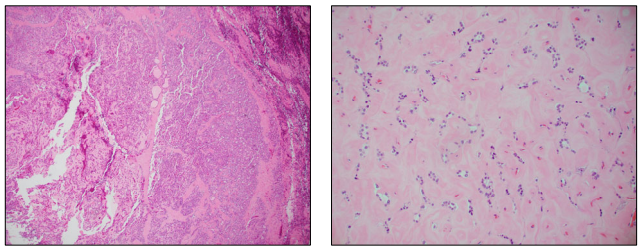
3.1. Developmental abnormalities

Dyshormonogenetic goiter



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3.2. Follicular cell-derived neoplasms

1. Benign tumors

- Thyroid follicular nodular disease (FND)
- Follicular thyroid adenoma (FA)
- Follicular adenoma with papillary architecture
- Oncocytic adenoma of the thyroid (OA)

***RAS*-like molecular profile in encapsulated neoplasms**

2. Low-risk neoplasms

- Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)
- Thyroid tumors of uncertain malignant potential (UMP)
- Hyalinizing trabecular tumor (HTT)

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3.2. Follicular cell-derived neoplasms (cont'd)

3. Malignant neoplasms

- Follicular thyroid carcinoma (FTC)
- Invasive encapsulated follicular variant papillary carcinoma (IEFVPTC)
- Papillary thyroid carcinoma (PTC)
- Oncocytic carcinoma of the thyroid (OCA)
- Follicular-derived carcinomas, high-grade
  - i. Differentiated high-grade thyroid carcinoma
  - ii. Poorly differentiated thyroid carcinoma
- Anaplastic thyroid carcinoma

***BRAF* V600E-like molecular profile in papillary and/or infiltrative growth pattern neoplasms**

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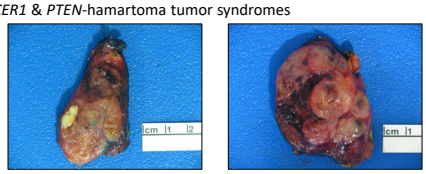
3.2.1. Benign tumors

Thyroid Follicular Nodular Disease (FND)

- Non-inflammatory, non-malignant enlargement of the thyroid gland
- Some of these lesions are molecularly clonal
- Could be associated with *DICER1* & *PTEN*-hamartoma tumor syndromes
- Acceptable terminology:
  - nodular follicular disease
  - adenomatous nodules
  - nodular hyperplasia
  - adenomatous hyperplasia
  - multinodular thyroid hyperplasia
  - multinodular goiter (clinical)



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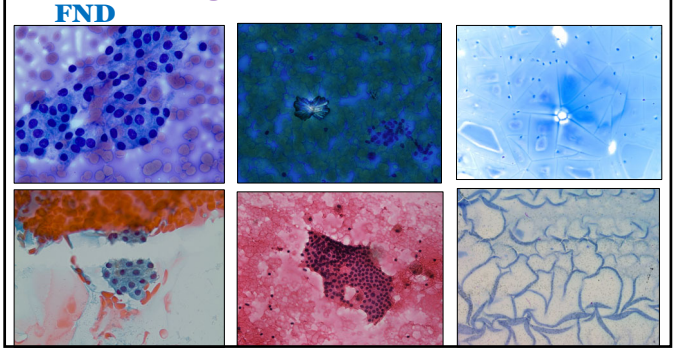
3.2.1. Benign tumors
FND



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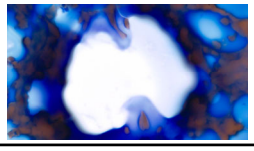
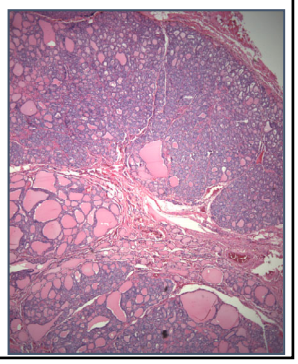
3.2.1. Benign tumors FND

- Hyperplastic process
- Clinical setting of multinodular goiter
- Absence of:

- Invasive growth
- Nuclear features of PTC





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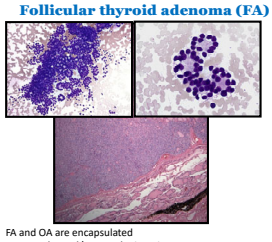
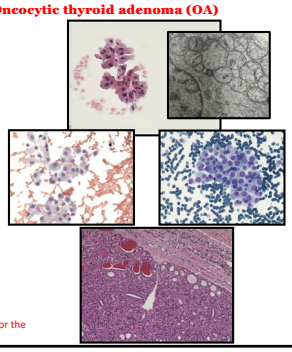
3.2.1. Follicular thyroid adenoma (FA)



3.2.1. Oncocytic thyroid adenoma (OA)



- FA and OA are encapsulated
- No capsular and/or vascular invasion
- No nuclear features of PTC
- The term "Hürthle cell" is discouraged
- The term "oncocytic" is used to describe follicular cells with abundant cytoplasm, distinct cell borders and prominent nucleoli
- Thyroid adenomas with >75% of oncocytic cells are classified as OA
- OA have distinct genomic alteration in mitochondrial genome (mtDNA) or the related *GRIM19(NDUFA13)* gene

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3.2.1. Benign tumors

Follicular thyroid adenoma with papillary architecture

- Autonomous hyperfunctioning nodules
- Clinical/subclinical hyperthyroidism
- Some occur in patients with McCune Albright syndrome, Carney complex, and *DICER*1 syndrome
- Encapsulated thyroid neoplasm composed of follicular epithelial cells
- Organized intrafollicular papillary architecture, with sub-follicle formation
- Absence of nuclear features of PTC, capsular invasion & psammoma bodies
- Activating *TSHR* mutations are detected in up to 70%, whereas *GNAS* and/or *EZH1* mutations are found in a small subset
- Should not be mistaken for FA with papillary hyperplasia (which is associated with *RAS* mutations and is not associated with hyperfunction and is more commonly seen in children and young adults)

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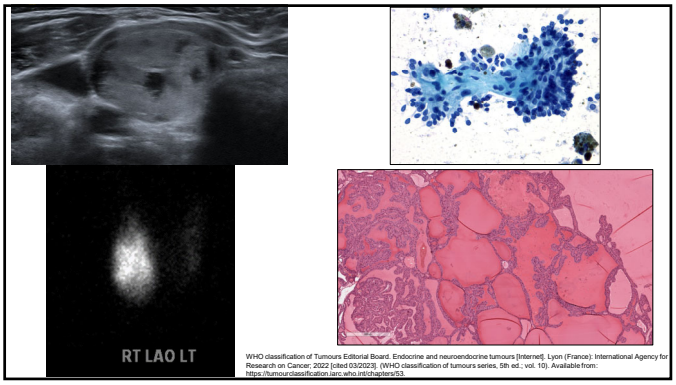

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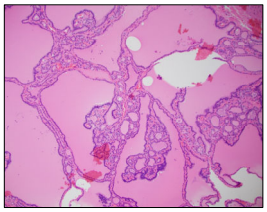
3.2.1. Benign tumors

Follicular thyroid adenoma with papillary architecture



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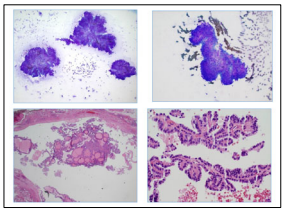
3.2.1. Benign tumors

Follicular thyroid adenoma with papillary hyperplasia



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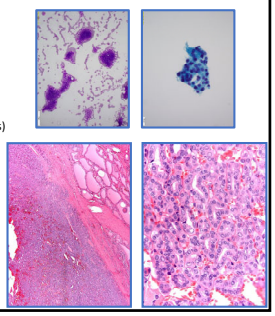
3.2.2. Low-risk neoplasms

NIFTP

Inclusion criteria:
- Encapsulated/well demarcated
- A follicular architecture with <1% papillae
- The nuclear features of PTC (score 2-3):
  1. Size and shape (elongation, enlargement, overlap)
  2. Membrane irregularities (irregular contours, grooves, pseudoinclusions)
  3. Chromatin characteristics (clearing, margination, glassy nuclei)

Exclusion criteria:
- Any invasion (capsular and/or vascular)
- Psammoma bodies
- Tumor necrosis
- Mitoses >3/ 2 mm^2
- >30% solid/ trabecular/insular growth
- Characteristics of other PTC subtypes (such as tall cell or columnar cell)
- *BRAF* V600E or *TERT* promoter mutations



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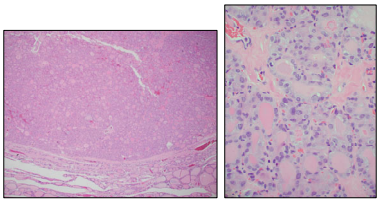
3.2.2. Low-risk neoplasms

NIFTP

New:

- Subcentimeter NIFTP
- Oncocytic NIFTP
- Large NIFTP (> 4 cm)
- Pediatric group NIFTP



- Those rare non-invasive follicular patterned tumors with PTC nuclei that are excluded from NIFTP because of a mitotic count >3/ 2 mm^2 are best reported as mitotically active encapsulated PTC with a predominant follicular growth pattern
- If the mitotic count is $\geq$ 5 / 2 mm^2 or if there is tumor necrosis they should be reported as non-invasive high grade FVPTC
- Staging is not performed for NIFTP

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3.2.2. Low-risk neoplasms

Thyroid tumors of uncertain malignant potential

- Tumors of uncertain malignant potential (UMP) are well-differentiated thyroid tumors with follicular architecture that are encapsulated or unencapsulated but well circumscribed, in which invasion remains questionable after thorough sampling and exhaustive examination.
- Subtypes:
  - Follicular tumor of uncertain malignant potential (FT-UMP)
  - Well-differentiated tumor of uncertain malignant potential (WDT-UMP)
- *HRAS*, *KRAS*, or *NRAS* mutations are identified in up to 30-40% of cases, NRAS p.Q61R being the most common mutation
- If *BRAF* V600E, *TP53* or *TERT* promoter mutations are detected, the tumor should be meticulously examined to rule out carcinoma

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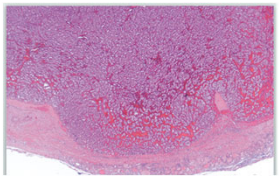
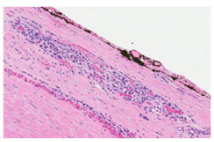
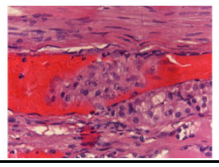
3.2.2. Low-risk neoplasms

WDT-UMP







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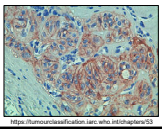
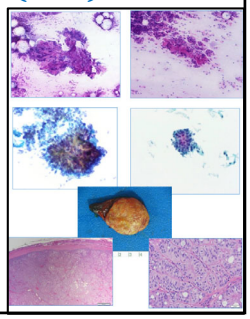
3.2.2. Low-risk neoplasms
Hyalinizing trabecular tumor (HTT)

- HTT is composed of large trabeculae of elongated or polygonal cells
- Intratrabecular hyaline material
- Nuclear features of PTC
- Characterized by the presence of *GLIS* rearrangements (*PAX8::GLIS1* and *PAX8::GLIS3)*
- Membranous Ki-67 immunostaining





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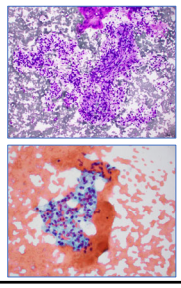
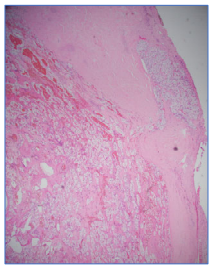
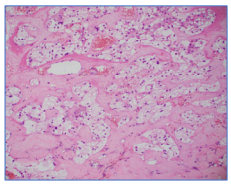
3.2.3. Malignant neoplasms

Follicular thyroid carcinoma (FTC)







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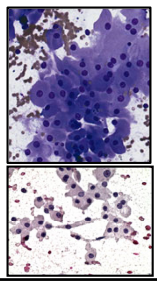
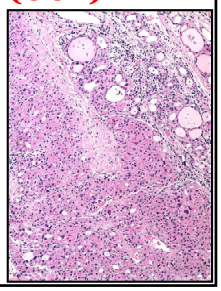
3.2.3. Malignant neoplasms

Oncocytic thyroid carcinoma (OCA)

- 5% of differentiated thyroid carcinomas in the USA
- Mean age ~ 60 years
- >75% of oncocytic cells
- Distant metastasis at presentation in 15-27% of patients
- Mitochondrial DNA mutations
- *RAS* mutations is at a lower rate than in FTC





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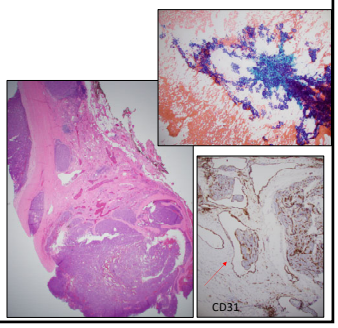
3.2.3. Malignant neoplasms

FTC & OCA

Subtypes:

- Minimally invasive (capsular invasion only)
- Encapsulated angioinvasive:
  - Limited angioinvasion (< 4 foci)
  - Extensive angioinvasion (4 or more foci)
- Widely invasive (obliterated or focally intact tumor capsule and/or gross invasion through the gland)



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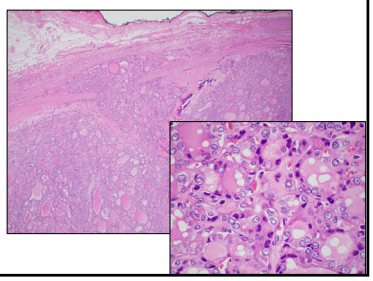
3.2.3. Malignant neoplasms

Invasive encapsulated follicular variant PTC (IEFVPTC)

- Malignant counterpart of NIFTP
- Encapsulation
- Follicular patterned architecture
- Nuclear features of PTC
- *RAS*-like mutational profile
- Capsular and/or vascular invasion.
  - Subtypes:
    - Minimally invasive
    - Encapsulated angioinvasive
    - Widely invasive



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3.2.3. Malignant neoplasms

Papillary thyroid carcinoma (PTC)

Changes:

- Using "subtype" instead of "variant"
- Microcarcinoma is no longer considered a subtype of PTC
- Subcentimeter PTC requires histologic subtyping (classic, follicular, etc.)
- "Encapsulated variant" is renamed as "encapsulated classic subtype"
- "Cribriform-morular variant of PTC" is no longer classified as a subtype of PTC
- Aggressive histologic forms: Tall cell, columnar cells, and hobnail PTC subtypes
  - Tall cells should have a height of at least 3 times their width and show dense eosinophilic cytoplasm and distinct cell membranes
  - Tall cell subtype should have at least 30% tall cells

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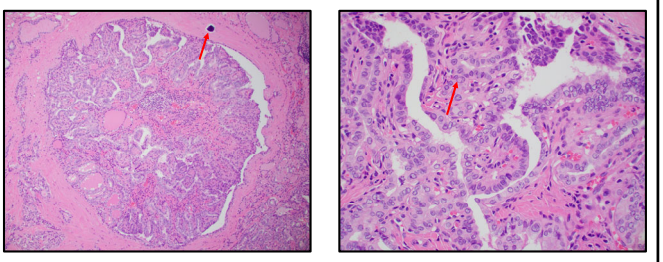
PTC, encapsulated classic subtype



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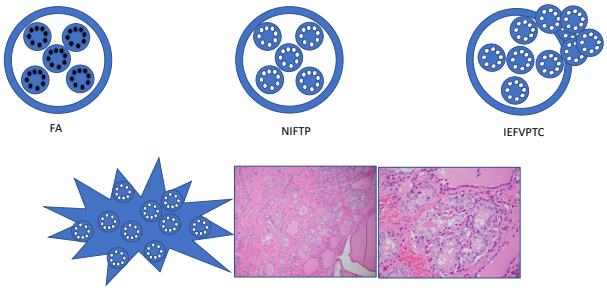
Follicular-patterned thyroid neoplasms



Infiltrative follicular subtype of PTC

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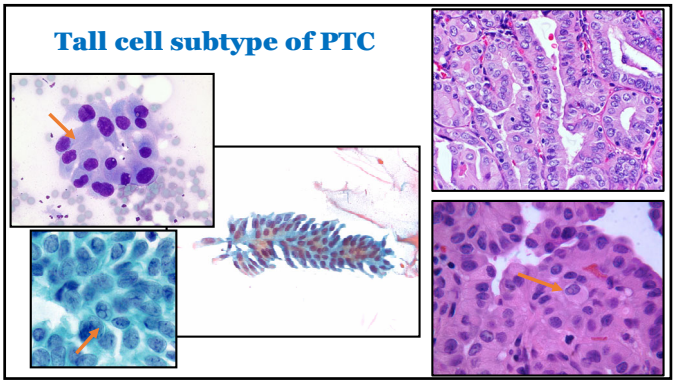
Tall cell subtype of PTC



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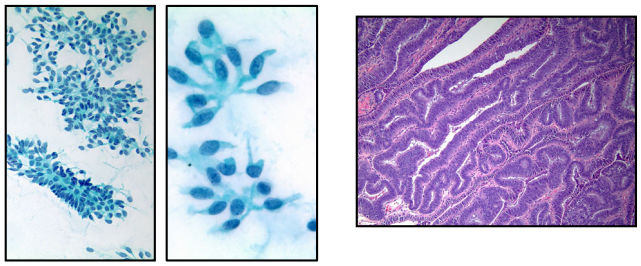
Columnar cell subtype of PTC



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3.2.3. Malignant neoplasms

High-grade follicular cell-derived non-anaplastic thyroid carcinoma

1. Poorly differentiated thyroid carcinoma (PDTC)

Foci c/w PTC, FTC, or OCA are **absent**

2. Differentiated high-grade thyroid carcinoma (DHGTC)

Foci c/w PTC, FTC, or OCA are **present**

- PDTC and DHGTC have aggressive clinicopathologic features and the prognosis is intermediate between well-differentiated carcinomas of follicular cells and anaplastic carcinoma
- Both *RAS*-like and *BRAF* V600E-like carcinomas can have high-grade features
- Progression is associated with secondary genetic events (*TP53*, *TERT* promoter, *PTEN* mutations)
- The mean disease-specific survival is approximately 5 years after the original diagnosis
- The overall survival at 5 years in most series is 50-70%
- Response to radioiodine treatment is poor in many patients

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Diagnostic criteria for high-grade follicular cell-derived thyroid carcinomas

	Poorly differentiated thyroid carcinoma (Turin proposal)	Differentiated high-grade thyroid carcinoma
Architectural pattern	Solid/trabecular/insular growth required	Papillary, follicular, solid[a]
Nuclear features	Absence of nuclear features of PTC is required	Any
Necrosis, mitosis and convoluted nuclei	At least one of the following three features: Mitotic count ≥3/2 mm² Tumor necrosis Convoluted nuclei	At least one of the following two features: Mitotic count ≥5/2 mm² Tumor necrosis
Anaplastic features	None	None

[a] Tumors with solid growth and PTC nuclear features are classified as high grade differentiated thyroid carcinoma

WHO classification of Tumours Editorial Board. Endocrine and neuroendocrine tumours [Internet]. Lyon (France): International Agency for Research on Cancer; 2022 [cited 03/2023]. (WHO classification of tumours series, 5th ed.; vol. 10). Available from: https://tumourclassification.iarc.who.int/chapters/53.

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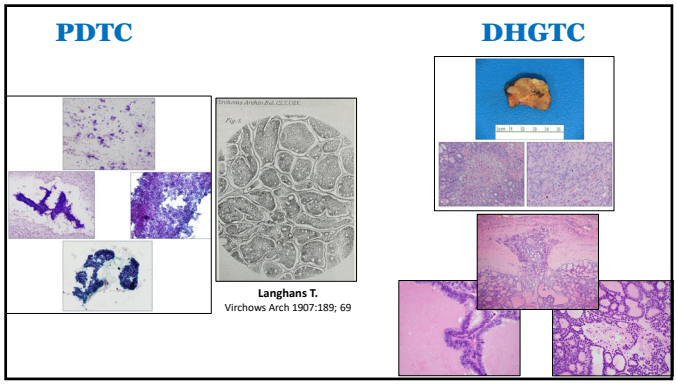

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Mutation profile of high-grade follicular cell-derived thyroid carcinomas according to subtype

Subtype	*BRAF* V600E	*RAS*[a]	*TERT*	*TP53*	*EIF1AX*	*PTEN*	*PIK3CA*
Poorly differentiated thyroid carcinoma (PDTC)	9%	44%	44%	15%	15%	6%	2%
Differentiated high grade thyroid carcinoma (DHGTC)	31%	6%	39%	3%	3%	0%	3%

[a] PDTC: *NRAS* 33%, *HRAS* 8% and *KRAS* 4%; DHGTC: *NRAS* 6%

WHO classification of Tumours Editorial Board. Endocrine and neuroendocrine tumours [Internet]. Lyon (France): International Agency for Research on Cancer; 2022 [cited 03/2023]. (WHO classification of tumours series, 5th ed.; vol. 10). Available from: https://tumourclassification.iarc.who.int/chapters/53.

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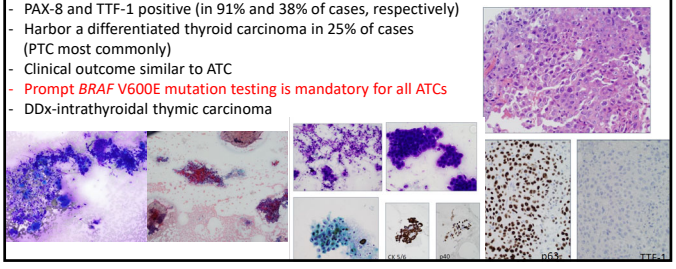
3.2.3. Malignant neoplasms

Squamous Cell Carcinoma (SCC) – a subtype of Anaplastic Thyroid Carcinoma (ATC)

- *BRAF* V600E mutation in 87% of cases with or without differentiated thyroid carcinoma
- *BRAF* V600E in 60% of cases without any differentiated thyroid carcinoma component
- PAX-8 and TTF-1 positive (in 91% and 38% of cases, respectively)
- Harbor a differentiated thyroid carcinoma in 25% of cases (PTC most commonly)
- Clinical outcome similar to ATC
- Prompt *BRAF* V600E mutation testing is mandatory for all ATCs
- DDx-intrathyroidal thymic carcinoma



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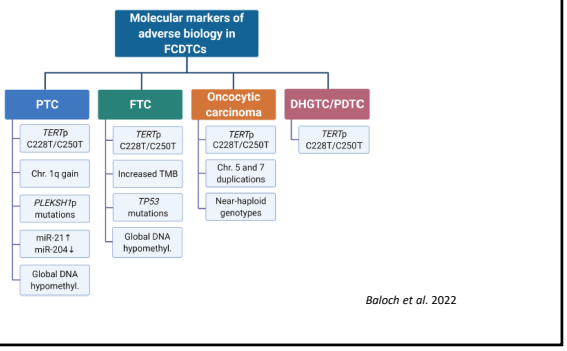

Baloch et al. 2022

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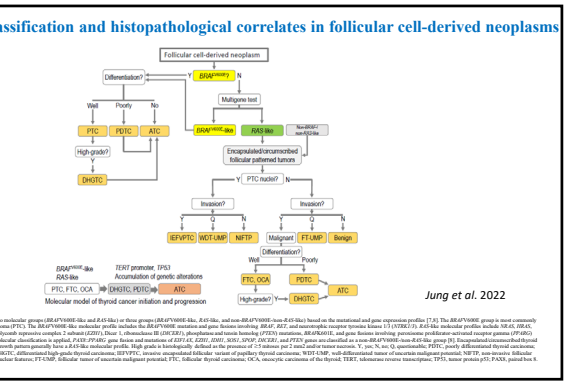

Jung et al. 2022

Thyroid neoplasms are classified as two molecular groups (*BRAF*V600E*-like and *RAS*-like) or three groups (*BRAF*V600E*-like, *RAS*-like, and non-*BRAF*V600E*/non-*RAS*-like) based on the mutational and gene expression profiles [7,8]. The *BRAF*V600E* group is most commonly represented by papillary thyroid carcinoma (PTC). The *BRAF*V600E*-like molecular profile includes the *BRAF*V600E* mutation and gene fusions involving *BRAF*, *RET*, and neurotrophic receptor tyrosine kinase 1/3 (*NTRK1/3*). *RAS*-like molecular profiles include *NRAS*, *HRAS*, *KRAS*, *EIF1AX*, enhancer of zeste 1 polycomb repressive complex 2 subunit (*EZH1*), Dicer 1, ribonuclease III (*DICER1*), phosphatase and tensin homolog (*PTEN*) mutations, *BRAF*K601E*, and gene fusions involving peroxisome proliferator-activated receptor gamma (*PPARG*) and *THADA*. When the three-group molecular classification is applied, *PAX8/PPARG* gene fusion and mutations of *EIF1AX*, *LDB1*, *HMG1*, *SOS1*, *SPOP*, *DICER1*, and *PTEN* genes are classified as a non-*BRAF*V600E*-/non-*RAS*-like group [9]. Encapsulated/circumscribed thyroid tumors with a predominant follicular growth pattern generally have a *RAS*-like molecular profile. High grade is histologically defined as the presence of ≥5 mitoses per 2 mm2 and/or tumor necrosis. Y, yes; N, no; Q, questionable; PDTC, poorly differentiated thyroid carcinoma; ATC, anaplastic thyroid carcinoma; DHGTC, differentiated high-grade thyroid carcinoma; IEFVPTC, invasive encapsulated follicular variant of papillary thyroid carcinoma; WDT-UMP, well-differentiated tumor of uncertain malignant potential; NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features; FT-UMP, follicular tumor of uncertain malignant potential; FTC, follicular thyroid carcinoma; OCA, oncocytic carcinoma of the thyroid; TERT, telomerase reverse transcriptase; TP53, tumor protein p53; PAX8, paired box 8.

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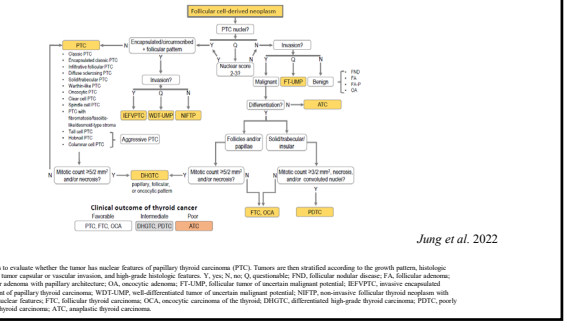

Jung et al. 2022

The first step is to evaluate whether the tumor has nuclear features of papillary thyroid carcinoma (PTC). Tumors are then stratified according to the growth pattern, histologic differentiation, tumor capsular or vascular invasion, and high-grade histologic features. Y, yes; N, no; Q, questionable; FND, follicular nodular disease; FA, follicular adenoma; FA-P, follicular adenoma with papillary architecture; OA, oncocytic adenoma; FT-UMP, follicular tumor of uncertain malignant potential; IEFVPTC, invasive encapsulated follicular variant of papillary thyroid carcinoma; WDT-UMP, well-differentiated tumor of uncertain malignant potential; NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features; FTC, follicular thyroid carcinoma; OCA, oncocytic carcinoma of the thyroid; DHGTC, differentiated high-grade thyroid carcinoma; PDTC, poorly differentiated thyroid carcinoma; ATC, anaplastic thyroid carcinoma.

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3.3. Thyroid C-cell derived carcinoma

Medullary thyroid carcinoma (MTC)

- Primary non-follicular cell-derived thyroid tumor with morphologic and immunohistochemical features of neuroendocrine derivation, including expression of Calcitonin and/or CEA
- 25% of patients with MTC will have MEN2
- *RET* and *RAS* mutations are the predominant drivers of MTC in 80-90% of cases
- Germline *RET* mutations testing is recommended for all patient regardless of family history
- Somatic only *RET* mutations are seen in ~50% of sporadic MTC
- Two-tiered histologic grading system is newly applied to the diagnosis of MTC (low-grade MTC and high-grade MTC)
- This system was shown to be independent from AJCC (8TH ED) stage group, age, sex, tumor size, margin status, post-operative CEA serum level in predicting locoregional recurrence, distant metastasis-free, disease-specific, and overall survival (*Nadjdawi et al.* 2021)
- High-grade MTCs were associated with lower disease-specific survival and recurrence-free survival rates

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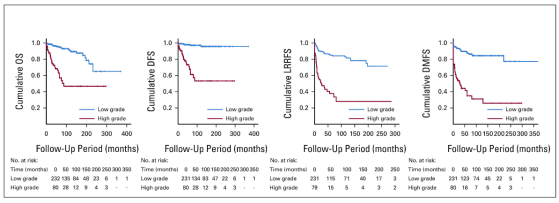
International Medullary Thyroid Carcinoma Grading System: A Validated Grading System for Medullary Thyroid Carcinoma

MTC	Mitotic count	Tumor necrosis	Ki67 index
High grade	≥5 mitoses per 2 mm²	Present	≥5%
Low grade	< 5 mitoses per 2 mm²	Absent	< 5%



Kaplan-Meier curves for survival according to the international medullary thyroid carcinoma grading system. DMFS, distant metastasis-free survival; DSS, disease-specific survival; LRRFS, locoregional recurrence-free survival; OS, overall survival.

Xu et al. 2022.

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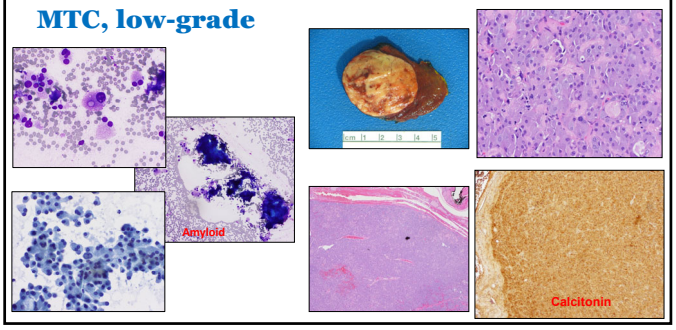
3.3. Thyroid C-cell derived carcinoma

MTC, low-grade



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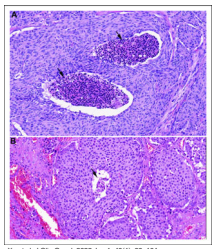
3.3. Thyroid C-cell derived carcinoma

MTC, high-grade



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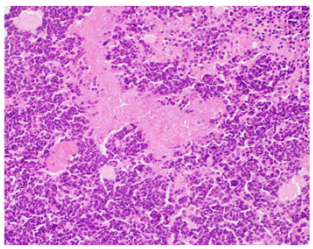

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3.4. Mixed medullary and follicular cell-derived carcinomas

- Represent less than 0.5% of all thyroid tumors
- PTC usually represents less than 25% of the tumor
- Two components are intimately admixed
- Each component can be identified by its **nuclear features**
- Immunohistochemical stains for **Calcitonin** and **Thyroglobulin** may be positive in corresponding tumor cells, or may be co-expressed
- **TTF-1** positivity can be seen in both components

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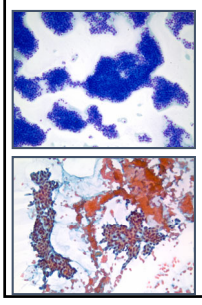
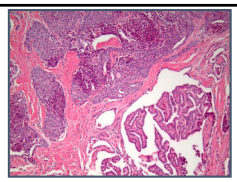
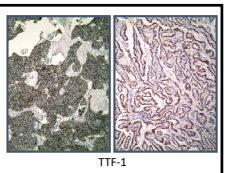
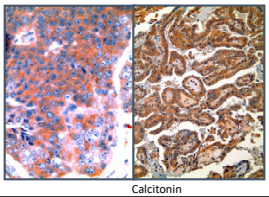
3.4. Mixed medullary and follicular cell-derived carcinoma



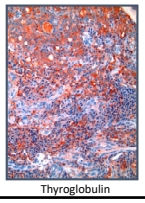




TTF-1



Calcitonin



Thyroglobulin

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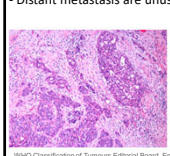
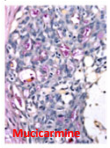
3.5. Salivary gland-type carcinomas of the thyroid

3.5.1. Mucoepidermoid carcinoma of the thyroid

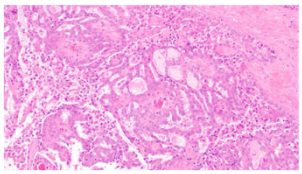
- Histogenesis:
  Ectopic salivary gland tissue, solid cell nests, thyroglossal duct remnants, metaplasia
- Mucus cells, intermediate cells, squamous cells
- *MAML2* rearrangement
- Indolent tumor with excellent outcome
- Distant metastasis are unusual





3.5.2. Secretory carcinoma of salivary gland type

- *ETV6* translocations are defining with the appropriate
- Positive S100, mammaglobin, GATA3, GCDFP-15
- Negative TTF-1 and Thyroglobulin
- Appear more aggressive than their salivary counterparts



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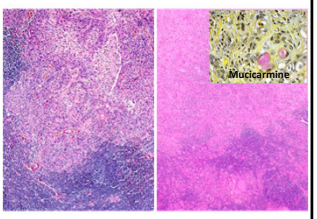
3.6. Tumors of uncertain histogenesis

3.6.1. Sclerosing mucoepidermoid carcinoma with eosinophilia (SMECE)

- Unilateral painless mass
- F:M ratio is 13:1
- The average age: 55 years (range 22-89)
- Associated with chronic lymphocytic thyroiditis
- Histogenesis:
  -Likely ultimobranchial body/solid cell nest origin
- Absence of *MAML2* and *BRAF* mutations
- TTF-1 is positive in ~50% of cases
- Thyroglobulin and PAX8 are typically negative



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3.6. Tumors of uncertain histogenesis

3.6.2. Cribriform morular thyroid carcinoma (CMTC)

- Described by **Harach et al.** in 1994 as "FAP-associated thyroid carcinoma: a distinct type of follicular neoplasm"
- Familial CMTC are associated with Familial Adenomatous Polyposis (FAP)
- The female to male ratio is 31:1 to 61:1
- FAP-associated thyroid tumors are multifocal and/or bilateral and have good prognosis
- Sporadic forms are unifocal
- Thyroid tumors may be the initial clinical presentation of FAP
- Genetic alterations involving *WNT*/beta catenin pathway (*APC* and *CTNNB1*) genes
- No association with *BRAF* V600E or *RAS* mutations
- Immunohistochemistry:
  - Cribriform areas: TTF-1, ER/PR positive, PAX8 negative of focal weak, Thyroglobulin-negative
  - Morules: CK5, CD10 positive, negative for TTF-1, PAX8, Thyroglobulin, ER/PR
  - Aberrant nuclear and cytoplasmic beta-catenin expression
- *APC*-gene analysis, screening for colonic and extracolonic manifestations of the disease and screening of family members should be recommended by the pathologist

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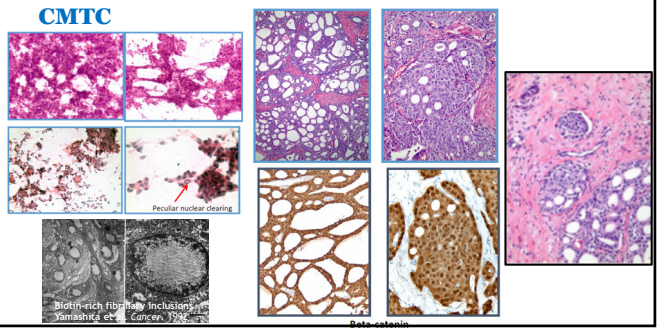
3.6. Tumors of uncertain histogenesis

CMTC



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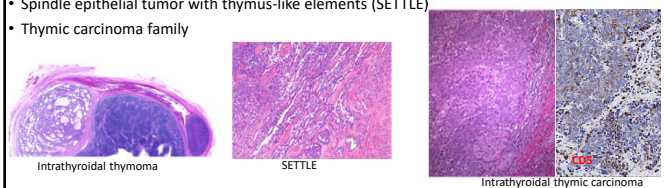
3.7. Thymic tumors within the thyroid

Histogenesis: Ectopic thymic or branchial pouch remnant differentiation along the thymic line

- Thymoma family
- Spindle epithelial tumor with thymus-like elements (SETTLE)
- Thymic carcinoma family



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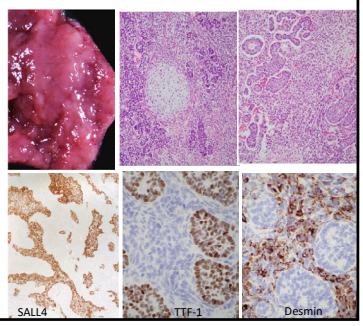
3.8. Embryonal thyroid neoplasms

Thyroblastoma

- Embryonal high-grade thyroid neoplasm
- Primitive follicular cells, small cells, and mesenchymal stroma
- Highly aggressive course
- Tumor is associated with *DICER1* gene mutations



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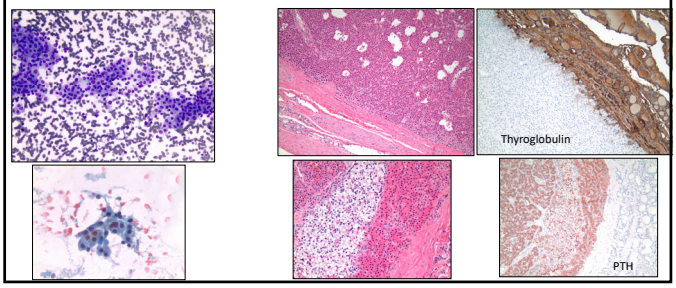
Intrathyroidal Parathyroid Adenoma



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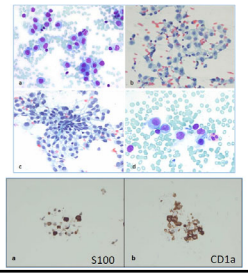
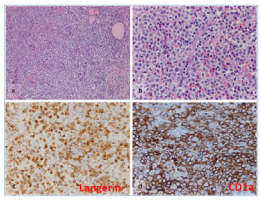
Hematolymphoid tumors

Langerhans cell histiocytosis





Saqi A, Kuker A, Ebner S, Ausiello J, Jobanputra V, Bhagat G, Giorgadze T. *Head and Neck Pathol.*2015

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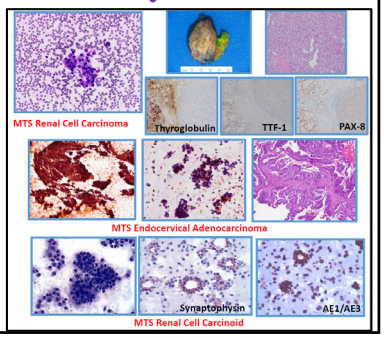
Metastatic Tumors to the Thyroid Gland

- In up to 2.1% in surgical pathology cases
- In up to 25% in autopsy cases
- Metastases from kidney (most common), lung, breast, skin, GI tract
- Metastatic neuroendocrine tumors
- Clinical history is important



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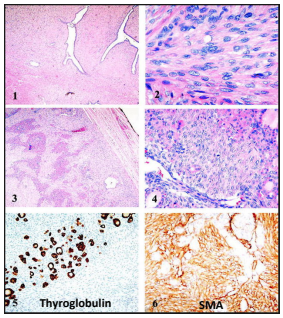
Tumor-to-tumor metastasis



Phyllodes Tumor Metastatic to Thyroid Hürthle Cell Adenoma: An Unusual Tumor-to-Tumor Metastasis.

Giorgadze et al. *Arch Pathol Lab Med* (2002) 126 (10): 1233–1236.

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Summary of important updates

- *Follicular adenoma with papillary architecture* is separated from FA
- *A family of Low-risk neoplasms* has been created
- NIFTP group changes
- *Invasive encapsulated follicular variant of papillary thyroid carcinoma* (IEFVPTC) is separated from PTC
- Microcarcinoma is no longer a subtype of PTC
- *Cribriform-morular carcinoma* is a distinct thyroid tumor and no longer a subtype of PTC
- Two-tiered grading system for high-grade follicular cell-derived non-anaplastic thyroid carcinoma cancers is introduced
- *Primary squamous cell carcinoma of the thyroid* is now considered a subtype of ATC
- Two-tiered grading system for MTC is introduced
- Thyroblastoma is added to the classification of thyroid tumors

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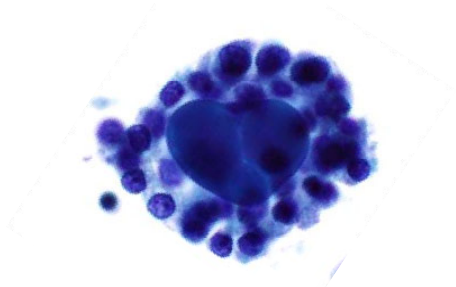

Thank You!

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The Use of Radiofrequency Ablation for Thyroid Disease

Sophie Dream, MD
Assistant Professor of Surgical Oncology
Endocrine Surgeon

knowledge changing life

1

Overview

- Overview of radiofrequency ablation
- Procedure indications for thyroid disease
- Technique
- Complications
- Expected Outcomes
- Comparison to other techniques
- Follow-up
- MCW Experience

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2

Thyroid Nodules

- 19-68% of patients will have ≥1 or more on ultrasound
- Majority are benign
  - 7-15% risk of thyroid cancer based on patient specific factors
- Traditional treatments for benign, growing nodules
  - TSH suppression—ATA recommends against this practice
  - Thyroidectomy-- low risk surgery

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3

Alternatives to Thyroidectomy

- Ultrasound guided ablation of thyroid nodules developed in early 2000s
  - Laser ablation
  - Ethanol Ablation
  - High intensity focused ultrasound (HIFU)
  - Microwave ablation (MWA)
  - Radiofrequency ablation
- RFA gained popularity outside the US over the last 20 years

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4

Radiofrequency Ablation

- High-frequency electrical current to induce thermal injury.
- Increasing acceptance as a treatment for thyroid disease.

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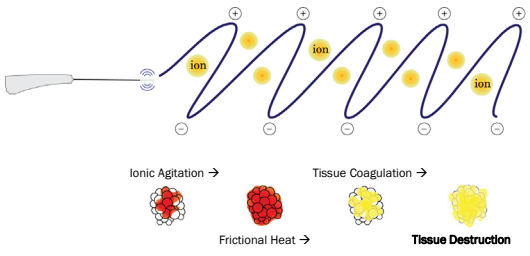

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Indications

- Benign thyroid nodules
  - Cosmetic concerns
  - Compressive symptoms
    - Pain, dysphasia, foreign body sensation, discomfort, cough
- Autonomous functioning thyroid nodule (AFTN)
- Recurrent thyroid cancers in non-surgical candidates

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Indications

Benign Thyroid Nodule
Pathologic diagnosis
Benign diagnosis at least two US-guided FNA or CNB
Benign diagnosis at least one US-guided FNA or CNB in AFTN
Benign diagnosis at least 1 US-guided FNA or CNB in thyroid nodules with highly specific benign US features

Kim et al. *Korean J Radiol.* 2018;19(4):632-655.
Garberoglio et al. *J Ultrasound.* 2015;18(4):423-430

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Thyroid Malignancy

- Potential role in patients with recurrent thyroid cancer who:
  - Prohibitive surgical risk due to comorbidities or multiple prior operations
  - Curative intent for <3-4 locally recurrent tumors <2cm in size
  - Palliation
- Not recommended for:
  - Primary thyroid cancers
  - Distant metastasis

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Contraindications

Surgical and Pathological Changes after Radiofrequency Ablation of Thyroid Nodules

Chiara Dobrinja,[1] Stella Bernardi,[2,3] Bruno Fabris,[2,3] Rita Eramo,[1] Petra Makovac,[1,3] Gabriele Bazzocchi,[4] Lanfranco Piscopello,[3] Enrica Barro,[2,3] Nicolò de Manzini,[1,3] Deborah Bonazza,[3,6] Maurizio Pinamonti,[3,6] Fabrizio Zanconati,[3,6] and Fulvio Stacul[4]

- Bethesda III/IV nodules
  - ? Possibly promotes tumor growth
  - Lose the ability to follow nodule characteristics on ultrasound

Dobrinja et al. *IJE*. 2015;2015:576576.

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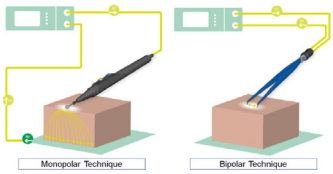
Contraindications

- Pregnant patients
- Patients with electrical implants—e.g., pacemakers



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Procedure

- Performed under ultrasound guidance
- Performed with local anesthetic
- Outpatient procedure, ~1 hours

Two Fundamental Methods
- A trans-isthmic approach
- Moving-shot technique

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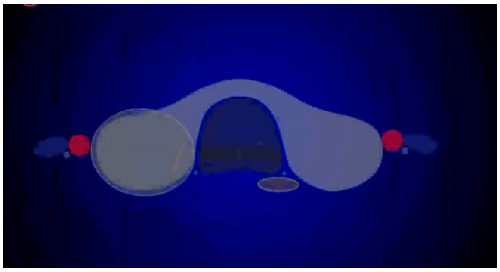
Technique



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Complications

Overall complication rate 3.5%

- Discomfort during the procedure (up to 100%)
- Changes in the voice (1-1.8%)
  - Most resolve within 3 hours after procedure completion
- Nodule rupture (0.14-2.4%)
- Hematoma (0-17%)
- Skin burn (0.3-3.7%)
- Tracheal Injury (0.07%)
- Hypothyroidism (0.07-6.7%)

Kim et al. *Eur Radiol.* 2017;27(8):3128-3137.
Dobnig et al. *Thyroid.* 2018;28(4):472-480.
Baek et al. *Radiology.* 2012;262(1):335-342.

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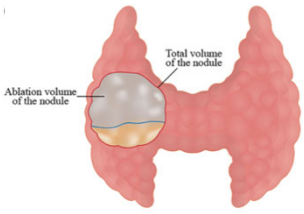
Risk of Hypothyroidism

- Thyroid lobectomy 10-40%
- RFA hypothyroidism (0.07-6.7%)
- Risk factors for post-RFA:
  - Ablation volume ratio
  - Pre-procedure TSH



Wang N, Zheng B, Wu T, et al. *Int J Hyperthermia.* 2021;38(1):1060-1068.

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Patient Satisfaction and VRR

Volume Reduction Ratio (VRR)
- V = πabc/6
- [(Initial Volume – Final Volume)/Initial Volume] × 100%

Cosmetic score:
- 1- No palpable mass
- 2- No cosmetic problem but a palpable mass
- 3- Cosmetic problem on swallowing only
- 4- Readily observable cosmetic problem

Symptom score (0–10 scores) on a Likert-scale

Guang et al. *BMC Cancer.* 2019;19(1):147.

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Expectations

- Increase in nodule volume for 1 month after RFA
- Mean volume reduction range (VRR): 52%-95% at 12 mnths
- Most common complications:
  - Discomfort
  - Voice changes (0.3% permanent)
  - Nodule rupture
- Improvements in symptoms to be expected at 6-12 months
  - Cosmetic and Symptom scores improve

Hamidi et al. *Mayo Clinic proceedings.* 2018;93(8):1018-1025
Kim et al. *Korean J Radiol.* 2018;19(4):632-655.
Suh et al. *Thyroid.* 2016;26(3):420-428.

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Expectations

- Volume reduction plateau at 1-3 years
- Multiple treatment sessions:
  - Range from 1-3 sessions; mean <1.3
  - Repeat RFA considered 6 months after initial RFA
    - <50% VRR
    - Persistent symptoms
    - Nodule regrowth
    - Increased nodule vascularity

Kim et al. *Korean J Radiol.* 2018;19(4):632-655.
Suh et al. *Thyroid.* 2016;26(3):420-428.

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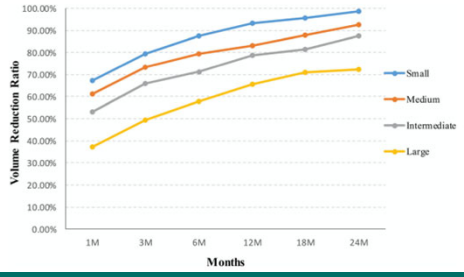
Non-functional Benign Nodules



Guang et al. *BMC Cancer.* 2019;19(1):147.

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Symptom and Cosmetic Score

Table 3 Changes in cosmetic score and symptom score of TNs at baseline and the last follow-up

	Small 5 ml (n = 38)		Medium 5.1–13 ml (n = 86)		Intermediate 13.1–30 ml (n = 43)		Large >30 ml (n = 27)	
	Cosmetic score	Symptom score	Cosmetic score	Symptom score	Cosmetic score	Symptom score	Cosmetic score	Symptom score
Baseline[a]	1.5 ± 0.5	0 ± 0	2.0 ± 0.6	0 ± 0	2.7 ± 0.7	3.8 ± 2.1	3.2 ± 0.7	7.1 ± 1.8
Last follow-up visit[b]	1.0 ± 0[c]	0 ± 0	1.2 ± 0.4[c]	0 ± 0	1.5 ± 0.4[c]	0.7 ± 0.5[c]	1.7 ± 0.5[c]	0.9 ± 0.6[c]

TNs thyroid nodules
[a]The cosmetic score and symptom score assessed before ablation
[b]The cosmetic score and symptom score assessed at the last follow-up visit
[c]< .05

Guang et al. *BMC Cancer.* 2019;19(1):147.

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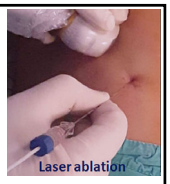
Long-Term Results of Thermal Ablation of Benign Thyroid Nodules: A Systematic Review and Meta-Analysis

Se Jin Cho[1,2], Jung Hwan Baek[1], Sae Rom Chung[1], Young Jun Choi[1], Jeong Hyun Lee[1]

[1]Department of Radiology and Research Institute of Radiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul; [2]Department of Radiology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea



- Metanalysis with 3-year follow-up
- 695 nodules treated with RFA; 528 nodules treated with LA
- RFA VRR 92.2% compared to LA VRR 43.3%
- 21.4% of LA group underwent surgery compared to 0 in RFA group
- Major complications 1.3% in RFA group vs 1.8% in LA group

Cho et al, Endocrinol Metab 2020;35:339-350

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RFA vs LA VRR over 36 months

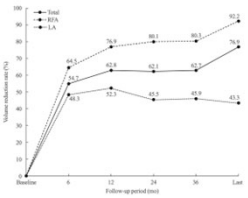

Fig. 2. The trends of pooled volume reduction rates for ablated nodules in the total subjects, total, and separately for the radiofrequency ablation (RFA) and laser ablation (LA) groups.

Cho et al, Endocrinol Metab 2020;35:339-350

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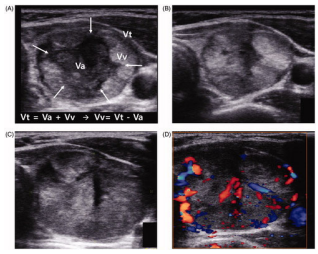
Recurrence



- Rate of recurrence ~5-20%
- Risk factors
  - -Marginal vascularity
  - -Large nodules
  - -Proximity to critical structures

Vital Volume=
Total Volume(V_t)-Ablated Volume (V_a)

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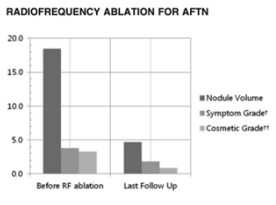
AFTN Outcomes

TABLE 1. CHARACTERISTICS OF PATIENTS WITH AUTONOMOUSLY FUNCTIONING THYROID NODULE BEFORE RADIOFREQUENCY ABLATION AND AT THE LAST FOLLOW-UP

	Before RFA	*Last follow-up*	*p value*
Mean largest diameter (cm)	3.8±1.4	2.1±1.2	<0.001
Mean volume (mL)	18.5±30.1	4.5±9.8	<0.001
Volume reduction (%)	—	81.7±13.6	
Vascular grade (0–4)[a]	3.1±0.7	0.9±1.0	<0.001
T3 (ng/dL)	179.3±102.5	133.3±63.1	<0.001
fT4 (ng/dL)	1.9±1.3	1.3±0.4	<0.001
TSH (μIU/mL)	0.12±0.12	1.22±0.93	<0.001
Symptom score[b]	3.3±2.1	0.9±1.0	<0.001
Cosmetic score[c]	3.8±0.5	1.9±0.9	<0.001



Sung et al. *Thyroid.* 2015;25(1):112-117.

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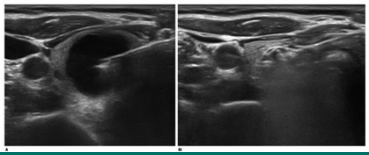
RFA vs Ethanol Ablation

- Ethanol ablation vs RFA for cystic nodules
  - Baek et al- RCT VRR of EA vs RFA (87.1% ± 11.6% vs 83.1% ± 28.7%)
  - Sung et al- RCT VRR EA vs RFA (97.7% ± 2.2% vs 93.5% ± 5.3%)
  - EA for cystic nodules is cheaper, remains first line



Sung et al. *Radiology.* 2013;269(1):293-300.
Baek et al. *Korean J Radiol.* 2015;16(6):1332-1340.
Hahn SY. Et al *Korean J Radiol.* 2019;20(4):609-620.

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Spa-Like Experience

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17. Wang N, Zheng B, Wu T, et al. Thyroid dysfunction following radiofrequency ablation for benign thyroid nodules: more likely to occur within one-week and in high-risk population. *Int J Hyperthermia.* 2021;38(1):1068-1068. doi:10.1080/02656736.2021.1950849

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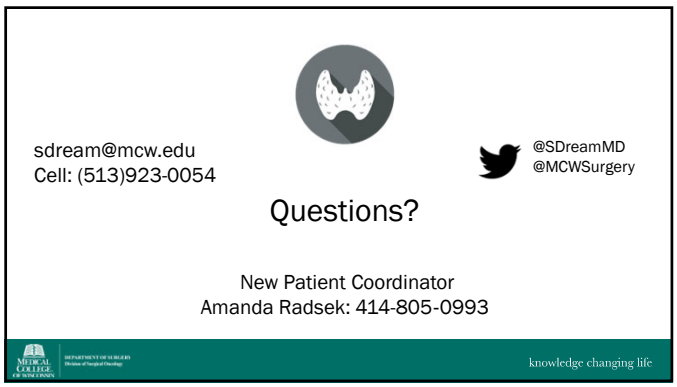
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@SDreamMD
@MCWSurgery
Questions?
New Patient Coordinator
Amanda Radsek: 414-805-0993
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1

Solorzano CC, Lee JE, Pisters PWT, Vauthey JN, Ayers GD, Jean M, Gagel RF, Ajani JA, Wolff RA, Evans DB. Nonfunctioning islet cell carcinoma of the pancreas: survival results in a contemporary series of 163 patients. Surgery 2001;130:1078-1085.

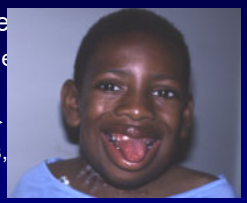
Yip L, Cote GJ, Shapiro SE, Ayers GD, Herzog CE, Sellin RV, Sherman SI, Gagel RF, Lee JE, Evans DB. Multiple endocrine neoplasia type 2: evaluation of the genotype-phenotype relationship. Arch Surg 2003;138:409-416.
Presented at the NESS, September, 2002

Yip L, Lee JE, Shapiro SE, Waguespack SG, Sherman SI, Hoff AO, Gagel RF, Arens JF, Evans DB. Surgical management of hereditary pheochromocytoma. J Am Coll Surg 2004;198:525-535.

2

Association between genotype and phenotype

- *RET* codon mutation pre
  Codon 634 → MTC, phe
  and HPT
  Codon 918 (MEN2B) →
  pheochromocytomas,



- *RET* codon mutation predicts MTC
  agg

Yip L, Cote GJ, Shapiro SE, Ayers GD, Herzog CE, Sellin RV, Sherman SI, Gagel RF, Lee JE, Evans DB. Multiple endocrine neoplasia type 2: evaluation of the genotype-phenotype relationship. Arch Surg 2003;138:409-416.
Presented at the NESS, September, 2002

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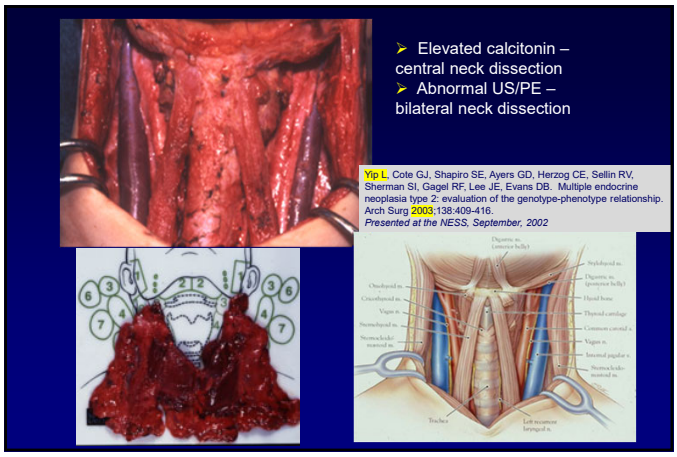
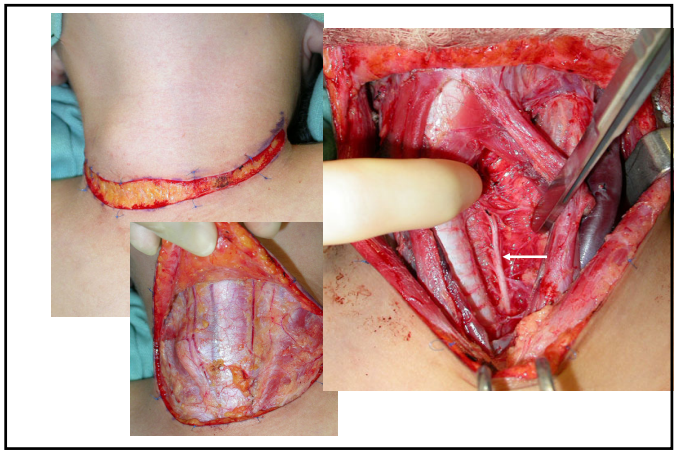

➢ Elevated calcitonin – central neck dissection
➢ Abnormal US/PE – bilateral neck dissection
Yip L, Cote GJ, Shapiro SE, Ayers GD, Herzog CE, Sellin RV, Sherman SI, Gagel RF, Lee JE, Evans DB. Multiple endocrine neoplasia type 2: evaluation of the genotype-phenotype relationship. Arch Surg 2003;138:409-416.
Presented at the NESS, September, 2002

4


7 yr. old with a 918 mutation

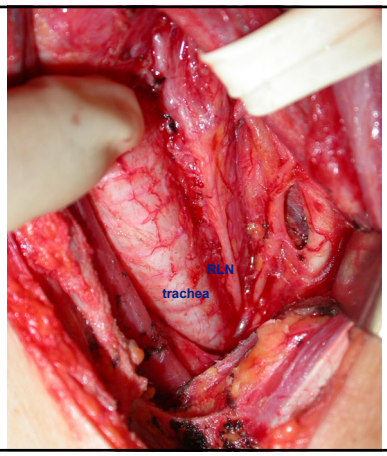
5



6

20 yr. old with a 918 mutation

7



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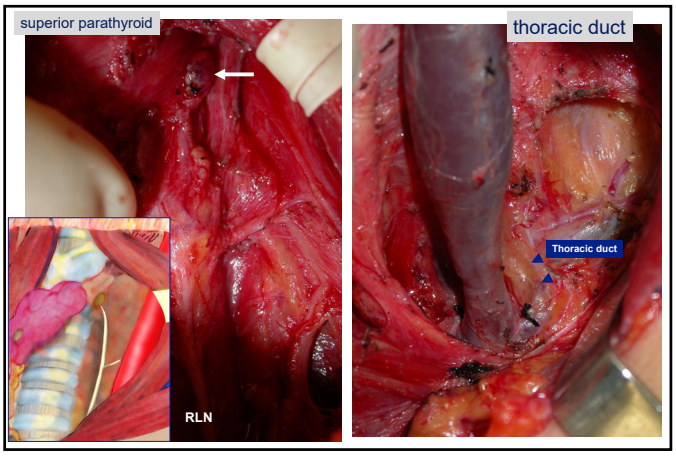

9

Risk Assessment for Distant Metastasis in Differentiated Thyroid Cancer Using Molecular Profiling: A Matched Case-Control Study

Molecular Profile of Locally Aggressive Well Differentiated Thyroid Cancers

Cancer Registries: Can We Improve the Quality of Thyroid Cancer Data?

Colleen M. Kiernan, MD, MPH[1], Martin A. Whiteside, PhD, MSPH[2], and Carmen C. Solorzano, MD[3]

[1]Department of Surgery, Vanderbilt University, Nashville, TN; [2]Tennessee State Department of Health, Tennessee Cancer Registry, Nashville; [3]Division of Surgical Oncology and Endocrine Surgery, Vanderbilt University Medical Center, Nashville, TN

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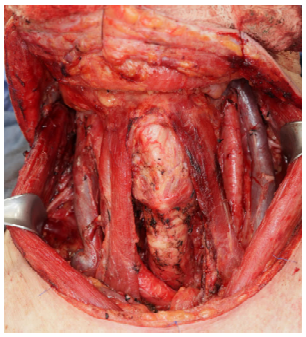
72 y.o. man with a neck full of PTC
survival < 2 yrs from diagnosis



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C. Right level 2, 3, 4, and 5:
- Ten lymph nodes positive for metastatic carcinoma (10/19). The lymph nodes are almost entirely replaced by tumor.

D. Left level 2, 3, 4, and 5:
- Six lymph nodes positive for metastatic carcinoma (6/24).

E. Thyroid gland and level 6 contents:
- Papillary thyroid carcinoma, bilateral, multifocal (see synoptic report).
Note: The largest tumor is located in the right lobe and measures 6.5 cm in greatest diameter. The second largest nodule is located in the left lobe and measures 3.8 cm in greatest diameter.
Eight lymph nodes positive for metastatic carcinoma

Biomarker Findings (Foundation Medicine):
Microsatellite Status - MS-Stable
Tumor Mutational Burden - 3 Muts/Mb

Genomic Findings:
BRAF V600E
PIK3CA H1047R
CDKN2A/B p16INK4a L78fs*41 and p14ARF H93fs*67
RB1 Q471* - subclonal
TERT promoter -124C>T

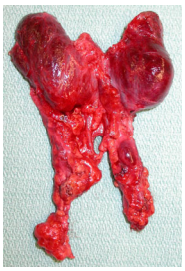
11

Prophylactic Central Compartment Neck Dissection in Papillary Thyroid Cancer and Effect on Locoregional Recurrence

David T. Hughes, MD[1], Jennifer E. Rosen, MD[2], Douglas B. Evans, MD[3], Elizabeth Grubbs, MD[4], Tracy S. Wang, MD, MPH[5], and Carmen C. Solórzano, MD[6]

[1]University of Michigan, Ann Arbor, MI; [2]MedStar Washington Hospital Center, Washington, DC; [3]Department of Surgery, Medical College of Wisconsin, Milwaukee, WI; [4]University of Texas M.D. Anderson Cancer Center, Houston, TX; [5]Medical College of Wisconsin, Milwaukee, WI; [6]Division of Surgical Oncology and Endocrine Surgery, Vanderbilt University, Nashville, TN

Conclusions. TT + pCCND in clinically node-negative papillary thyroid cancer will detect occult lymph node metastasis in approximately half of patients. This may change their postoperative management with regard to adjuvant radioiodine therapy. There is a higher risk of hypoparathyroidism with pCCND, and the effect on rates of locoregional recurrence remains uncertain.



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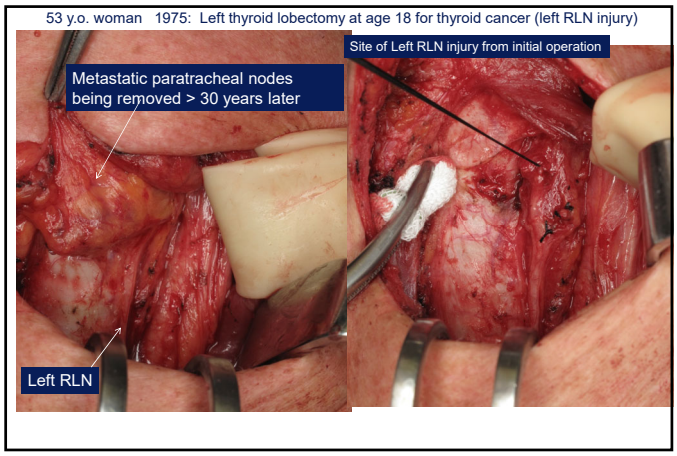
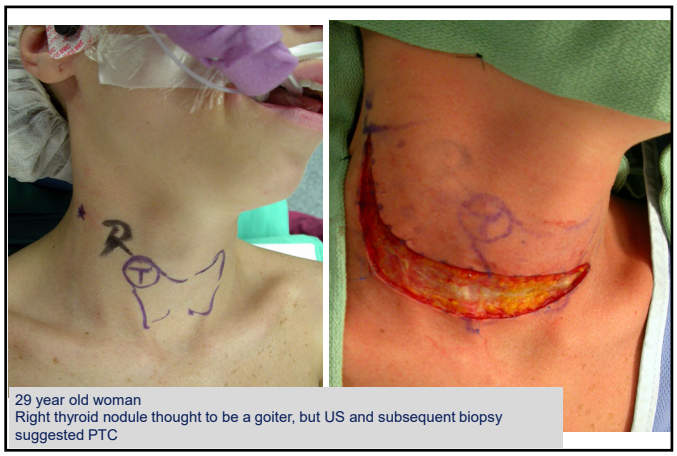
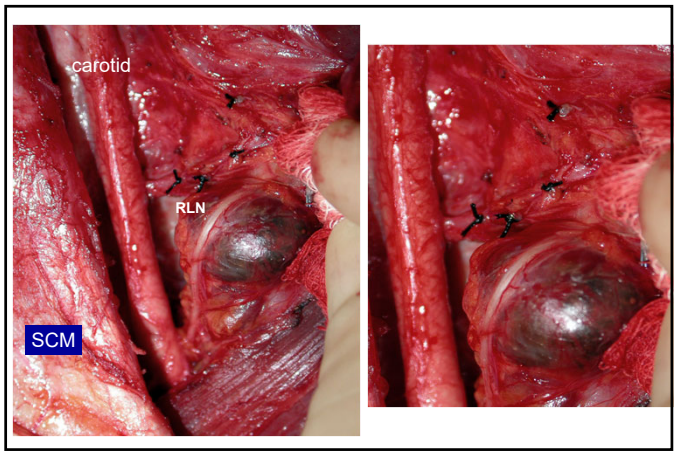

53 y.o. woman 1975: Left thyroid lobectomy at age 18 for thyroid cancer (left RLN injury)
Site of Left RLN injury from initial operation
Metastatic paratracheal nodes
being removed > 30 years later
Left RLN

13


29 year old woman
Right thyroid nodule thought to be a goiter, but US and subsequent biopsy
suggested PTC

14


carotid
RLN
SCM

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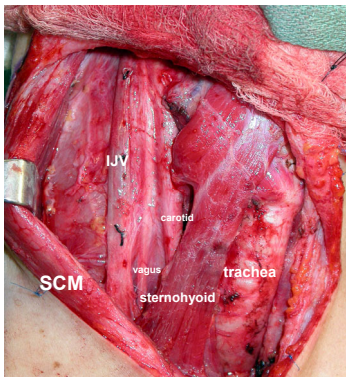

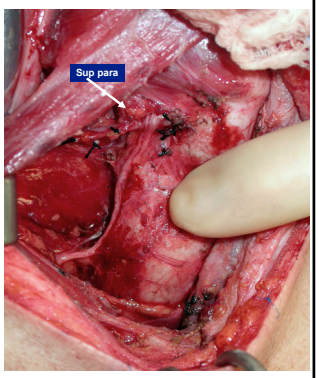

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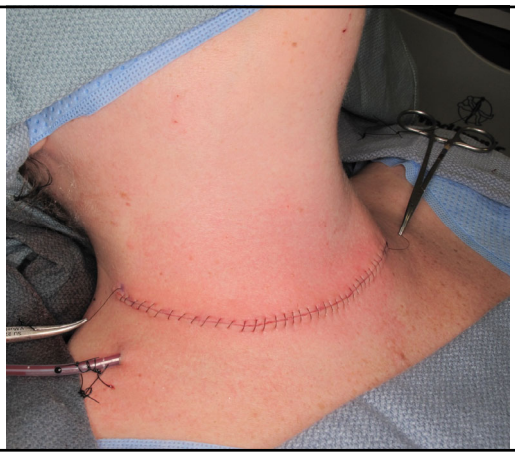

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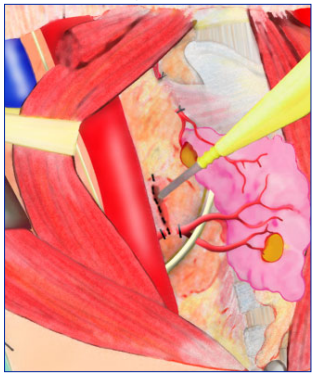
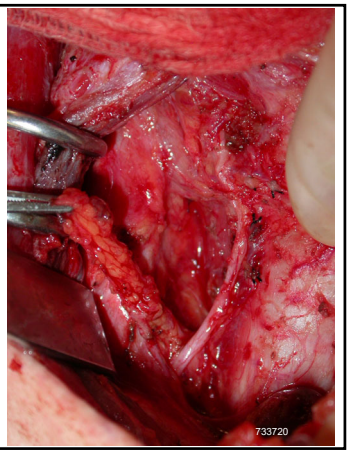
Right RLN





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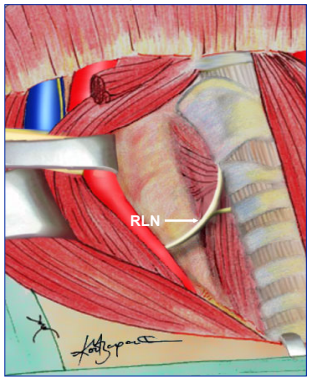
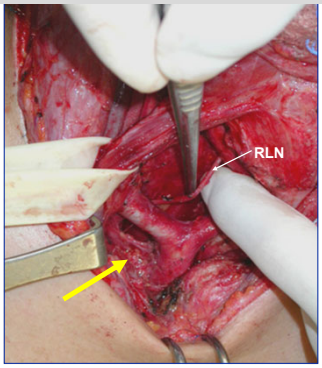
Right RLN



Watch for the node below (caudal to) the innominate artery



19

Final Diagnosis

A. Tissue at distal recurrent nerve, biopsy:
- Fibroadipose tissue involved by papillary thyroid carcinoma.
Note (A): Sections show papillary thyroid carcinoma in fibroadipose tissue. S100 highlights small nerves.

B. Confirm parathyroid, biopsy:
- parathyroid tissue.

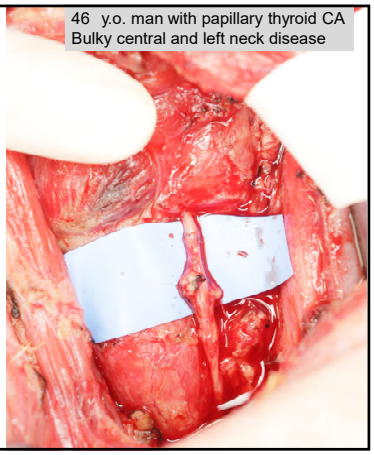
C. Lymph node, left levels 2A, 3, 4 & 5, neck dissection:
- Two out of fourteen lymph nodes, positive for metastatic papillary thyroid carcinoma (2/14).
- Largest metastatic focus is 5.2 cm.

D. Thyroid and level 6 contents, total thyroidectomy and neck dissection:
- Papillary thyroid carcinoma, classic type involving the left lobe.
- Tumor size: 2.5 cm.
- Lymphovascular invasion is identified.
- Perineural invasion is identified.
- Extrathyroidal extension is identified.
- The surgical resection margins are positive for carcinoma.
- Eight of thirteen lymph nodes, positive for metastatic carcinoma (8/13).
- Size of largest metastatic focus: 1.7 cm.
- Extranodal extension: Identified.
- Benign thymic tissue.
- AJCC (8th ed.) TNM: pT4a, pN1b.
- See synoptic report for additional information.

E. Nerve, left recurrent nerve, excision:
- Fibrous tissue around nerve involved by papillary thyroid carcinoma.

S 09061328

46 y.o. man with papillary thyroid CA
Bulky central and left neck disease



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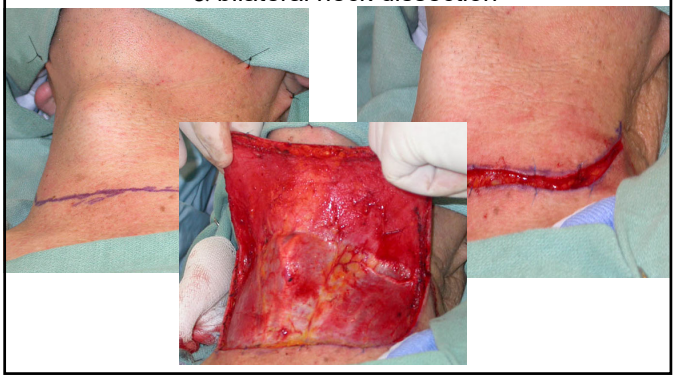
Thyroidectomy with central
& bilateral neck dissection



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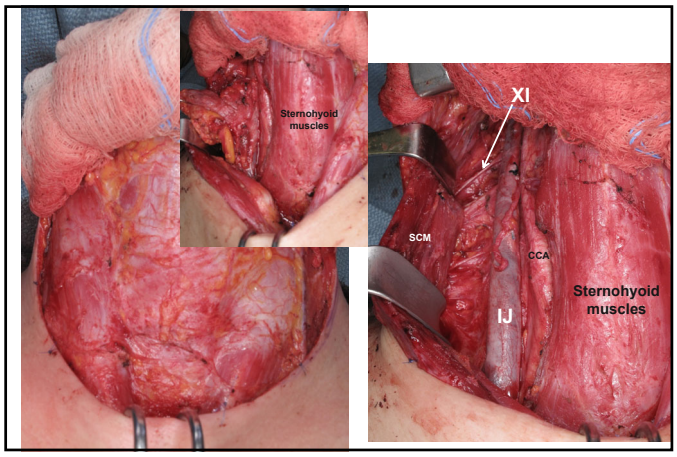
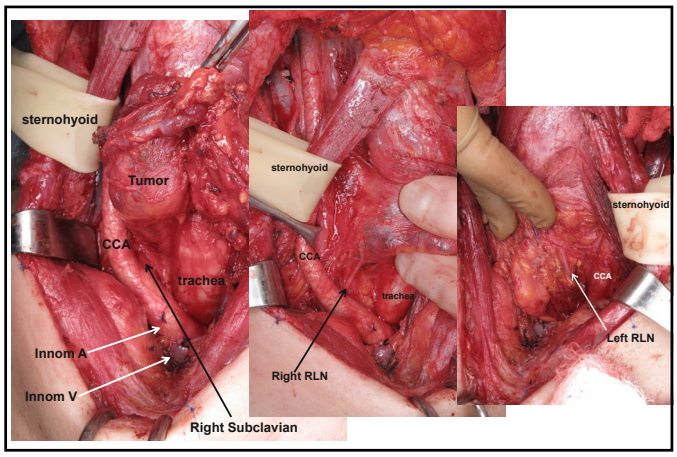
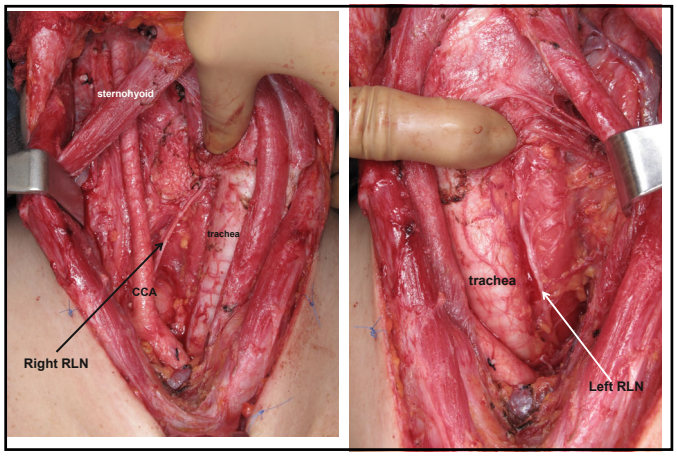

Sternohyoid muscles
XI
SCM
CCA
IJ
Sternohyoid muscles

22


sternohyoid
Tumor
CCA
trachea
Innom A
Innom V
Right Subclavian
sternohyoid
CCA
trachea
Right RLN
sternohyoid
CCA
Left RLN

23


sternohyoid
trachea
CCA
Right RLN
trachea
Left RLN

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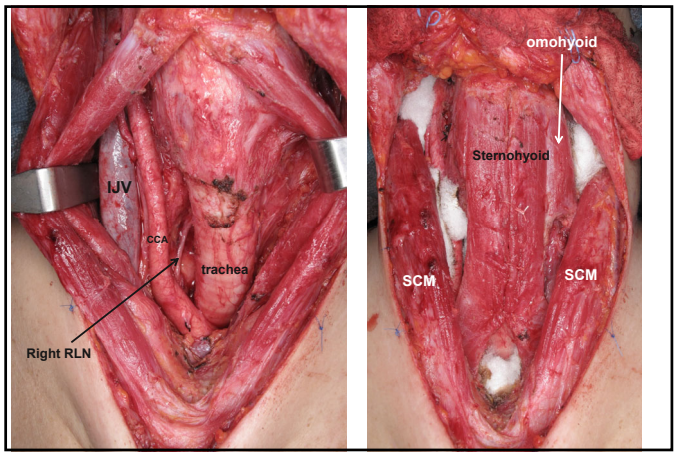
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Right RLN
omohyoid
Sternohyoid
SCM
SCM

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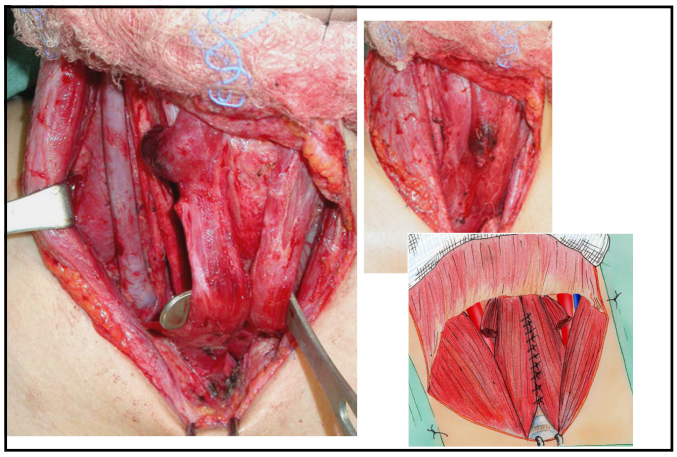

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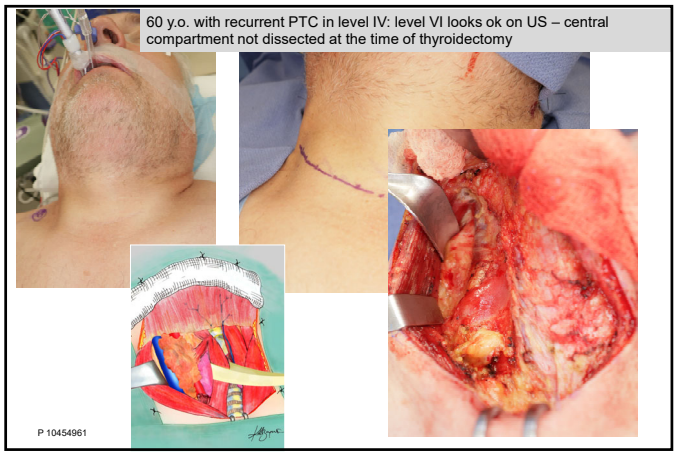
60 y.o. with recurrent PTC in level IV: level VI looks ok on US – central compartment not dissected at the time of thyroidectomy
P 10454961

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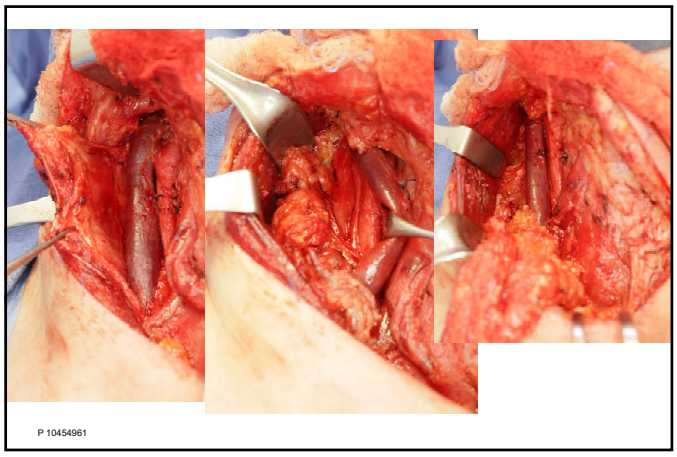

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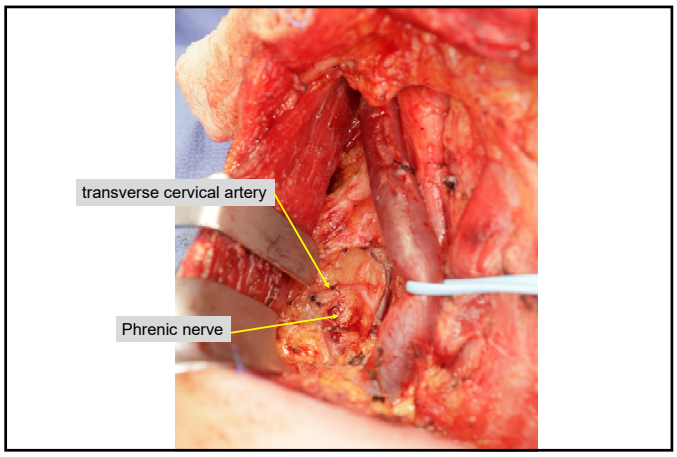

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30

MEDICAL COLLEGE OF WISCONSIN
2023 ENDOCRINE SURGERY AND
NEUROENDOCRINE TUMOR SYMPOSIUM

Management of the Voice During Cervical Surgery

Joel H. Blumin, MD, FACS
Professor, Department of Otolaryngology & Communication Sciences
Chief, Division of Laryngology & Professional Voice

1

Commercial or Financial Disclosure

I have nothing to disclose

Off-Label Medications or Devices

Many injectables and implants for the larynx are used off-label. I will discuss this in the context of the presentation and utilize generic names as appropriate

2

Overview

- Why does it matter?
- Pre operative assessments
- Post operative management

3

Laryngeal Nerves

- Vagus nerves → recurrent and superior laryngeal nerves
  - Motor, sensory, autonomic innervation
- Vagus nerve in carotid sheath
- RLN adjacent to thyroid and parathyroid headed from TE groove to behind CT joint and paraglottic space
- SLN (external branch) to CT muscle
- Part of operation should be to identify and protect laryngeal nerves

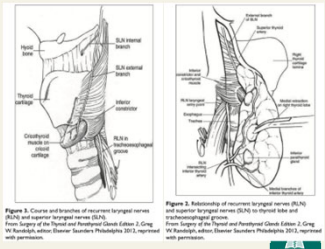


Figure 3. Course and branches of recurrent laryngeal nerves (RLN) and superior laryngeal nerves (SLN).
From: Surgery of the Thyroid and Parathyroid Glands Edition 2. Greg W. Randolph, editor. Elsevier Saunders Philadelphia 2013, reprinted with permission.

Figure 2. Relationship of recurrent laryngeal nerves (RLN) and superior laryngeal nerves (SLN) to thyroid lobe and tracheoesophageal groove.
From: Surgery of the Thyroid and Parathyroid Glands Edition 2. Greg W. Randolph, editor. Elsevier Saunders Philadelphia 2013, reprinted with permission.

4

Why does it matter?

- Unilateral injury = hoarse voice
  - Weak, breathy
  - Asthenic
  - Poor vocal endurance/easy vocal fatigue
  - Reduced vocal range
- Poor cough
- Dysphagia
  - Pharyngeal and laryngeal weakness
  - Aspiration to thin liquids
- Bilateral injury = airway or breathing problems
  - Voice usually OK or minimally altered

5

Rates of laryngeal nerve injury

- Varies depending on paper you read
- Range from low single % to about 30%
- Typically cited at 0.85%-3.5% unilateral and 0.39%-2.3% bilateral from large database/cohort papers
- Francis, et al. *Otolaryngol Head Neck Surg*, 150:548-57, 2014
  - Medicare SEER database review for well differentiated thyroid cancer
  - 8.2% unilateral
  - 1.3% bilateral
  - Decreasing numbers over decades studied
    - Not associated with use of intraoperative nerve monitoring (data dive)

6

Why does it matter?

- Voices matter
  - Our personal interface for communication with others
  - Identification of self
  - Highly variable self assessment
    - Some will identify minor alterations as major contributors to morbidity
- We have interventions to help patients

7

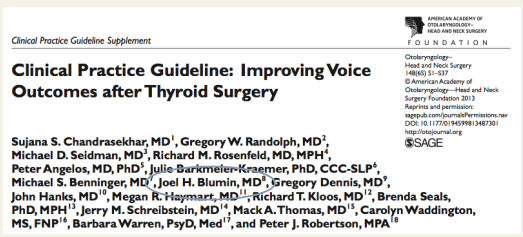
Why does it matter?

- Shaw & Pierce, *Ann Otol Rhinol Laryngol*, 118:6-12, 2009
- Closed claims review of malpractice insurers for vocal fold paralysis
  - Most common reasons
    - Thyroid/parathyroidectomy (39%)
    - Anterior cervical spine
    - Cardiothoracic
    - Carotid endarterectomy
    - Lateral neck operations
    - Laryngopharyngeal operations
- Reasons for filing a lawsuit:
  - Improper surgical performance
  - Consent issues
  - Surgery not indicated
  - *Delay or failure to recognize and/or refer for treatment*

8

Guideline

Improving Voice Outcomes after Thyroid Surgery



Clinical Practice Guideline Supplement

AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

Clinical Practice Guideline: Improving Voice Outcomes after Thyroid Surgery

Otolaryngology–Head and Neck Surgery
148(6S) S1–S37
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DOI: 10.1177/0194599813487301
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9

Background

- Thyroid operations have increased about 3x over last several decades with increasing incidence of thyroid cancer identified
- Voice can be altered in up to 80% of patients following thyroid or other neck operations
- There is a potential inconsistency regarding recognition of impact to voice by both surgeons and patients
  - Improve awareness
  - Thyroid operations performed by surgeons of different backgrounds
- (at the time of publication) No current guidelines for this topic
- Most of the recommendations are Grade C – based on observational studies

10

Highlights of Thyroid/Voice Guidelines

- Baseline voice assessment
- Preoperative laryngeal assessment of those with impaired voices
- Preoperative laryngeal assessment of some with non-impaired voices

11

What do we do to assess?

- Voice
  - Ask patient or family their own assessment of their voice
  - Conversational speech
  - Standardized passages
  - Record

- Larynx
  - Look
    - Mirror
    - Rigid Hopkins rod style scope
    - Flexible nasopharyngeal scope
  - Lighting
    - Halogen
    - Xenon/stroboscopy
  - Record

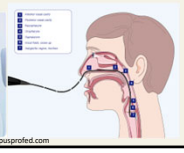
12

Physical Exam

- Laryngoscopy
  - Fiberoptic flexible versus rigid
    - Can do provocative testing with flexible
  - Videodocumentation
  - Stroboscopic or halogen/continuous lighting




Source: www.pentaxmedical.com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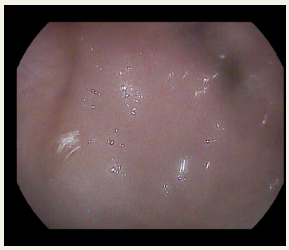
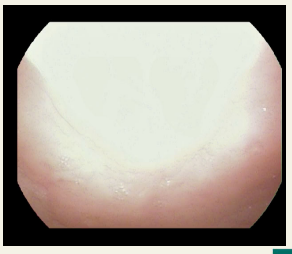

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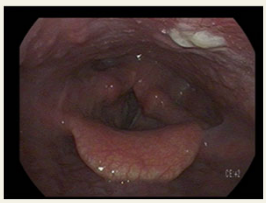
Statement 2B: Preoperative Laryngeal Assessment of the Non-Impaired Voice

- Recommendation
  - If thyroid cancer with suspected extrathyroidal extension
  - Prior neck operations
    - This would include neck dissections, carotid operations, anterior cervical spine operations, esophagectomy, prior thyroid or parathyroid operations
    - Recovery of voice or non-impaired voice does not necessarily equal no motion impairment
    - ~40% of patients with a unilateral paralysis may not be symptomatic or hoarse



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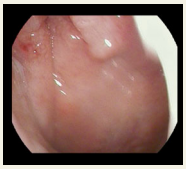
Highlights of Thyroid/Voice Guidelines

- Post operative voice assessments
- Post operative laryngeal evaluations
  - Recovery of voice or non-impaired voice does not necessarily equal no motion impairment
- Otolaryngology referral

16

Management of the impaired voice

- Timing
  - As soon as the patient wants; do not need to wait
- Assess
  - Review operative notes and anesthesia notes
  - Voice evaluation
  - Laryngeal evaluation
    - Immobility/paresis/paralysis
    - Traumatic intubation
  - Laryngeal electromyography



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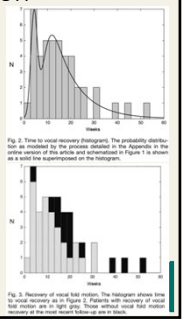
Recovery of voice and motion

- Typically, about six to nine months
  - Longer on left than right side
  - Data from clinical experience as well as from modeling
    - Mau, et al. *Laryngoscope*, 127:2585-90, 2017
    - N=727 patients
    - Model predicts 86% recover at six months and 96% at nine months
- No reliable intervention to change time course



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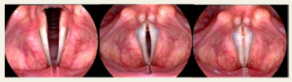
Management of the impaired voice - immobility

- Larynx forms a valve
- With immobility or partial mobility, the valve is weak
  - Voice is typically weak, breathy, or asthenic



- Interventions designed to improve closure of the larynx
  - Surgical/procedural interventions
  - Voice therapy with speech-language pathologist

19

Procedural Interventions

- Improve glottic closure
  - Augment immobile vocal fold
  - Mobilize immobile vocal fold towards midline
- Temporary (self limited) interventions
  - Injection laryngoplasty
- Permanent interventions
  - Injection laryngoplasty
  - Framework procedures
  - Reinnervation

Table 10. Rehabilitative options for unilateral vocal fold paralysis (treatment and procedures are typically performed for improving voice and/or swallowing).

Procedure	Effect	Benefit	Notes
Voice Therapy by a speech-language pathologist	Temporary or permanent improvement	Adjustment and compensation to altered laryngeal physiology	Exercises to improve the voice and/or swallowing Noninvasive treatment
Injection laryngoplasty—injection of material into the vocal fold*	Temporary (typically months)	Restores vocal fold position and bulk	Can be repeated when the injection material disappears Often can be performed in the office, but may also be performed in the operating room
Framework procedures—operations to improve vocal fold position	Permanent	Restores vocal fold position	Near immediate restoration of voice
	Some consider potentially reversible		Performed in the operating room and requires a neck incision
Reinnervation—an operation to improve vocal fold position	Permanent	Restores vocal fold position and bulk True restoration of physiologic reinnervation is not achievable	The final surgical outcome can take up to a year A vocal fold injection is typically performed at the same time to rehabilitate voice during this healing period Performed in the operating room and requires a neck incision

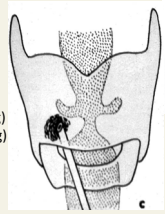
*Commonly injected agents include hyaluronic acid gels, autologous fat, human or bovine collagen, micronized human dermis, methylcellulose gel, and calcium hydroxyapatite paste. Many of these products are marketed as dermal fillers and used off-label in the larynx.

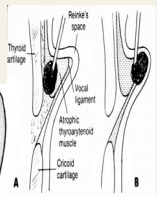
CPG-Improving Voice Thyroid. *Oto HNS* 148(6s), 2013

20

Injection Laryngoplasty

- Commonly performed in the office
  - Patient awake
  - Local/topical anesthesia
  - A few minutes
  - Immediate results
- Materials
  - Hyaluronic acid gels (medium lasting)
  - Carboxymethyl cellulose gels (short lasting)
  - Calcium hydroxylapatite paste (long lasting)
  - Autologous fat (long lasting)
  - Silk paste (new/long lasting)





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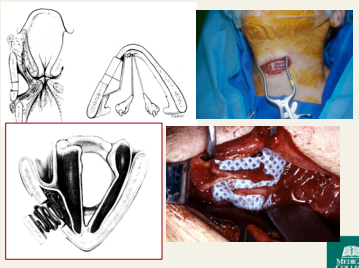
Injection Laryngoplasty

- Goal to bridge their voice during time of spontaneous recovery
- Reliable improvements in voice and cough
  - Improvements in swallowing can be variable
- Multiple publications show long term improvements of voice superior with early injection
  - Can take with grain of salt – injection laryngoplasty does not impede spontaneous recovery, but not sure if it improves it
- We commonly use hyaluronic acid gels as they last 3-6 months which bridge patients during the time of spontaneous recovery
  - Can repeat these office injections multiple times if desired

22

Long term/permanent interventions

- Injection laryngoplasty
  - Long term agents
- Framework procedures
  - Thyroplasty
  - Arytenoid adduction
- Reinnervation of RLN
  - Ansa-RLN
  - Selective adductor/abductor reinnervation



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Outcomes after interventions

- Generally favorable
  - 90-95% effective with improvement of voice outcomes
- No good studies to determine 'best' option for patients. Choices for procedural management tend to be provider and patient specific.

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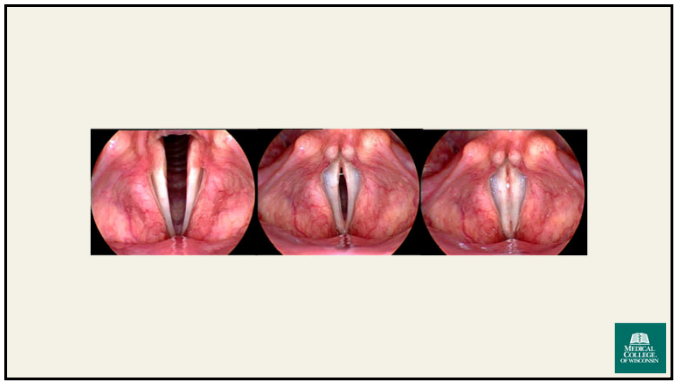

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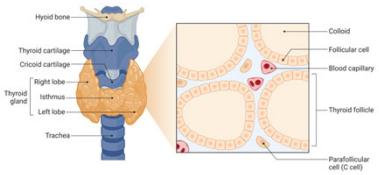
PRECISION MEDICINE IN DIFFERENTIATED THYROID CA



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1

Disclosures

- Research funding: Natera
- Advisory board member: Taiho Oncology
- I have no conflict of interest related to this presentation

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2

Agenda

- Introduction
- Molecular targets in differentiated thyroid cancers (DTC)
- Pivotal trials of targeted therapies in DTC
- Why target multiple pathways at the same time?
- Our precision medicine workflow at MCW
- Studies in tumor agnostic setting

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Definition of radioactive iodine (RAI) refractory DTC

- No iodine uptake at known sites of disease
- Confirmed disease progression within 6-12 months
- After RAI treatment with confirmed iodine uptake
- Total cumulative dose of RAI of >600 mCi
- FDG avid disease

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4

Chemotherapy in thyroid cancers-historical perspective

Study	Subtypes	ORR	OS
Adriamycin Gottlieb and Hill, NEJM 290(4); 193-7	DTC(15); MTC(5); ATC(9)	37%	4-11m
Adria vs Adria and Cisplatin; Shimaoka et al, 1985 Cancer 56(9); 2155-60	DTC(35); MTC(10); ATC(39)	17 vs. 26%	5 vs. 7m
Adria + Cisplatin; Williams et al, 1986 Can Treat Rep 70(3); 405	DTC(7); MTC(6); ATC(7)	9.1%	11.8m
Bleo, Adria, Cisplatin; De Besi et al., 1991 J Endo Inest 14;475-80	DTC(8); MTC(9); ATC(5)	42%	11m

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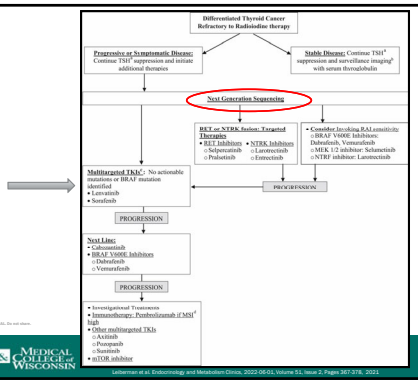
5



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Leiberman et al. Endocrinology and Metabolism Clinics, 2022-06-01, Volume 51, Issue 2, Pages 367-378, 2021

6

Not enough targetable mutations

- Next generation sequencing (NGS) can analyze a broad panel of genes to detect the four main classes of genomic alterations known to drive cancer growth:

1. Base substitutions,
2. Insertions and deletions,
3. Copy number alterations (CNAs)
4. Rearrangements or fusions

- The field of precision oncology has come a long way since the human genome project, but we still don't have enough targeted therapies.

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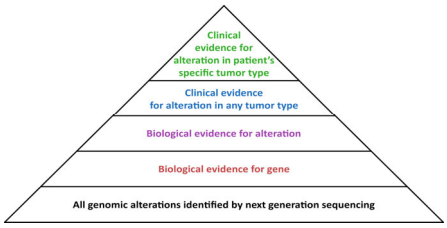
Actionable alterations associated with clinical response



Ref : Hannah Wise et al Precision Oncology: Three Small Steps Forward Cancer Cell 2019 35825-826001: (10.1016/j.ccell.2019.05.009)

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Common molecular alterations in thyroid cancers

1. The Cancer Genome Atlas (TCGA) project provided a detailed description of the molecular alterations in 496 cases of papillary thyroid carcinoma with significant impact in the understanding of pathogenesis,
2. TCGA results showed heterogeneity in gene expression among tumors with BRAF V600E mutation.
3. Other common driver mutation is RAS, NRAS &HRAS activate MAPK and PI3K/AKT pathway.
4. Mutation in the promoter region of gene encoding telomerase reverse transcriptase(TERT) is also associated with worse prognosis. PTC harboring both BRAF and TERT mutation have significantly worse prognosis.
5. Vascular endothelial growth factor (VEGF) stimulates endothelial cell proliferation and is key to tumor angiogenesis and growth

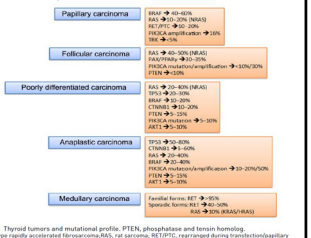

Figure 1. Thyroid tumors and mutational profile. PTEN, phosphatase and tensin homolog. *BRAF*, b-type rapidly accelerated fibrosarcoma;RAS, rat sarcoma; RET/PTC, rearranged during transfection/papillary thyroid carcinoma; PI3KCA, phosphatidylinositol 3-kinase oncogene; TRK, receptor thyrosine kinase; PAX8/PPAR, paired box 8/peroxisome proliferator-activated receptor gamma; PTEN, phosphatase and tensin homolog; TP53, tumor protein p53; CTNNB1, catenin (cadherin-associated protein beta 1); AKT1, v-akt murine thymoma viral oncogene homolog 1;RET, rearranged during transfection.

T. Alonso-Gordoa; Ther Adv Med Oncol 2018, Vol. 7(1):23–38

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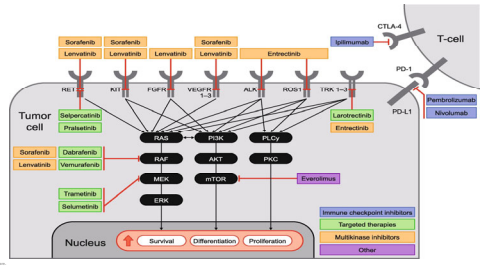
Targeted therapies in thyroid cancer



Froedtert & Medical College of Wisconsin — Cancer Treatment Reviews 2022 106D0I: (10.1016/j.ctrv.2022.102380) — Genomic Sciences Precision Medicine Center

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Decision Trial 2014	Lancet July 2014	Phase III
Sorafenib in RAI-refractory DTC	N = 417 (207 in Sorafenib vs 210 in placebo arm)	
Primary end point Secondary end point	Progression free survival(PFS) Overall survival (OS), test safety and tolerability	
Eligibility Criteria	RAI-refractory DTC progressing within the past 14 months according ; at least one measurable lesion by CT/MRI according to RECIST; ECOG 0–1; adequate bone marrow, liver, and renal function; and serum t(TSH)<0·5mIU/L.	
Methods	Multicenter, randomized (1:1), double-blind, placebo-controlled, phase 3 study, crossover allowed	
Results	PFS was 10.8 mths in Sorafenib vs 5.8mths in placebo arm. No overall survival benefit	
Response rates	12 % partial response no complete response	
Adverse events	Most common adverse events in the sorafenib arm were hand–foot skin reaction (76·3%), diarrhea (68·6%), alopecia (67·1%), and rash/desquamation (50·2%).	

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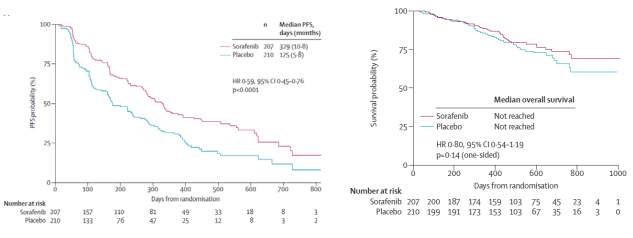
DECISION TRIAL



Froedtert & Medical College of Wisconsin — Brose MS et al. Lancet 2014; 384(9940):319-28 — Genomic Sciences Precision Medicine Center

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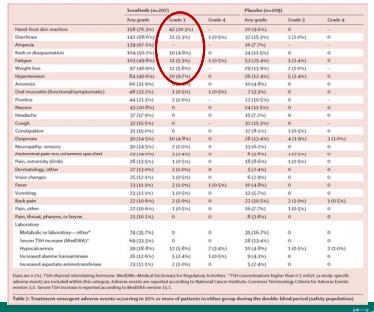
DECISION TRIAL: Adverse events



Brose MS et al. Lancet 2014; 384(9940):319-28

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Select Trial 2015	NEJM Feb 2015	Phase III
Lenvatinib in RAI-refractory DTC	N = 392 (261 in Lenvatinib vs 131 in placebo arm)	
Primary end point Secondary end point	Progression free survival(PFS) Overall survival (OS)	
Eligibility Criteria	RAI-refractory DTC progressing within the past 12 months according ; at least one measurable lesion by CT/MRI according to RECIST; ECOG 0–1; adequate bone marrow, liver, and renal function; and serum t(TSH)<05mIU/L. Subjects who received 0/1 VEGF therapy	
Methods	Multicenter, randomized (2:1), double-blind, placebo-controlled, phase 3 study, crossover allowed	
Results	PFS was 18.3 mths in Sorafenib vs 3.6mths in placebo arm. No overall survival benefit	
Response rates	63.2 % partial response, 1.5 %complete response	
Adverse events	Most common adverse events in Lenvatinib arm were hypertension (in 67.8% pt), diarrhea (59.4%), fatigue or asthenia (59.0%), decreased appetite (50.2%), decreased weight (46.4%), and nausea (41.0%)	

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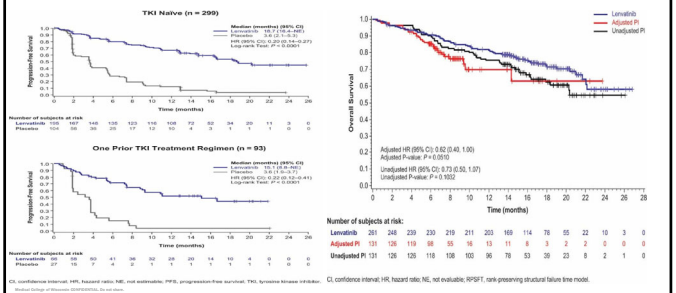
SELECT TRIAL



Schlumberger M, et al. N Engl J Med. 2015;372(suppl 1):621-630.

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Adverse effects

- The incidence of treatment-related adverse effects (of all grades) as assessed by the investigator was 97.3% in the lenvatinib group and 59.5% in the placebo group

Adverse effects	Lenvatinib	Placebo
Grade 3 or higher HTN	41.8%	2.3%
Proteinuria	31.0%	1.5%
Hypocalcemia	6.9 %	0%
Pulmonary embolism	2.7 %	1.5 %
Grade 3 Diarrhea	8.0 %	0 %
118 Deaths	71 (27.2%)	47 (35.9%)
The majority of these deaths were due to disease progression (53 [74.6%] and 35 [74.5%] in the Lenvatinib and placebo groups. 6 death in Lenvatinib group were thought to be treatment related.		

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Which is better?
Sorafenib or Lenvatinib?

Agent	Trial name	Design	Enrolled (*n*)	OS, months (95% CI)	PFS, months (95% CI)	RECIST best response (%) CR	PR	SD	PD	Tumor shrinkage by waterfall plot methods (%)
SOR	DECISION [81]	RCT vs. PLC	417; SOR: 207; PLC: 210	NE	SOR: 10.8 (9.1-12.9); PLC: 5.8 (5.3-7.8)	0	SOR: 12; PLC: 0.5	SOR: 42; PLC: 33	NR	SOR: 87.9; PLC: 26.7
LEN	SELECT [82]	RCT vs. PLC	392; LEN: 261; PLC: 131	NE	LEN: 18.7 (15.1-NE); PLC: 3.6 (2.2-3.7)	LEN: 1.5; PLC: 0	LEN: 63.2; PLC: 1.5	LEN: 15; PLC: 30	LEN: 7; PLC: 40	LEN: 98.6; PLC: 36.5

Abbreviations: CI, confidence interval; CR, complete response; LEN, lenvatinib; NE, not estimable; NR, not reported; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PLC, placebo; PR, partial response; RCT, randomized controlled trial; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SOR, sorafenib.

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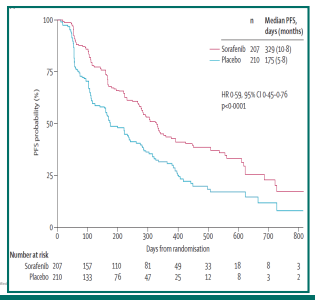
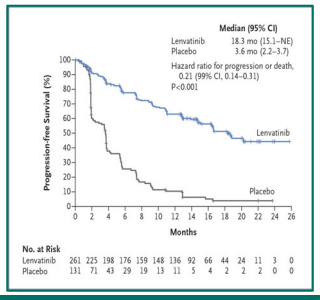
Sorafenib vs Lenvatinib PFS





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Limitations

I. Median Overall Survival was not reached
II. Cross over from Placebo to sorafenib/lenvatinib could have confounded the survival analysis and blinding (?adjusted analysis)
III. More fatal adverse event in treatment arm of study
IV. Lack of information on the patient's quality of life in Select trial and worse QOL in sorafenib arm of Decision trial.

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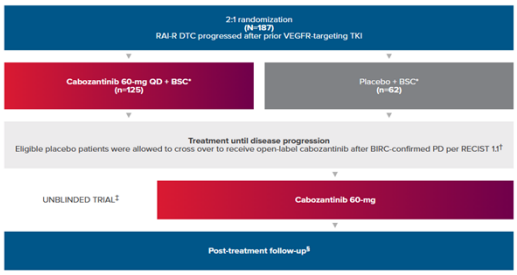
COSMIC 311



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Baseline characteristics

	Total Population	
Median age, years (range)	65 (31-85)	
ECOG 0	46%	
ECOG 1	54%	
	CABOMETYX	Placebo
One previous VEGFR TKI	**73% (91/125)**	77% (48/62)
Two previous VEGFR TKIs	**27% (34/125)**	23% (14/62)

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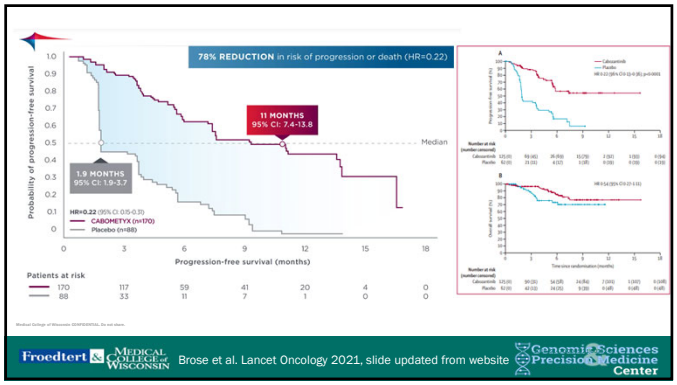
78% REDUCTION in risk of progression or death (HR=0.22)
11 MONTHS
95% CI: 7.4–13.8
Median
1.9 MONTHS
95% CI: 1.9–3.7
HR=0.22 (95% CI: 0.15–0.31)
CABOMETYX (n=170)
Placebo (n=88)
Probability of progression-free survival
Progression-free survival (months)
Patients at risk
170 117 59 41 20 4 0
88 33 11 7 1 0 0
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Brose et al. Lancet Oncology 2021, slide updated from website
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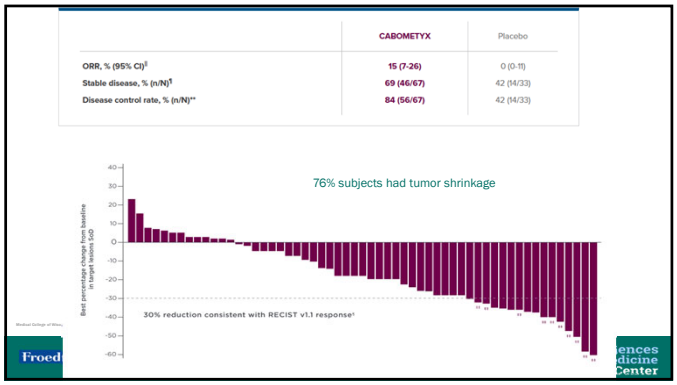
CABOMETYX
Placebo
ORR, % (95% CI)‖
15 (7-26)
0 (0-11)
Stable disease, % (n/N)¶
69 (46/67)
42 (14/33)
Disease control rate, % (n/N)**
84 (56/67)
42 (14/33)
76% subjects had tumor shrinkage
Best percentage change from baseline in target lesions SoD
30% reduction consistent with RECIST v1.1 response¶
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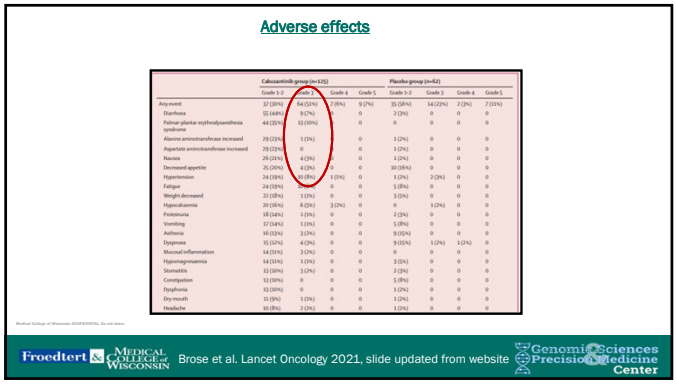
Adverse effects
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Brose et al. Lancet Oncology 2021, slide updated from website
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Tissue agnostic approval of targeted therapies

- First tissue-agnostic treatment approval was granted by the FDA to **pembrolizumab** in patients with high microsatellite instability (MSI-H) tumors in 2017.
- Followed by larotrectinib and entrectinib for the treatment of cancers harboring NTRK fusions in 2018 and 2019

FDA grants accelerated approval to dabrafenib in combination with trametinib for unresectable or metastatic solid tumors with BRAF V600E mutation

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Oncogenic driver	Targeted treatment	Clinical trial reference	Number of patients with thyroid cancer included in efficacy analysis	Efficacy in patients with thyroid cancer			
				Response rate*	Median duration of response (months)	Median OS (months)	Median PFS (months)
NTRK gene fusion	Larotrectinib	Waguespack S et al. ATA 2021	PTC: 20 FTC: 2 ATC: 7	ORR: 71% (2 CR, 18 PR, 4 SD)	24-month DoR: 81%	24-month OS: 76%	24-month PFS: 69%
	Entrectinib	Bazhenova L et al. ESMO 2021 Marcus et al. CCR 2021	TC: 13 (subtype not specified)	ORR: 53.8%	13.2	NR	NR
RET gene fusion or mutation	Pralsetinib	Gainor et al. Lancet 2021	PTC: 9	ORR: 89% (89% PR)	NE	NR	NR
	Selpercatinib	Wirth L.J. NEJM 2020	*RET* fusion-positive thyroid cancer, previously treated: 19(PTC: 13; PDTC: 3; ATC: 2; Hürthle cell: 1) Treatment naïve: 8 (subtype not specified)	*RET* mutation, previously treated ORR: 78.9% (2 CR, 13 PR) Treatment naïve ORR: 100% (1 CR, 7 PR)	*RET* mutation, previously treated: 18.4 Treatment naïve: NR	*RET* mutation, previously treated: 27.4 Treatment naïve ORR: NR	NR

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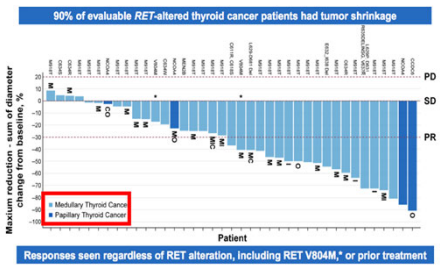
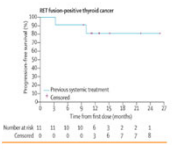
Pralsetinib in Arrow trial

90% of evaluable *RET*-altered thyroid cancer patients had tumor shrinkage





Responses seen regardless of RET alteration, including RET V804M,* or prior treatment

Froedtert & Medical College of Wisconsin — Subbiah & Hu The Lancet Diabetes & Endocrinology 2021 — Genomic Sciences & Precision Medicine Center

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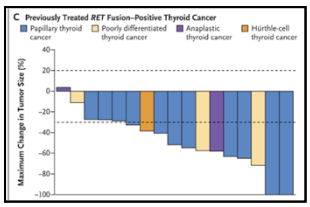
Selpercatinib



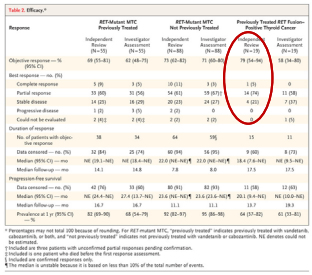


Table 2. Efficacy.*

Response	RET-Mutant MTC Previously Treated		RET-Mutant MTC Not Previously Treated		Previously Treated RET Fusion–Positive Thyroid Cancer	
	Independent Review (N=55)	Investigator Assessment (N=55)	Independent Review (N=80)	Investigator Assessment (N=80)	Independent Review (N=79)	Investigator Assessment (N=79)
Objective response — % (95% CI)	69 (55–81)	62 (48–75)	73 (62–82)	71 (60–81)	79 (54–94)	58 (34–80)
Best response — no. (%)						
Complete response	5 (9)	3 (5)	10 (13)	3 (3)	1 (1)	0
Partial response	33 (60)	31 (56)	54 (67)	59 (67)	14 (74)	11 (58)
Stable disease	14 (25)	16 (29)	20 (23)	24 (27)	4 (21)	7 (37)
Progressive disease	1 (2)	3 (5)	2 (2)	0	0	0
Could not be evaluated	2 (4‡)	2 (4‡)	2 (2)	2 (2)	0	1 (5)
Duration of response						
No. of patients with objective response	38	34	64	59§	15	11
Data censored — no. (%)	32 (84)	25 (74)	60 (94)	56 (95)	9 (60)	8 (73)
Median (95% CI) — mo	NE (19.1–NE)	NE (18.4–NE)	22.0 (NE–NE)¶	22.0 (NE–NE)¶	18.4 (7.6–NE)	NE (8.5–NE)
Median follow-up — mo	14.1	14.8	7.8	8.0	17.5	17.5
Progression-free survival						
Data censored — no. (%)	42 (76)	33 (60)	80 (91)	82 (93)	11 (58)	12 (63)
Median (95% CI) — mo	NE (24.4–NE)	27.4 (11.7–NE)	23.6 (NE–NE)¶	23.6 (23.6–NE)¶	20.1 (9.4–NE)	NE (10.0–NE)
Median follow-up — mo	16.7	16.7	11.1	11.1	13.7	19.3
Prevalence at 1 yr (95% CI) — %	82 (69–90)	68 (54–79)	92 (82–97)	95 (86–98)	64 (37–82)	61 (33–81)

* Percentages may not total 100 because of rounding. For *RET*-mutant MTC, "previously treated" indicates previously treated with vandetanib, cabozantinib, or both, and "not previously treated" indicates not previously treated with vandetanib or cabozantinib. NE denotes could not be estimated.
† Included are three patients with unconfirmed partial responses pending confirmation.
‡ Included is one patient who died before the first response assessment.
§ Included are confirmed responses only.
¶ The median is unstable because it is based on less than 10% of the total number of events.

Wirth et al. NEJM 2020

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Oncogenic driver	Targeted treatment	Clinical trial reference Author/Year	Number of patients with thyroid cancer included in efficacy analysis	Efficacy in patients with thyroid cancer			
				Response rate*	Median duration of response (months)	Median OS (months)	Median PFS (months)
BRAF V600E mutation	Dabrafenib	Falchook G.S Thyroid. 2015	DTC: 14	ORR: 29%(4 PR)	NR	NR	11.3
	Dabrafenib	Shah M JCO. 2017	PTC: 26 (22 evaluable)	ORR: 50%	15.6	NR	11.4
	Dabrafenib and trametinib	Shah M J CO. 2017	PTC: 27 (24 evaluable)	ORR: 54%	13.3	NR	15.1
	Vemurafenib	Brose M.S Lancet 2016	PTC: 51 Treatment naive: 26 Previous VEGFR: 25	Treatment naive ORR: 39% (10 PR)Previous VEGFR ORR: 27% (6 PR)	Treatment naive: 16.5 Previous VEGFR: 7.4	Treatment naive: NR Previous VEGFR: 14.4	Treatment naive: 18.2 Previous VEGFR: 8.9

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STUDY NUMBER	TREATMENTS	THYROID CANCER TYPE	PHASE	ESTIMATED ENROLMENT (N)	STATUS	ESTIMATED STUDY COMPLETION DATE
NCT03181100	Atezolizumab with chemotherapy	ATC/PDTC	II	50	Recruiting	July 2023
NCT03914300	Cabozantinib, nivolumab, and ipilimumab	Advanced DTC	II	24	Recruiting	July 2023
NCT04061980	Encorafenib and binimetinib and/or nivolumab	*BRAF V600E*-positive DTC	II	40	Recruiting	August 2024
NCT04675710	Pembrolizumab, dabrafenib, and trametinib	ATC, PDTC	II	30	Recruiting	June 2024
NCT04731740	Pembrolizumab and lenvatinib or chemotherapy	PDTC, ATC	II	36	Suspended	December 2023
NCT03246958	Nivolumab and ipilimumab	DTC, MTC, ATC	II	53	Active, not recruiting	March 2025
NCT04560127	Camrelizumab and apatinib	DTC	II	10	Recruiting	December 2022
NCT04521348	Camrelizumab and famitinib	MTC, ATC, DTC	II	115	Recruiting	June 2023

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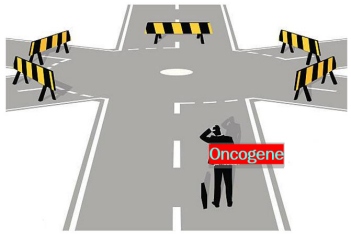
Why target multiple pathways at the same time?



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Our Precision Oncology Team

Razelle Kurzrock MD
Professor of Medicine,
Associate Director, Clinical Research
MCW Cancer Center and
Linda T. and John A. Mellowes Center for Genomic Sciences and Precision Medicine
Founding Director, Michels Rare Cancers Research Laboratories
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Tracy Kersten APNP
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Matt Lasowski MS
CCRP
Program Manager
Precision Medicine Program

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Workflow of Precision Clinic and Molecular Tumor Board

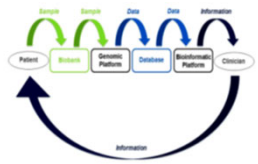
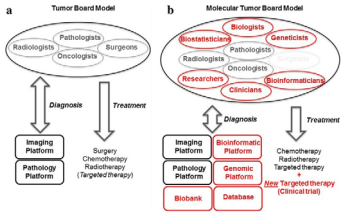


Fig. 1 Model of the data medicine process. Biological sample flows and biobanks are shown in green. Data flows and databases are shown in light blue. Information flows are shown in dark blue



Ref: Molecular Tumor Boards: Ethical Issues in the New Era of Data Medicine Henri-Corto Stoekle et al Sci Eng Ethics (2018) 24:307–32

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Real world prospective clinical trial of targeted therapies

(I PREDICT)Investigation of Profile-Related Evidence Determining Individualized Cancer Therapy

Activation Date: February 13, 2015
Total Consented: N = 506
Total Treated: N = 267 (53%)
Treatment Decisions Guided by: CGP and MTB discussion

Study Novelty
• Customized combinations
• Newly diagnosed patients with lethal malignancies
PI: Razelle Kurzrock, MD
Director, Center for Personalized Cancer Therapy

Ref: I PREDICT Sicklick et al, Nature Medicine 2019

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(I PREDICT)Investigation of Profile-Related Evidence Determining Individualized Cancer Therapy

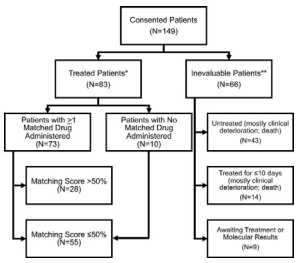

Table 1 | Patient demographics, molecular pathology, and treatment history

Consented patients (N)	149
Treated patients (N (% of consented patients))	83 (55.7)
Patients with ≥1 matched treatment (N (% of consented patients))	73 (49.0)
Patients with no matched treatments administered (N (% of consented patients))	10 (6.7)
Age[a] (median, 95% CI, range)	62 (59–65, 21–86)
Sex[a] (N (%))	
Women	55 (66.3)
Men	28 (33.7)
Ethnicity[a] (N (%))	
White	67 (80.7)
Asian	4 (4.8)
African-American	1 (1.2)
Other or unknown	11 (13.3)
Tumor type[a] (N (%))	
Gastrointestinal and hepatopancreatobiliary	35 (42.2)
Gynecologic	14 (16.9)
Breast	12 (14.5)
Central nervous system	6 (7.2)
Genitourinary	3 (3.6)
Head and neck	3 (3.6)
Lung	3 (3.6)
Other[b]	7 (8.4)
Number of total genomic alterations[c] (median, range; VUS-excluded)	5 (1–19)
Number of administered drugs[c] (median, range)	2 (1–5)
Median number of prior therapies in the metastatic setting[c] (median, IQR)	2 (1–3)

Matching score, defined as the number of alterations targeted with an administered drug divided by the total number of actionable alterations detected in the patient's tumor

Ref: I PREDICT Sicklick et al, Nature Medicine 2019
https://doi.org/10.1038/s41591-019-0407-5

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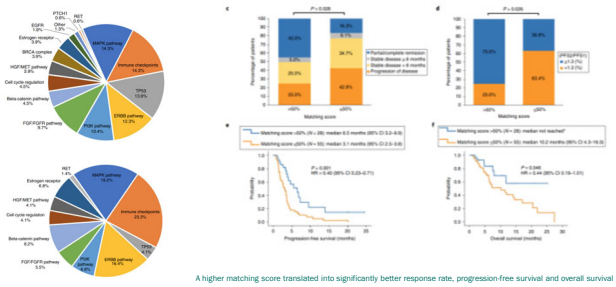
35

(I PREDICT)Investigation of Profile-Related Evidence Determining Individualized Cancer Therapy



A higher matching score translated into significantly better response rate, progression-free survival and overall survival

Ref: I PREDICT Sicklick et al, Nature Medicine 2019 https://doi.org/10.1038/s41591-019-0407-5

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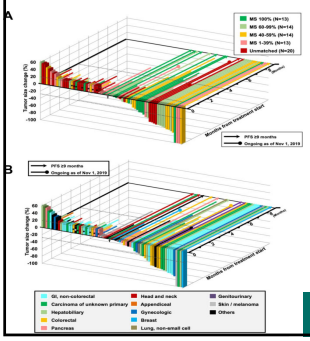
36

(I PREDICT)Investigation of Profile-Related Evidence Determining Individualized Cancer Therapy (treatment naïve population)



- 76 of 145 patients (52%) were treated
- Most commonly for non-colorectal gastrointestinal cancers, carcinomas of unknown primary, and hepatobiliary malignancies
- 53% women; median age, 63 years.
- median number of deleterious genomic alterations per patient was 5.
- 44 treated patients received ≥ 1 molecularly matched therapy.

Matching score, defined as the number of alterations targeted with an administered drug divided by the total number of actionable alterations detected in the patient's tumor

Ref: I PREDICT Sicklick et al, Genome Medicine 2019
https://doi.org/10.1186/s13073-021-00969-w

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37

QUESTIONS FROM THE GROUP ?

My email: ashreenivas@mcw.edu

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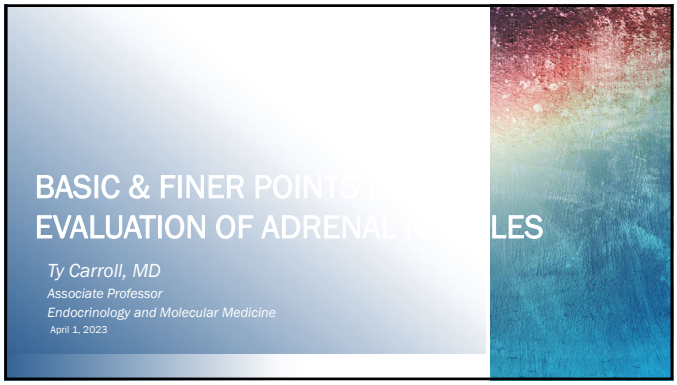


1

DISCLOSURES

- I am a consultant and investigator for Corcept Therapeutics and investigator for Recordati with regards to Cushing's syndrome.

2

LEARNING OBJECTIVES

- Review the importance of (& how to) evaluate AN
  - Biochemical testing
  - Imaging
- Discuss the caveats and pitfalls in AN evaluation
  - Biochemical testing
  - Imaging
  - Follow up of nodules

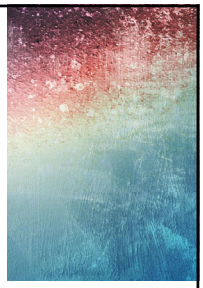
3

WHERE DO WE START?

- Nomenclature
  - Nodules
  - Masses
  - Incidentalomas
  - Tumors
- Definition
  - 1 cm of greater discrete lesion in the adrenal gland

Young, N Engl J Med 2007;356:601-10

4



WHY SHOULD WE CARE?

5

ADRENAL NODULES ARE COMMON

- Prevalence: 1-8% of the population
  - Increased frequency with aging
- Equally prevalent in males:females

Kokko, et al., *Lancet.* 1967;1(7488):468-470.
Hedeland, et al., *Acta Med Scand.* 1968;**184**(3):211-214.
Prinz et al., JAMA. 1982;248(6):701-704.
Song, et al., AJR Am J Roentgenol. 2008;191(5):1163-1169.

6

ADRENAL NODULES ARE IMPORTANT

- 2% are adrenocortical cancer
- 10-35% are functional hormonal hypersecretion

Pheochromocytoma: 3%-5%	Aldosterone-secreting: 1%-2%	Cortisol-secreting: 3-30%

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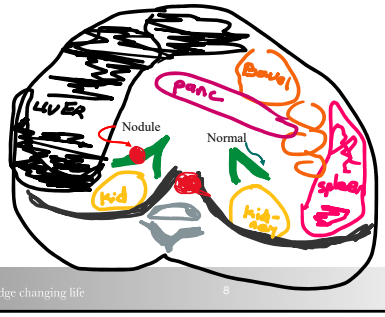
Prinz et al., JAMA. 1982;248(6):701-704
Zeiger, M.A. et al. 2011 JCEM. 96:2004–2015
Bovio S, et al. 2006 J Endocrinol Invest 29:298–302
Song, et al., AJR Am J Roentgenol. 2008; 190(5):1163-1168
Herrera MF, et al. 1991 Surgery 110:1014–1021

7

INSERT GREAT ADRENAL NODULE IMAGE



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Carroll original patent pending

8

WHO TO TEST FOR HORMONE EXCESS?

Everyone with an adrenal nodule!!

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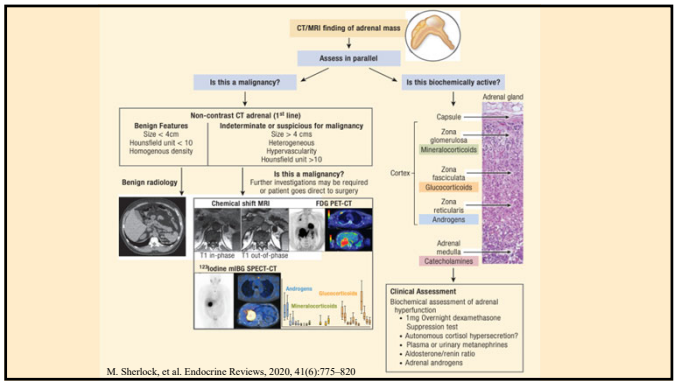
9

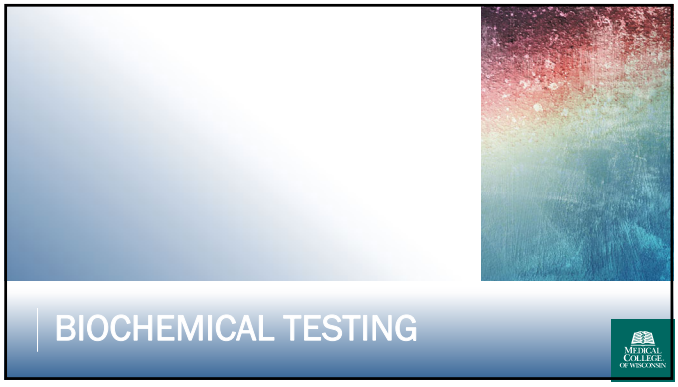
WHAT HORMONE EXCESS TO TEST FOR?

- Pheochromocytoma
- Primary aldosteronism
- Cortisol excess
- Androgen excess
  - Only if symptoms to suggest

10



11



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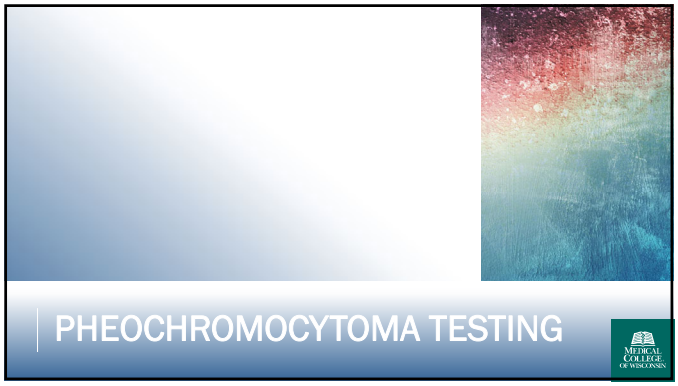


13

WHO NEEDS TESTING FOR PHEO?

- In all patients without a clear adenoma on imaging
  - The likelihood of a pheo is low in patients with a clear adenoma
    - 0.5% of pheochromocytoma have density <10 HU
  - Patients with clear evidence of a clear adenoma, don't need testing for pheo?

Sane T, et al JCEM 2012 97 2077-2083.
Schalin-Jantti C, et al. *Endo and Metab* 2015 30 481-487.
Buitenwerf, et al., *Eur J Endocrinol.* 2018;178(5):431-437.

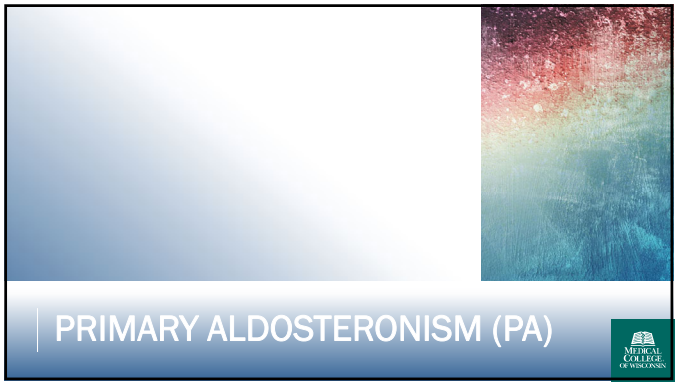
14

PHEOCHROMOCYTOMA TESTING

- Plasma metanephrines or 24 hr urine metanephrines
  - 90-95% sensitivity
  - 85-90% specificity
    - Lower in older individuals

Lenders JW et al. *JAMA.* Mar 20 2002;287:1427-34. Darr et al., *Endocrine.* 2017;56(495-503.
Eisenhofer et al., *Ann Clin Biochem.* 2013;50:62-69. Eisenhofer et al., *Clin Chem.* 2018;64:1646-1656.

15



16

WHO NEEDS TESTING FOR PA?

- Anyone with an adrenal nodule with hypertension or hypokalemia

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PRIMARY ALDOSTERONISM TESTING

- Is the renin activity <1?
  - No, then it's not PA
  - Yes→ what is the aldosterone?
- Aldosterone >10?
  - Yes, that is a positive screening test
- Aldo:renin activity
  - Ratio >20-30 and Aldo >10 (positive screen)

18

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WHO NEEDS TESTING FOR CORTISOL EXCESS?

- Anyone with an adrenal nodule.

20

SCREENING OF CORTISOL EXCESS

- 1 mg overnight dexamethasone suppression test (DST)
  - Normal post-dex cortisol is <1.8 µg/dL
- Other testing that can be helpful is AM ACTH and DHEA-s

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INITIAL IMAGING OF ADRENAL NODULES

Method	Criteria
Noncontrast CT	**≤10 HU**
MRI – chemical shift[b]	Loss of signal intensity on out-phase imaging consistent with lipid-rich adenoma
CT with delayed contrast media washout[b,c]	Absolute washout >60% Relative washout >40%
18F-FDG-PET[b]	Absence of FDG uptake or uptake less than the liver[d]

Fassnacht M, et al. EJE (2016) 175, G1–G34

23

24

25

PHEOCHROMOCYTOMA SCREENING FOR PATIENTS WITH ESRD

- Norepinephrine 3x ULN and dopamine 2x ULN
- Epinephrine references do not change
- Metanephrines probably not helpful

Stumvoll M, et al., Am J Nephrol 1995;15:147
Morioka M, et al., Int J Urol 200;9:700
Marini M, et al., Ann Endocrinol 1994;54:337

26

CORTISOL EXCESS SCREENING FOR PATIENTS WITH ESRD

- Ask someone else
  - There are lots of experts here

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MEDICATIONS INTERACTIONS WHILE SCREENING FOR PRIMARY ALDOSTERONISM

- All medications ok except spironolactone or eplerenone
- Ok to test while patient on spironolactone or eplerenone
  - If the renin is <1 testing is valid
  - If the renin is >1 testing may not be valid

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HIGH SUSPICION FOR PA WITH NEGATIVE TESTING

- 49% of patients had at least one aldosterone measurement below 15 ng/dL
- 29% had at least 2 aldosterone below 15 ng/dL
- 29% had at least 1 aldosterone below 10 ng/dL

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Yozamp N, et al., Hypertension. 2021;77:891–899

30

31

MILD CORTISOL EXCESS

- Caused by autonomous cortisol production from nodular adrenal disease
- Can be very mild but unregulated cortisol excess
  - Not "textbook" Cushing's syndrome
  - No obligate progression to florid disease

Chiodini I, et al. Ann Intern Med 2007;147:541-8

32

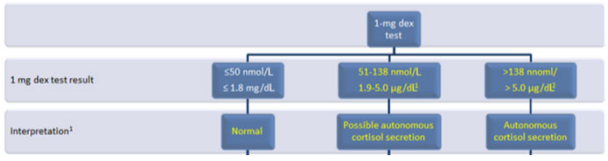
MILD CORTISOL EXCESS

- Long duration of cortisol excess
- Features
  - Metabolic bone disease
    - Compression fractures
  - Resistant hypertension
  - Glucose intolerance
    - Diabetes
  - Metabolic syndrome
  - ?Cardiovascular disease
- Not-so-incidental adrenal nodule

Chiodini I, et al. Ann Intern Med 2007;147:541-8
Tauchmanova L, et al JCEM 2002; 87: 4872-78

33

ESE ALGORITHM FOR MCE



Passnacht M, et al. EJE (2016) 175: G1–G34

34

TESTING ALGORITHM FOR MCE

- DST cortisol >1.8 µg/dL
- Then obtain AM ACTH and DHEA-s
  - Low DHEA-s
    - Suggestive of MCE
  - ACTH <5 pg/mL
    - Suggestive of MCE
  - ACTH 5-20 pg/mL
    - Possible MCE
- Consider late-night salivary cortisol
- Other cardiometabolic disease

35

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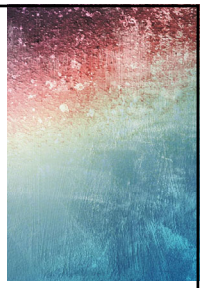
FOLLOW UP HORMONAL EVALUATION

- AACE/AAES: Hormonal evaluation should be performed at the time of diagnosis and then **annually for 5 years**
- ESE/ENSAT: We **suggest against repeated hormonal work-up**… unless new clinical signs of endocrine activity appear
- ESE/ENSAT: In patients with 'autonomous cortisol secretion' without signs of overt Cushing's syndrome, we **suggest annual clinical reassessment for cortisol excess and comorbidities potentially related to cortisol excess**

Zeiger M, et al Endocr Pract. 2009;15 (Suppl 1)
Fassnacht M, et al. EJE (2016) 175, G1–G34

37



CAVEATS ON IMAGING

38

HETEROGENEOUS NODULES

- ROI to calculate density has to be homogenous
- ROI should cover 2/3 of the nodule
  - Avoid areas of heterogeneity

Taffel M, et al., *Radiol Clin North Am.* 2012;**50**(2):219-243
Blake MA, et al., *Radiol Clin North Am.* 2008;**46**(1):65-78

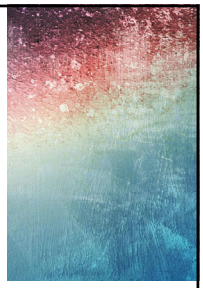
39

INCREASED DENSITY NODULES

- CT density >10HU
- What about CT washout?
  - Suboptimal performance in diagnosing malignancy
  - Sensitivity 16% (95% CI, 3-40) & specificity of 86% (95% CI, 64-97)
- Not recommended at 2nd line imaging

Fassnacht M, et al. EJE (2016) 175, G1–G34

40



IMAGING FOLLOW UP

41

AACE/AAES FOLLOW UP IMAGING

- Patients who do not meet criteria for surgical resection need radiographic ***reevaluate in 3-6 months then annually for 1-2 years***

Zeiger M, et al Endocr Pract. 2009;15 (Suppl 1

42

ESE/ENSAT FOLLOW UP IMAGING

- If the noncontrast CT is consistent with a benign adrenal mass (Hounsfield units ≤10) that is homogeneous and <4cm, **no further imaging is required**
- If the adrenal mass is indeterminate on noncontrast CT there 3 management options:
  - Another imaging modality
  - Interval imaging in 6–12 months (CT or MRI)
  - Surgery without further delay

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Fassnacht M. et al. EJE (2016) 175, G1–G34

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CONCLUSION

- All patients with AN should have a hormonal evaluation
  - Plasma free metanephrine or 24 hour urine
    - In patients without clear adenomas
  - Aldosterone and renin activity
    - In patients with HTN or hypokalemia
  - 1 mg overnight dexamethasone suppression
    - AM ACTH, DHEA-s, LNSC if DST is abnormal

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CONCLUSION[2]

- Biochemical follow up testing can be done in patients with mild cortisol excess
  - Especially if new cardiometabolic abnormalities
- If <~4cm and benign appearance
  - No follow up imaging is probably needed

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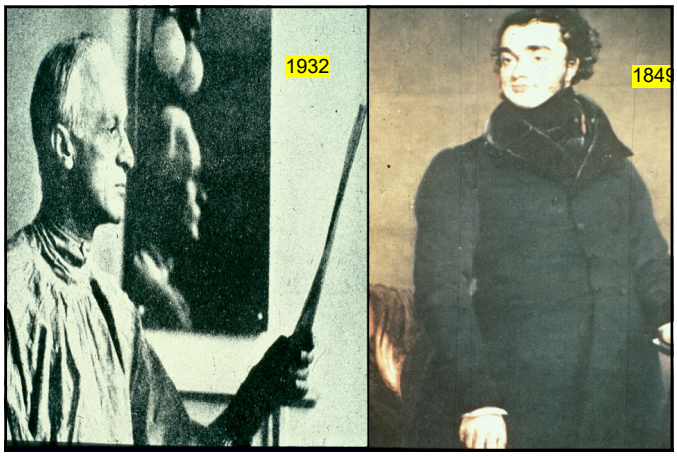
Neoplastic Hypercortisolism and Post-op Adrenal Insufficiency

2023 Endocrine Surgery & Neuroendocrine Symposium
April 1, 2023

James W Findling MD
Professor of Medicine and Surgery
Medical College of Wisconsin

1

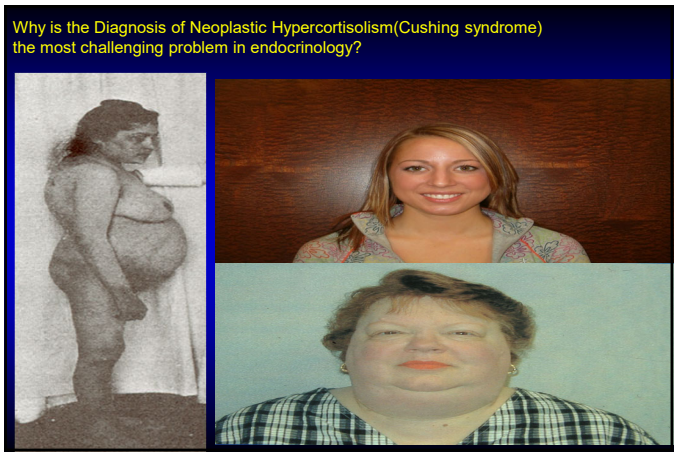


2

December 29, 1910
MG 23 year old woman

obesity
hirsutism
hypertension
amenorrhea

3

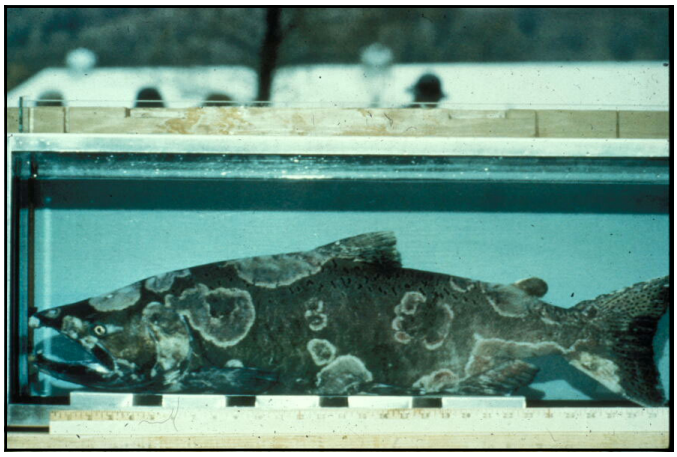

Why is the Diagnosis of Neoplastic Hypercortisolism(Cushing syndrome)
the most challenging problem in endocrinology?

4

5


1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16

6



7

Endogenous Hypercortisolism

Neoplastic/Pathologic	Non-neoplastic/Physiologic
ACTH secreting neoplasm	**Phenotype similar**
Pituitary (Cushing disease)	Alcohol induced/drug withdrawal
Ectopic	Chronic Kidney Disease 5
	Neuropsychiatric disorders
Adrenal Nodular Disease	Uncontrolled diabetes
Adenoma/Carcinoma	Pregnancy
Bilateral Nodular Disease	Glucocorticoid resistance
Macronodular	**Phenotype not similar**
Primary pigmented micronodular	Starvation equivalent disorders
	Critical illness
	Chronic intense exercise
	And many more to be characterized

8

Who should we screen?

Spanish Study Group: prospective study probabilistic model

Leon-Justel A, et al JCEM 2016; 101(10) 3747-3754

353 patients w/ obesity (BMI>30), DM (A1C>7), HBP (>2 drugs), PCOS
Screened with late-night salivary cortisol and 1 mg DST

219 normal studies
35 both abnl
99 discordant studies: repeat→7 both abnl

26/42 had proven CS (17 CD, 3 ectopic, 6 adrenal)
7.4% of screened patients had neoplastic hypercortisolism

9

Odds Ratio (p-value):

- Osteoporosis: 4.6 (0.003)
- Dorsocervical fat: 3.3 (0.004)
- Muscle atrophy: 15.2 (<0.001)
- Obesity: 0.2 (0.01)
- Diabetes: 0.26 (0.002)

- Adrenal nodules: 25-30% have mild cortisol excess

10

Cushing's Syndrome Suspected

Exclude exogenous glucocorticoid exposure

Perform one of the following tests

24-h UFC (≥2 tests) | Overnight1-mg DST | Late night salivary cortisol (≥ 2 tests)

ANY ABNORMAL RESULTS

Normal (CS unlikely)

Exclude non-neoplastic causes of hypercortisolism

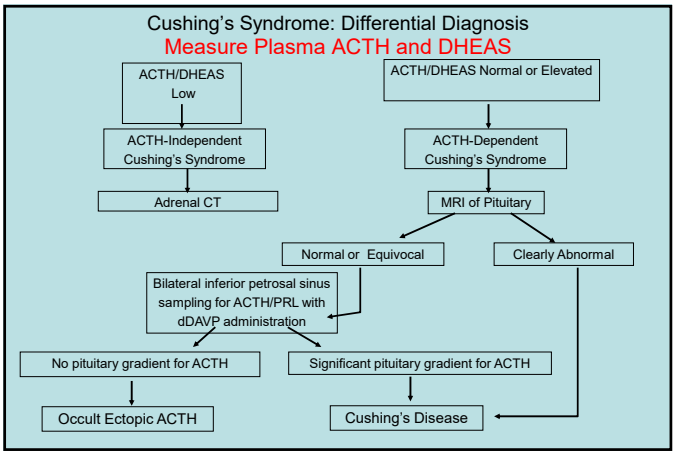
Consult endocrinologist

Nieman LK, Biller BMK, Findling JW, Newell-Price J, Savage MO, Stewart PM, Monton VM. The diagnosis of Cushing's syndrome: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 93:1526-1540, 2008.

11

Cushing's Syndrome: Differential Diagnosis

Measure Plasma ACTH and DHEAS



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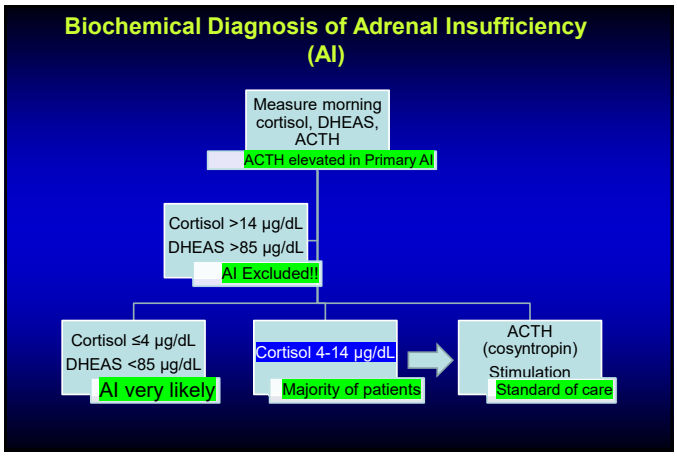
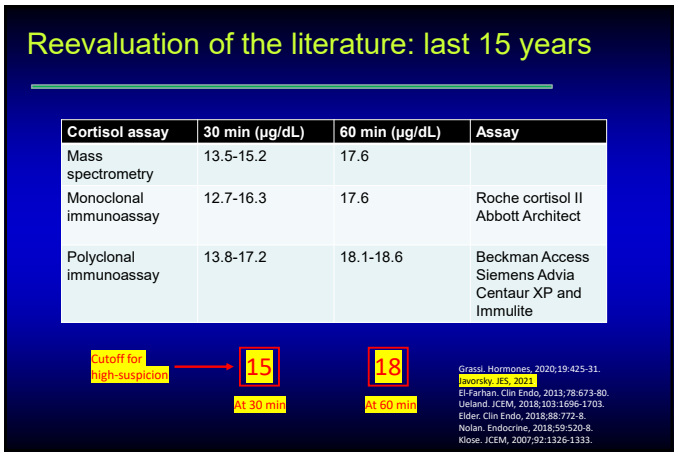
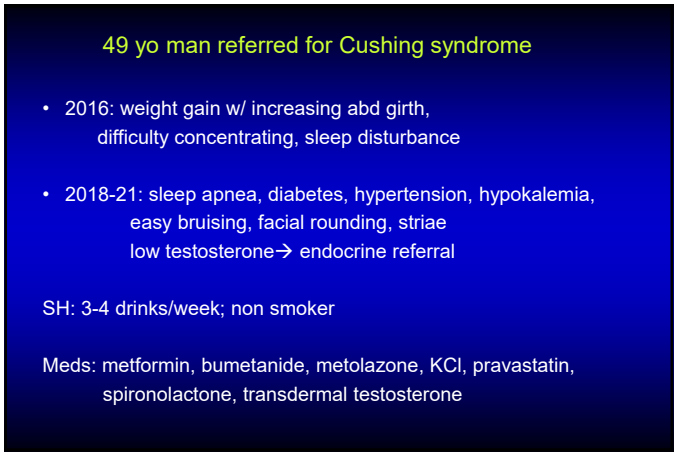

Biochemical Diagnosis of Adrenal Insufficiency (AI)
Measure morning cortisol, DHEAS, ACTH
ACTH elevated in Primary AI
Cortisol >14 µg/dL
DHEAS >85 µg/dL
AI Excluded!!
Cortisol ≤4 µg/dL
DHEAS <85 µg/dL
AI very likely
Cortisol 4-14 µg/dL
Majority of patients
ACTH (cosyntropin) Stimulation
Standard of care

13


Reevaluation of the literature: last 15 years
Cortisol assay | 30 min (µg/dL) | 60 min (µg/dL) | Assay
Mass spectrometry | 13.5-15.2 | 17.6 |
Monoclonal immunoassay | 12.7-16.3 | 17.6 | Roche cortisol II Abbott Architect
Polyclonal immunoassay | 13.8-17.2 | 18.1-18.6 | Beckman Access Siemens Advia Centaur XP and Immulite
Cutoff for high-suspicion
15
At 30 min
18
At 60 min
Grassi. Hormones, 2020;19:425-31.
Javorsky. JES, 2021
El-Farhan. Clin Endo, 2013;78:673-80.
Ueland. JCEM, 2018;103:1696-1703.
Elder. Clin Endo, 2018;88:772-8.
Nolan. Endocrine, 2018;59:520-8.
Klose. JCEM, 2007;92:1326-1333.

14


49 yo man referred for Cushing syndrome
• 2016: weight gain w/ increasing abd girth, difficulty concentrating, sleep disturbance
• 2018-21: sleep apnea, diabetes, hypertension, hypokalemia, easy bruising, facial rounding, striae low testosterone→ endocrine referral
SH: 3-4 drinks/week; non smoker
Meds: metformin, bumetanide, metolazone, KCl, pravastatin, spironolactone, transdermal testosterone

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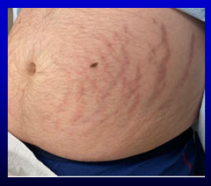
Examination

BP 132/78 P88 Wt 152 kg (336#) BMI 42

Cushingoid facies w/ increased supraclavicular fullness
No goiter; grossly distended abdomen w/ wide violaceous striae
2+ edema; muscle strength seemed normal
Normal mood and affect



16

Laboratory/Imaging

Na 134 K 3.5 Cl 97 Bicarb 33 Ca 9.2 BUN 20 creatinine 1.4
Glucose 102 AST 70 (9-40) ALT 55 (12-64) Alk Phos 138 (38-127)

Cortisol 27.7 µg/dL ACTH 36 pg/mL DHEAS 152 µg/dL

LNSC: 11.9 and 9.3 nmol/L (<3.2 nmol/L)
1 mg DST: cortisol 13.5 µg/dL
UFC: 15 µg/24h

Pituitary MRI: normal

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Desmopressin acetate (DDAVP) stimulation

Vassiliadi DA, Tsagarakis S, EJE 2018; 178:R201-R214

- Provocative ACTH stimulation during IPSS
- Early detection of recurrent Cushing disease
- Distinguishing neoplastic v non-neoplastic hypercortisolism

Interpretation (DDAVP 10 mcg IV):
Abnormal: increase ACTH >30 pg/ml or peak >70 pg/mL
increase cortisol > 6 mcg/dL and/or peak >18 mcg/dL

Normal subjects usually have meager response or actually decline

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dDAVP* Stimulation Test

	Basal	+10	+20	+30	+60
ACTH (pg/mL)	19	19	19	17	15
Cortisol (µg/dL)	21	17	16	15	

*10 mcg IV

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Phosphatidylethanol (PEth)

- Component
  Latest Ref Rng & Units *11/16/2021*
- Peth 16:0/18.1 ***402 ng/mL***
- PEth 16:0/18:1 (POPEth)
  Less than 10 ng/mL.....Not detected
  Less than 20 ng/mL.....Abstinence or light alcohol consumption
  20 - 200 ng/mL.....Moderate alcohol consumption
  Greater than 200 ng/mL.....Heavy alcohol consumption or chronic alcohol use

20

Phosphatidylethanol (PEth)

Phosphatidylethanol (PEth) is a group of phospholipids formed in the presence of ethanol, phospholipase D and phosphatidylcholine.
PEth is known to be a direct alcohol biomarker.

PEth is incorporated into the phospholipid membrane of red blood cells and has a general half-life of 4-10 days and a window of detection of 2-4 weeks.
However, the window of detection is longer in individuals who chronically or excessively consume alcohol.

Nguyen VL et al 2018, Alcoholism Clinical & Experimental Research.

21

59 yo woman

- 150 pound weight gain over fifteen years
- Facial hirsutism
- Diabetes mellitus Type 2 for two years with A1C 8.3% on insulin
- Hypertension for 10 years on 3 drugs
- Hyperlipidemia on statin
- OSA
- Severe muscle weakness (needs wheelchair)

22

Examination

- BP 135/82, Pulse 75, Wt: 359# (163 kg) Ht: 67in (1.708m): BMI 55.8 kg/m^2.
- Cushingoid appearing woman with facial fullness, plethora, acanthosis nigricans, skin tags, and increased supraclavicular and dorsocervical fat.
- . She has very severe proximal muscle weakness and cannot get out of a chair without assistance. 2+ pretibial edema is present. There are no abdominal striae.

23

Biochemistry

Endocrine Society 2008 Guidelines:

Urine free cortisol (normal < 45 µg/24hr)

32 µg/24hr
41 µg/24hr

Has Cushing's syndrome been excluded?

24

-Late-night salivary cortisols 12, 4.6, 7.3, and 6.7 nmol/L (normal: <3.2 nmol/L)

-Overnight 1 mg DST: cortisol 8.3 mcg/dL (normal <1.8 mcg/dL)

Pituitary MRI: normal

CT abdomen: Bilateral adrenal nodules

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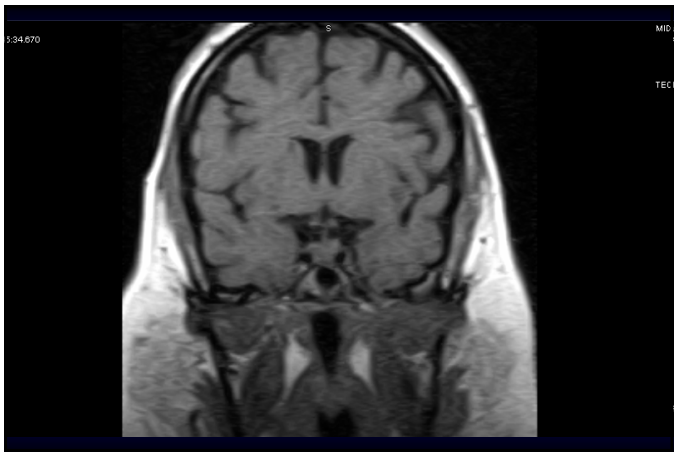

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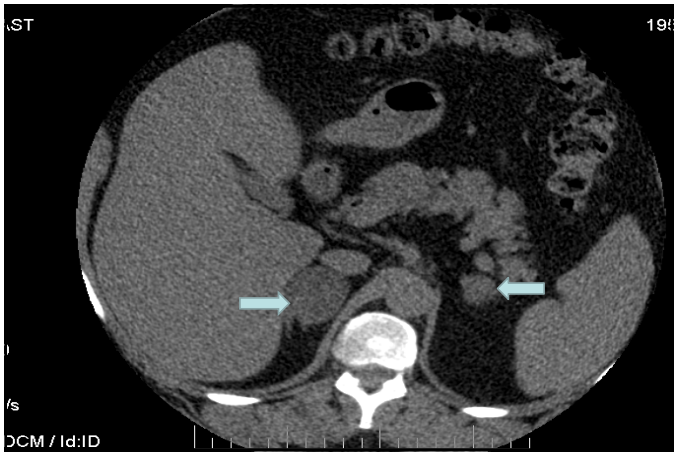

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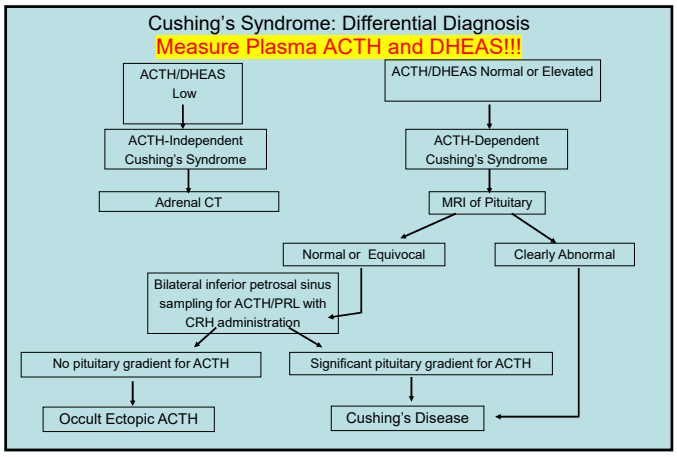

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Confirmatory tests:

Plasma ACTH: 57 pg/ml
DHEAS: 113 µg/dL (nl: 35-256 µg/dL)

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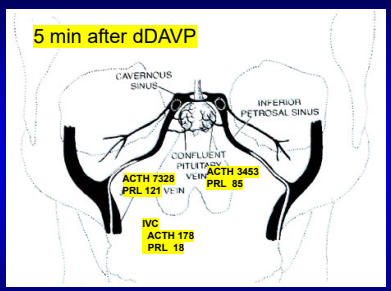
Differential diagnosis of ACTH dependent hypercortisolism



Bilateral inferior petrosal sinus sampling with dDAVP stimulation

30

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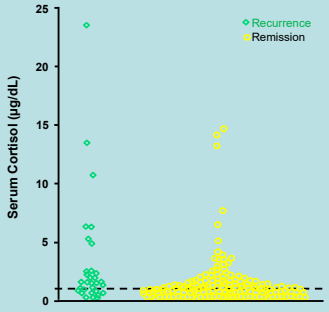
Can We Predict Recurrence Based on Post-Operative Cortisol?

- Nadir serum cortisol
  - Day 3, 4, and 5 after TSS
- Stratified by long-term follow-up remission status
- Mean f/u 10.6 years



Lindsay J R et al. JCEM 2011;96:2057-2064

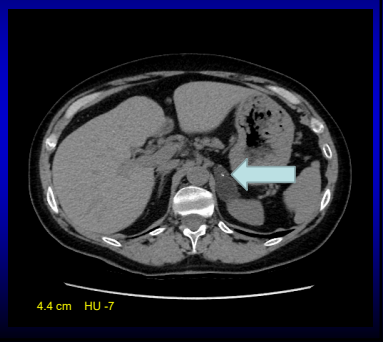
32

54 yo woman presents with kidney stone w/ partial obstruction of right ureter

10 yr h/o hypertension (3 meds)
Osteoporosis rx: zoledronic acid
Fasting glucose 113 mg/dL

Exam BP 130/92 61" 150# BMI 28
Non Cushingoid;

LAB: normal electrolytes, calcium, hemogram



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Lab Data:

Basal morning lab:
Cortisol 10.4 µg/dL (290 nmol/L)
ACTH 5.4 pg/mL (1.2 pmol/L)
DHEAS 13 µg/dL (360 nmol/L)

1 mg DST:
Cortisol 9.5 µg/dL (260nmol/L)
ACTH <1.1 pg/mL

24 hr UFC: 24 µg/24h (normal: 3-45)
65 nmol/L

LNSC: 6.1 and 5.8 nmol/L (normal: 0.3-3.2)
.22 mcg/dL and .20 mcg/dL

34

Cosyntropin stimulation testing on POD1 allows for selective glucocorticoid replacement therapy after adrenalectomy for hypercortisolism

Ortiz D, Findling JW, Carroll T, et al Surgery 2016; 159:259-266

Table I. Comparison of hypercortisolism patients requiring and not requiring glucocorticoid replacement ($n = 22$)

Variables	*Total* (n = 22)	*Glucocorticoids* (n = 11)	*No glucocorticoids* (n = 11)	P *value*
Median age, y (range)	60 (23–72)	51 (23–66)	62 (45–72)	.02
Female, *n* (%)	17 (77)	9 (81)	8 (73)	.61
Median BMI, kg/m^2 (range)	30.5 (17.6–39.5)	31.4 (20.8–39.3)	29.2 (17.6–38.8)	.02
Diabetes, *n* (%)	5 (23%)	2 (18.2%)	3 (27.3%)	.62
Hypertension, *n* (%)	9 (41%)	4 (36.4%)	5 (45.5%)	.67
Preoperative biochemical levels, median (range)				
Median salivary cortisol, nmol/L (range)	4.2 (0.3–21)	3.2 (1.0–21)	4.4 (0.3–8.1)	.67
Dexamethasone suppression test, median cortisol level, µg/dL (range)	2.7 (1.4–8.2)	2.7 (1.4–8.0)	2.3 (2.0–8.2)	.41
Median plasma ACTH, pg/mL (range)	9.1 (<1–20.9)	7.6 (<1–16.5)	9.8 (<1–20.9)	.49
24h urine cortisol, µg/24 h (range)	25.7 (7–127)	21.4 (12–127)	31.1 (7–58.6)	.91
Postoperative day 1 biochemical plasma levels, median (range)				
Median plasma ACTH level, pg/mL (range)	17.4 (<1–237)	12.7 (<1–237)	25.9 (3.3–51.6)	<.01
Median basal cortisol, µg/dL (range)	10.5 (0–34.1)	2.2 (0–11.4)	19.8 (0.8–34.1)	<.01
Median 60-min cortisol, µg/dL (range)	21.4 (2–44.8)	10.4 (2–22.7)	26.6 (20.1–44.8)	<.01

ACTH, Adrenocorticotrophic hormone; *BMI*, body mass index.

35

Required reading:

https://www.nytimes.com/interactive/2018/08/30/magazine/hurricane-harvey-houston-floods-texas-emergency.html

36

Summary

- Neoplastic hypercortisolism should be considered in patients with clinical features of the Cushing syndrome, patients with nodular adrenal disease, unexplained osteoporosis, and medically challenging metabolic syndrome
- Overnight 1 mg DST and LNSC are the most valuable diagnostic screening studies
- Plasma ACTH/DHEAS starts the evaluation of cause and pituitary/adrenal imaging and IPSS provides differential diagnosis
- Non-neoplastic hypercortisolism may be indistinguishable from neoplastic hypercortisolism and the dDAVP stimulation test may be helpful
- Post-op secondary adrenal insufficiency forecasts a clinical and biochemical remission of hypercortisolism

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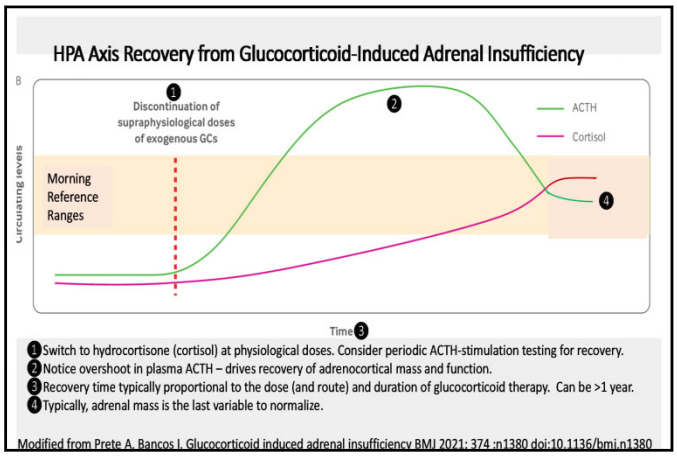

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Long-Term Outcomes of Mild Adrenal Cortisol Excess

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Division of Endocrinology and Molecular Medicine

Endocrine Surgery and Neuroendocrine Tumor Symposium
April 1st, 2023

1

Disclosures

- Investigator for Corcept Therapeutics with regards to medical treatment for hypercortisolism.

2

2

Outline

1. Diagnosis
2. Clinical outcomes
3. Management options

3

3

Terminology

Mild adrenal dependent cortisol excess

~~Subclinical Cushing~~ syndrome

Mild autonomous cortisol excretion (MACE)

Mild autonomous cortisol secretion (MACS) ★

Autonomous cortisol secretion (ACS)

4

4

1 Diagnosis

5

Screening for mild adrenal cortisol excess

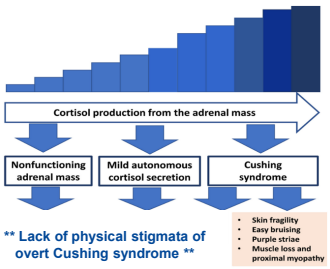
All patients with adrenal nodules should be screened.

1-mg overnight dexamethasone suppression test (DST):

I. ≤ 1.8 μg/dL → normal

II. 1.9 – 5.0 μg/dL → "possible" autonomous cortisol secretion

III. > 5.0 μg/dL → "confirmed" autonomous cortisol secretion



** Lack of physical stigmata of overt Cushing syndrome **

6

Fassnacht et al. *Eur J Endocrinol* (2016), Delivanis et al. *Clin Pharmacol Ther* (2017)

6

Additional tests helpful to confirm mild adrenal cortisol excess

1. **Exclude false positive results.**
   - ✓ Dexamethasone level
   - ✓ Repeat DST with higher dose (2-mg, 8-mg)

   Obese individuals, s/p gastric bypass
2. **Confirm ACTH-independent hypercortisolism.**
   - ✓ Basal ACTH and DHEAS
   - ✓ Post-DST ACTH level

   Basal ACTH <10, DHEAS <40
   Post-DST ACTH suppressed
3. **Evaluate the degree of cortisol excess.**
   - ✓ Late night salivary cortisol
   - ✓ 24-hour urine cortisol

   Often normal in mild cortisol excess

7 ACTH = adrenocorticotropin hormone; DHEAS = dehydroepiandrosterone sulfate; DST= dexamethasone suppression test

Froedtert & Medical College of Wisconsin

7

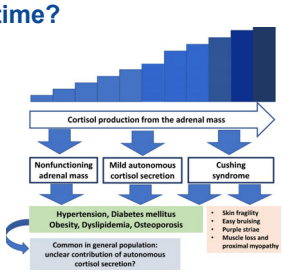
2 Clinical Outcomes

8

What happens to mild adrenal cortisol excess over time?

Systematic review of 2745 patients with adrenal tumors followed for mean of 50 months

- ✓ 4.3% → non-secretory to new mild adrenal cortisol excess
- ✓ 0.2% → mild adrenal cortisol excess to overt Cushing syndrome
- ✓ **Pre-existing mild adrenal cortisol excess unlikely to resolve (<0.1%)**



9 Elhassan et al. *Ann Intern Med* (2019), Delivanis et al. *Clin Pharmacol Ther* (2017)

Froedtert & Medical College of Wisconsin

9

Is mild adrenal cortisol excess clinically relevant?

Annals of Internal Medicine — REVIEW

Natural History of Adrenal Incidentalomas With and Without Mild Autonomous Cortisol Excess

A Systematic Review and Meta-analysis

Yasir S. Elhassan, MBBS; Fares Alahdab, MD; Alessandro Prete, MD; Danae A. Delivanis, MD, PhD; Aakanksha Khanna, MD; Larry Prokop, MLS; Mohammad H. Murad, MD, MPH; Michael W. O'Reilly, PhD; Wiebke Arlt, MD, DSc; and Irina Bancos, MD

- 32 studies summarizing data on cardiometabolic conditions at baseline and new events during follow-up
- 4121 patients (mean age 60.2 years, 62% women) with non-functioning adrenal nodules or mild adrenal cortisol excess
- Mean follow-up time of 50.2 months

10

Elhassan et al. *Ann Intern Med* (2019)

10

Clinical Outcomes: Cardiometabolic Disease

NFAT= non-functioning adrenal tumor
MACE= mild autonomous cortisol excess

Hypertension
- Baseline: NFAT 58% vs **MACE 64%**
- New or worsening disease: NFAT 10% vs **MACE 22%**

Obesity /weight gain
- Baseline: NFAT 39% vs **MACE 41%**
- New or worsening disease: NFAT 9% vs **MACE 21%**

Dyslipidemia
- Baseline: NFAT 34% vs **MACE 34%**
- New or worsening disease: NFAT 11% vs **MACE 13%**

Type 2 diabetes mellitus
- Baseline: NFAT 14% vs **MACE 28%**
- New or worsening disease: NFAT 5% vs **MACE 14%**

Cardiovascular events
- Baseline: NFAT 9% vs **MACE 6%**
- New or worsening disease: NFAT 6% vs **MACE 16%**

Cardiometabolic conditions are highly prevalent at the time of diagnosis and are more likely to develop and worsen in MACE compared to NFAT on follow-up.

11

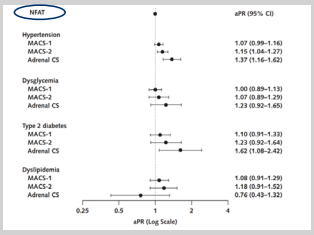
Elhassan et al. *Ann Intern Med* (2019)

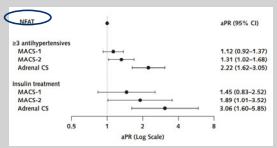
11

Cardiometabolic risk increases with the degree of cortisol excess

Multi-center cross-sectional study of 1305 prospectively recruited persons with benign adrenal tumors.

- NFAT= 1-mg DST ≤ 1.8 µg
- MACS-1= 1-mg DST > 1.8 µg/dL
- MACS-2= 1-mg DST > 5.0 µg/dL



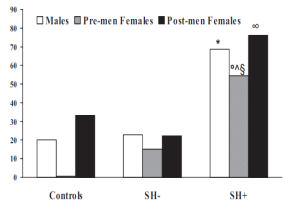


1. Prevalence and severity of HTN higher in patients with more severe cortisol excess.
2. Patients with more severe cortisol excess more likely to require insulin therapy for type 2 DM.

Prete et al. *Ann. Intern. Med* (2022).

12

Mild cortisol excess associated with lower bone mass and higher fracture rates



Cross-sectional study of 88 patients with mild cortisol excess compared to controls:

1. Bone mass lower at the femoral neck and lumbar spine in patients with mild cortisol excess compared to controls.
2. Prevalence of vertebral fractures (radiographic) higher in mild cortisol excess regardless of sex and gonadal status.
3. **58.3% of patients with fractures had T-scores above -2.5.**

2/3 abnormal tests: 1-mg DST > 3.0 µg/dL, urinary free cortisol > 70 µg/24 h, and ACTH < 10 pg/mL

Chiodini et al, *JCEM* (2009)

13

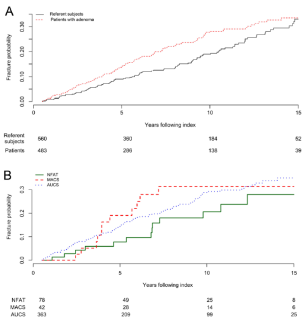
13

Higher risk of clinical fractures on follow-up

Population-based study in Olmsted County, MN

1,004 patients with adrenal adenoma vs age- and sex-matched controls followed for median of 6.8 years.

1. Higher prevalence of any fracture (48% vs 41%), vertebral fracture (6% vs 4%), and at combined osteoporotic sites (17% vs 13%).
2. Increased risk (HR 1.27, 95% CI 1.07-1.52) for developing new fractures during follow-up.



Li et al. *Eur J Endocrinol* (2021)

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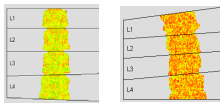
Other bone assessments that may be helpful…



1. **Trabecular bone score (TBS)**
   - Indirect measure of bone quality.
   - Reduced TBS compared with controls.
   - TBS correlates with number and severity of vertebral fractures in patients with mild adrenal cortisol excess.
2. **Bone turnover markers**
   - Lower bone formation markers (osteocalcin and PINP)
   - Reduced osteocyte function/number (sclerostin).
   - Increase in bone turnover markers after adrenalectomy for cortisol excess.

Eller-Vainicher et al. *JBMR* (2012), Athimulam et al. *JCEM* (2020)

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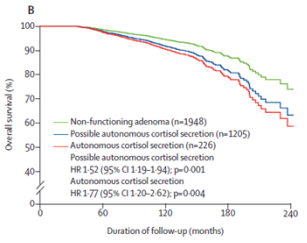
Clinical Outcomes: Mortality

- Discrepant data with variable follow-up duration in systematic reviews.
- Retrospective multicenter cohort of 3656 patients with adrenal adenomas followed for at least 3 years (median of 7 years).
- All-cause mortality increases with the degree of cortisol autonomy.
  - Adjusted for sex, age, and HTN, dyslipidemia, any diabetes, and prior CV events



Deutschbein et al. *Lancet Diabetes Endocrinol* (2022)

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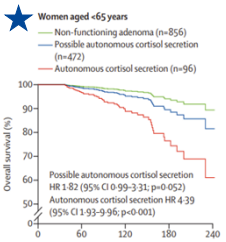
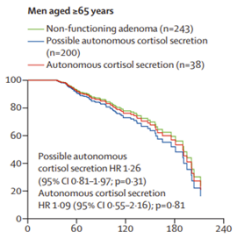
Sex and age-dependent disparity in mortality



Women younger than 65 years had highest relative risk of death.



Men older than 65 years not at increased risk.

Deutschbein et al. *Lancet Diabetes Endocrinol* (2022)

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Clinical outcomes with emerging data…

1. **Body composition**
   - Lower muscle mass and high proportion of visceral fat when compared to controls.
2. **Cognition**
   - Higher frequency of memory complaints compared to those with non-functioning adrenal tumors.
   - Impaired performance on working memory and visuospatial domains.
3. **Frailty**
   - Higher frailty index, fall rate, and sleep difficulties compared to patients with non-functioning adrenal tumors.

Delivanis et al. *Eur J Endocrinol* (2021), Liu et al, *JCEM* (2023), Singh et al, *JCEM* (2020)

18

18

3 Management options

19

What are the options for management?

1. Conservative follow-up
2. Adrenalectomy
3. Medical therapy

20

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Management

1. **Conservative follow-up**
   - Periodic reassessment with proactive screening and treatment of comorbidities
2. Adrenalectomy
3. Medical therapy

- As a group, at risk for new or worsening cardiovascular comorbidities, cardiovascular events, decreased bone mass, and vertebral fractures
- Individual risk hard to quantify → degree of hypercortisolism, duration of hypercortisolism, and individual susceptibility to cortisol excess

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21

Management

1. Conservative follow-up
2. **Adrenalectomy**
3. Medical therapy

22

22

What is the impact of adrenalectomy on outcomes?

Meta-analysis of 23 studies with 584 patients with median follow-up of 28 months:

Table 3 Effect of adrenalectomy on outcomes in patients with subclinical Cushing's syndrome.

Outcome	Number of studies	% improved	Difference in means	CI 95% lower limit	CI 95% upper limit	I^2 (%)
Hypertension ($n=265$)	21	60.5%		50%	71%	72
Diabetes mellitus type 2 ($n=120$)	20	51.5%		39%	64%	59
Dyslipidemia ($n=102$)	13	24%		13%	35.5%	58
Obesity ($n=128$)	16	45%		32%	57%	64
Systolic blood pressure (mmHg)	8		−12.72	−18.33	−7.1	61
Diastolic blood pressure (mmHg)	7		−9.34	−14.83	−3.85	76
BMI (kg/m^2)	7		−1.96	−3.32	−0.59	68
Fasting glucose (mmol/L)	4		−7.99	−13.9	−2.09	27
HbA1c (SMD)*	3		−0.96	−1.43	−0.49	53
LDL cholesterol (mg/dL)	2		−0.12	−37.7	37.5	53
HDL cholesterol (mg/dL)	3		2.9	−3.4	9.2	53
Triglycerides (mg/dL)	3		−23	−36.7	−9.2	0

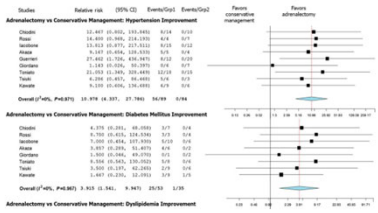
**** No trials have demonstrated reduction in cardiovascular events or mortality ****

23 Bancos et al. *Eur J Endocrinol* (2016)

23

Adrenalectomy vs Conservative Follow-Up

1. Patients who underwent adrenalectomy had significant risk reduction in HTN and DM vs those managed conservatively.
2. No significant improvement in obesity or dyslipidemia
3. Benefit not higher in patients with DST > 3 mcg/dL



Reliance on observational data
No robust randomized controlled trials

24 Bancos et al. *Eur J Endocrinol* (2016)

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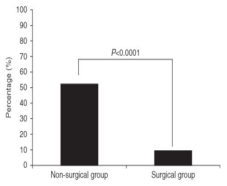
Adrenalectomy associated with reduced risk of fractures on follow-up



1-mg DST >5.0 µg/dL
2/3 abnormal tests: 1-mg DST >3.0 µg/dL, urinary free cortisol >70 µg/24 h, and ACTH <10 pg/mL

Surgical intervention (n=32) vs conservative follow-up (n=23) for ~30 months

1. Patients followed conservatively were more likely to develop new vertebral fractures on imaging (52.2% vs. 9.4%) compared to surgical group.
2. Surgery associated with 30% vertebral fracture risk reduction, independent of age, sex, spine BMD, 1-mg DST result, and prevalent vertebral fracture.

25 Salcuni et al. *JCEM* (2016)

25

Management

1. Conservative follow-up
2. **Adrenalectomy**
3. Medical therapy

- Improvement in cardiovascular factors is variable. No demonstrated benefit in mortality or cardiovascular events.
- Individualized decision→ age, clinical comorbidities, degree of hypercortisolism, adrenal nodule imaging characteristics, patient preference.
- Post-operative adrenal insufficiency and glucocorticoid withdrawal.

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26

Management

1. Conservative follow-up
2. Adrenalectomy
3. **Medical therapy**
   - Adrenal steroidogenesis inhibitor
   - Glucocorticoid receptor blocker

- Cost
- Monitoring for side effects
- Potential role in bilateral disease and those who are poor surgical candidates
- Potential role in understanding effect of cortisol excess on symptoms and comorbidities

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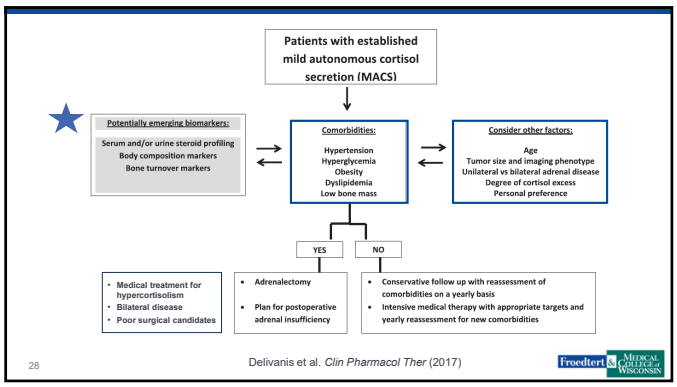

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Summary

1. Mild adrenal cortisol excess is characterized by inappropriate and autonomous cortisol production:
   - Abnormal 1-mg DST (not false positive)
   - Low basal ACTH and DHEAS supportive
   - 24-hour urine cortisol and salivary cortisol measurements typically normal
2. Mild adrenal cortisol excess is associated with increased rates of hypertension, obesity, dyslipidemia, type 2 DM, cardiovascular events, low bone mass, fractures, and mortality.
3. Treatment decisions should be individualized and may include observation with screening and treatment of comorbidities, surgery, or medical therapy for hypercortisolism.

29

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Questions or Comments?

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30

Management of ACTH-Dependent Hypercortisolism

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1

Disclosures

Grant Recipient

Principal investigator for institution-directed research for studies sponsored by Strongbrindge/Xeris Phamaceutical, Chiasma, Inc/Amryt Pharma and Recordati Rare Disease

Consulting Fees

HRA Pharmaceuticals, Ipsen, Recordati Rare Disease, Strongbridge/Xeris Pharmaceutical, Chiasma, Inc/Amryt Pharma, Camurus

2

Objectives

I. Understand the role of surgery for ACTH-secreting tumors
II. Describe the medical treatment options for hypercortisolism
III. Recognize the role of multimodality treatment for recurrence

3

Case 1

25 y.o. F, G0P0, with weight gain, straie and hyperglycemia

- 24-hr UFC 150 µg/day (3xUNL); repeated 162 µg/day
- late night salivary cortisol (LNSC): 5xUNL; repeated 6xUNL
- serum cortisol after 1-mg dexamethasone: 6.1 µg/dL (normal <1.8)
- serum cortisol 17 µg/dL, plasma ACTH 80 pg/mL (UNL 64)

Localization studies:

- pituitary MRI: 6-mm adenoma
- desmopressin test: ↑plasma ACTH by 110%

----- Pituitary surgery:

- POD1 serum cortisol 1.1 mcg/dL
- Path: ACTH-positive adenoma

4

Immediate Postoperative Cortisol Level

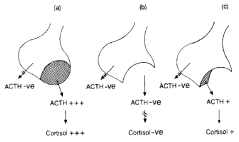

Fig. 1 A diagram to illustrate the hypothetical situation associated with transsphenoidal surgery for Cushing's disease. a, Preoperative state; b, post-operative 'cure'; all tumour removed, ACTH secretion is suppressed from the normal gland and serum cortisol is non-detectable; c, some tumour remains and cortisol secretion is detectable. Secretion + + +, above normal; +, detectable; –, suppressed. ■, ACTH secreting tumour.

Trainer et al. Clinical Endocrinology. 1993

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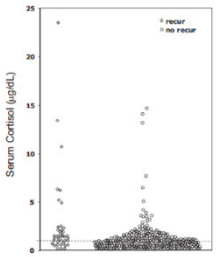
Caveats



N=332

Some patients achieved late remission

Recurrence rates were similar for serum cortisol < 2 µg/dL or 2-5 µg/dL

No single cutoff value excluded recurrences

Lindsay et al. JCEM. 2011

6

Postoperative remission after transsphenoidal surgery

- CD remission rates 59-94% (meta-analysis 76%, 95% CI: 72-79%)
- Predictors of remission
  - Very low cortisol levels immediately postop
  - Preoperative MRI
    - Microadenoma: higher changes of remission than macroadenoma or no adenoma
    - Non-invasive adenomas: higher changes of remission than invasive
  - Histologic confirmation of the ACTH-adenoma
- Recurrence of hypercortisolism: 8-66%

Ioachimescu AG. Endocrine Clinics of North America. 2018

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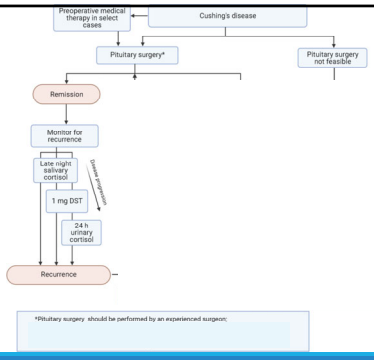

Fleseriu et al. Lancet Diabetes Endocrinol. 2021

8

Case 1, three years later

- Weight gain and new straie
- Late night salivary cortisol (LNSC) ↑, UFC normal
- Pituitary MRI: negative
- G0P0, recently married, no immediate plans for pregnancy

9

Management of recurrent CD

Radiation
Biochemical remission: 55-66%
Delayed efficacy (>1 year)
Hypopituitarism:
- 30-40% after 2 years
- Conventional > stereotactic

Reoperation
Biochemical remission: 38-90%
Remission more likely for:
- tumors visible on MRI
- non-invasive tumors
- expert neurosurgeon

Hypopituitarism

Medical treatment
Significant progress
AE, drug-drug interactions
Lack of long-term data

Bilateral adrenalectomy
Immediate resolution of hypercortisolism
Permanent cortisol & aldosterone deficiency
Corticotroph tumor progression (Nelson's syndrome): up to 60%
Used when other options failed & in women desiring pregnancy

Jones and Swearingen. Pituitary 2022. Gheorghiu Best Pract Res Clin Endocrinol Metab. 2021
Fountas and Karavitaki, Endocrinol Metab Clin North Am 2020. Rubinstein et al. Clin. Endocrinol. Metab. 2019

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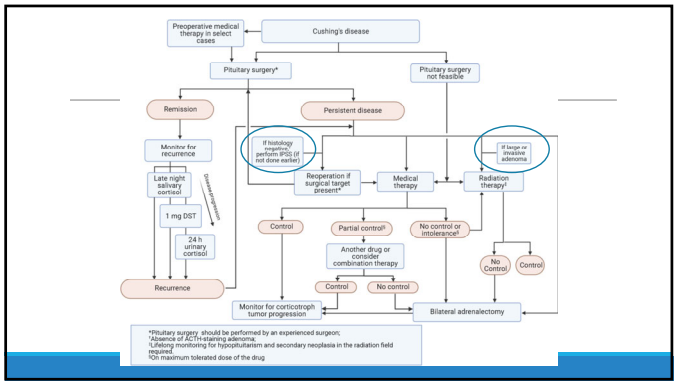

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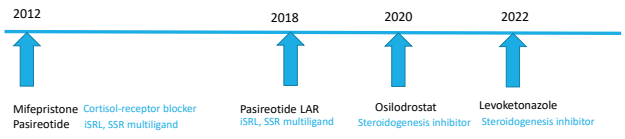
FDA-approved medications



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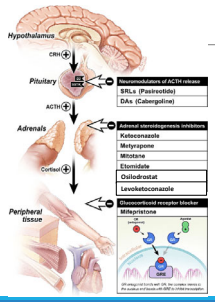
Mechanisms



- Tumor Targeting
- Adrenal Steroidogenesis Inhibition
- Cortisol Receptor Blockade

Modified from Fleseriu et al. Pituitary. 2015

13

Pasireotide

- Normal UFC in 40% pts receiving monthly injections
  - Milder hypercortisolism predicts biochemical response
- Tumor shrinkage in 40% pts
  - Significant residual tumor
  - Tumor progression
  - Nelson syndrome
- Hyperglycemia in up to 70% pts
  - Monitor BG in all patients
  - Intensify BG-lowering regimen in patients with DM

14

Cabergoline

Doses from small retrospective studies : 0.5–7 mg/week p.o.

EFFICACY

Biochemical Control (normal UFC)

- 25-40%
- 20-30% escape

Tumor:

- 50% cases with shrinkage

SIDE EFFECTS

- GI: nausea
- Orthostatic hypotension
- Psychiatric: impulse control disorders
- Valve disease ? (high doses)

Fleseriu et al. Pituitary. 2015
Giraldi and Ioachimescu. Endocrinol Metab Clin North Am. 2020

15

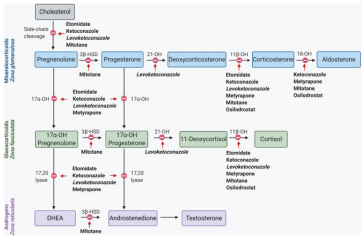
Cabergoline in clinical practice

- Mild Hypercortisolism
- Residual tumor growth
- Pregnancy
- Adjunct tx to steroidogenesis inhibitors or SRL

16

Adrenal Steroidogenesis Inhibitors

- Ketoconazole
- Levoketoconazole
- Metyrapone
- Osilodrostat



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Adrenal Steroidogenesis Inhibitors

HYPERCORTISOLISM

- Usually effective after dose titration
- Clinical changes parallel cortisol levels

PRECAUTIONS

- Tumor may enlarge
- ACTH levels usually ↑
- Precursor build-up
- Risk of corticoadrenal insufficiency
- Drug-drug interactions (CYP3A4 inhibition)
- Hepatotoxicity
- QT prolongation

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Mifepristone

FDA approved to control hyperglycemia secondary to Cushing's syndrome

CORTISOL EFFECTS

- Improves glucose metabolism
- Improves clinical manifestations
- Effects do not correlate with cortisol or ACTH levels
  - Dose titration based on clinical evaluation

PRECAUTIONS

- Tumor may enlarge
- Hypokalemia
  - Excess cortisol binds to the aldosterone receptor
- Blocks progesterone receptor (abortifacient, risk of vaginal bleeding)
- Manifestations of adrenal insufficiency
  - Require supraphysiologic dose of dexamethasone

Fleseriu et al. Pituitary. 2015; Pivonello et al. Front Endocrinol (Lausanne). 2020

19

Case 2

45 y.o. M with weight gain, straie and hyperglycemia

- 24-hr UFC 155 µg/day (x3 above UNL)
- serum cortisol after 1-mg dexamethasone: 6.8 µg/dL (normal <1.8)
- serum cortisol 17 µg/dL, plasma ACTH 88 pg/mL (UNL 64)
- Localization studies:
- pituitary MRI: no adenoma
----- Inferior Petrosal Sinus Sampling: no significant central-to-peripheral gradient
----- chest CT scan: 1.9 cm pulmonary nodule; bilateral adrenal enlargement
----- Path: bronchial ACTH+ neuroendocrine tumor
----- Postoperative serum cortisol: 0.8 µg/dL

20

Ectopic ACTH Cushing's Syndrome (EAS)

- ❑ Abnormal expression of POMC gene in non-pituitary tumors
- ❑ Historically, aggressive pathology with severe hypercortisolism reported
  - ❑ Small cell lung cancer
  - ❑ Male with rapid progression of hypercortisolism with a catabolic syndrome, muscle weakness and hyperpigmentation
  - ❑ Hypokalemia, compression fractures, opportunistic infections
  - ❑ Very high ACTH and cortisol levels
- ❑ Currently, benign NET reported
  - ❑ Gradual onset of hypercortisolism similar with pituitary CS
- ❑ Differentiation requires hormonal dynamic testing and imaging studies
- ❑ All tests should be considered "probabilistic rather than algorithmic"

Hayes & Grossman. Endocrinol Metabl Clin N Am. 2018.

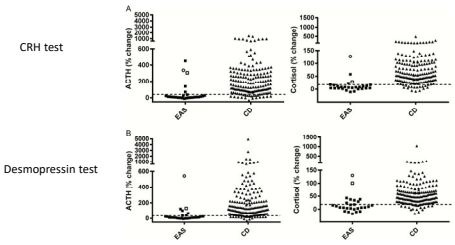
21

Hormone workup in EAS

- Usual screening tests for hypercortisolism
  - Very high cortisol and ACTH levels in malignant NET
- HDDST: cortisol levels do not suppress
- CRH or Desmopressin administration: ACTH and cortisol levels do not stimulate
- Caveats: well-differentiated NET may express CRH and V1b (V3) vasopressin receptors
- Using multiple tests improves accuracy
- Gold standard: IPSS - lack of central-to-peripheral gradient
  - Caveats: cyclical hypercortisolism, catheter placement, expert centers

22

ACTH (left) and Cortisol (right) responses



Frete et al. JCEM. 2020

23

"Needles in a haystack or hiding in plain sight"

- Location
  - Lung: Neuroendocrine Tumor (25%) > small cell lung carcinoma (20%)
  - Other: thymus (11%), pancreas (8%), thyroid (6%) and adrenal (5%)
  - Occult: 25%
- Imaging studies
  - - contrast-enhanced CT neck and chest
  - - contrast-enhanced CT/MRI abdomen and pelvis
  - - Ga-DOTA-somatostatin analogue PET/CT
  - - FDG-PET if all the above negative
    - Localizes approx. 65% of NET associated with ectopic CS

Hayes&Grossman. Journal of Neuroendocrinology. 2022

24

Bilateral adrenalectomy in EAS

1. Life-threatening complications (emergency procedure)
   - Median surgical morbidity 15%
   - Median surgical mortality 3%
   - Medical tx of hypercortisolism should be attempted preoperatively
2. Severe hypercortisolism unresponsive to medical treatment
3. Indolent tumor not found on serial imaging
4. Unresectable indolent tumor
5. Medical therapy not well tolerated

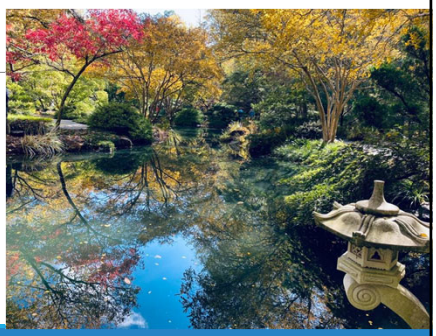
25

Conclusions

- ACTH-dependent CS presentation is heterogenous
- Primary treatment is tumor removal
- Clinical and biochemical monitoring for recurrence is required in all patients
- Multi-modality therapy is necessary for persistent postop hypercortisolism or recurrence
- Individualized multidisciplinary management takes into account
  - Severity of hypercortisolism, tumor size and location, comorbidities and fertility

26

Thank you!



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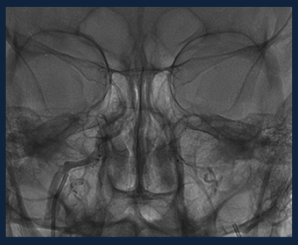
Inferior Petrosal Sinus Sampling

Marc A. Lazzaro, MD

Associate Professor of Neurology and Neurosurgery
Medical College of Wisconsin



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1

Inferior Petrosal Sinus Sampling (IPSS)

Disclosures

- No commercial interests

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2

Inferior Petrosal Sinus Sampling (IPSS)

Objectives

- Explain the role of inferior petrosal sinus sampling in identifying the source of ACTH in Cushing syndrome
- Describe the anatomy of the inferior petrosal sinuses
- Review the risks of inferior petrosal sinus sampling

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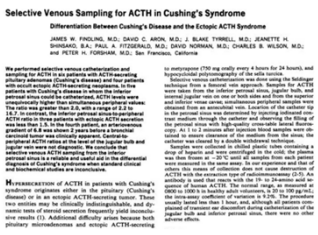
3

Inferior Petrosal Sinus Sampling (IPSS)

Overview
- Venous catheter procedure
- Bilateral inferior petrosal sinus and peripheral venous catheterization
- Series of simultaneous samples for adrenocorticotropic hormone (ACTH) to assist determining pituitary gland or ectopic source.

4

IPSS Early Description



Selective Venous Sampling for ACTH in Cushing's Syndrome

Differentiation Between Cushing's Disease and the Ectopic ACTH Syndrome

JAMES W. FINDLING, M.D., DAVID C. ARON, M.D.; J. BLAKE TYRRELL, M.D.; JEANETTE H. SHIMIZAKO, B.A.; PAUL A. FITZGERALD, M.D.; DAVID NORMAN, M.D.; CHARLES B. WILSON, M.D.; and PETER H. FORSHAM, M.D.; San Francisco, California

- Initial description of reliability of IPSS in Cushing syndrome
- 10 patients
- 5/6 patients with Pituitary adenoma and whose IPS could be catheterized, ACTH ratio to peripheral was greater than 2.0
- In ectopic source patients, the ratio was less than 1.5
- Jugular vein sampling was not diagnostic

Findling JW et al. Ann Intern Med. 1981 May;94(5):647-52

5

IPSS Procedure

- No sedation, local anesthetic for venous puncture
- Bilateral femoral vein access
- Heparinization and heparin flush lines
- Bilateral inferior petrosal sinus microcatheterization
- Simultaneous sampling at times: -5, 0, 3, 5, 10, and 30 minutes from DDAVP
  - Right IPS
  - Left IPS
  - Peripheral vein (femoral vein)

6

IPSS Procedure

- 6 personnel required for sampling
- Team is paired into 1 scrubbed and 1 non-scrubbed person
  - 3 simultaneous samples are drawn by the scrubbed personnel
  - The non-scrubbed personnel receive sample, verify time and sample location, transfer samples to EDTA tubes and place on ice
  - One non-scrubbed person assigned to manage clock

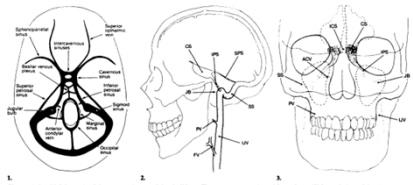
7

Patient Experience

- No sedation
- Local anesthetic used for venous puncture
- May experience brief headache, ear pain, "crunching sound," flushing sensation with CRH/desmopressin injection
- 1-2 hour procedure
- 2 hours flat bedrest before discharge

8

IPSS Anatomy



Miller DL, Doppman JL. Radiology 1991; 178:37-47

9

IPSS Anatomy

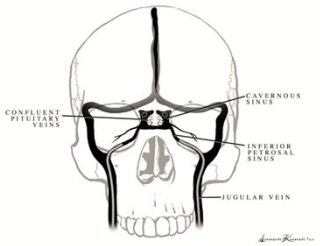
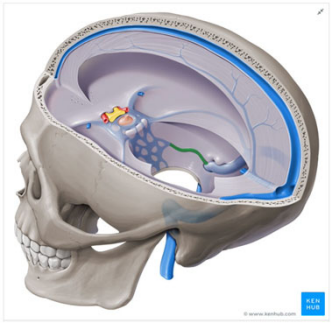


Fig. 1. Cerebral venous anatomy for IPSS.

Lad SP et al. Neurosurg Focus 2007; 23(3):E2

10

IPSS Anatomy



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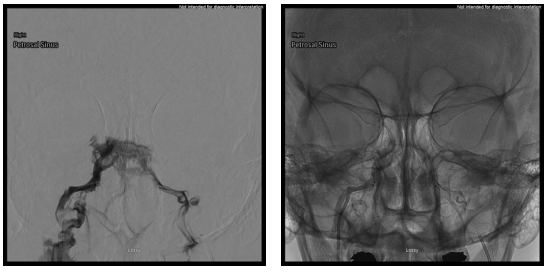
IPSS Catheter venogram



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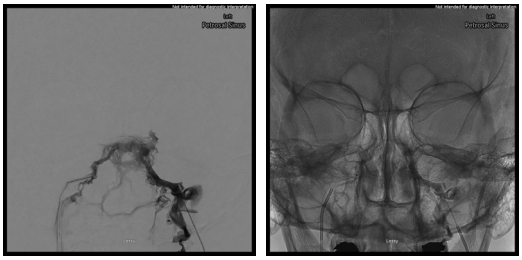
IPSS Catheter venogram



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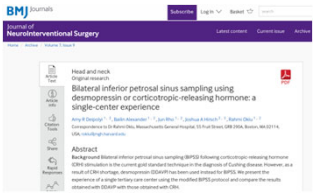
ACTH stimulation

Shift to DDAVP after Corticorelin became unavailable



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IPSS Prolactin measurement

Prolactin measurement as marker of successful IPS catheterization

- Inferior petrosal sinus to peripheral (IPS/P) prolactin ratio of greater than 1.8 before CRH indicated successful catheterization.

Findling JW, Kehrle ME, Raff H. J Clin Endocrinol Metab. 2004 Dec; 89(12):6005-9

- False-negative IPSS ACTH results have been associated with a prolactin IPS/P ratio of less than 1.3.

Mulligan GB, et al. Endocr Pract. 2011 Jan-Feb; 17(1):33-40

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15

IPSS Prolactin measurement

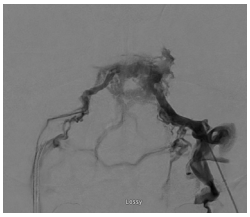
A prolactin-normalized ACTH ratio has been proposed to differentiate Cushing disease and ectopic source in unsuccessful catheterization

- Normalized ACTH/prolactin IPS/P ratios:
  - <0.7 is consistent with ectopic AS
  - >1.3 is consistent with Cushing disease
  - 0.7 to 1.3 is indeterminate

Sharma ST, Raff H, Nieman LK J Clin Endocrinol Metab. 2011 Dec; 96(12):3687-3694

16

Challenges



Catheterization challenges

- Femoral vein access
- Internal jugular vein valve
- Variation in cavernous sinus drainage

Catheter position stability and sampling rate

Specimen handling

- Labeling, transportation, processing, result reporting

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IPSS outcomes

Procedural success

- Series of 335 procedures
- Successful inferior petrosal sinus catheterization in 98%
- 0.9% risk of serious complication or death
- Groin hematoma 4%

Miller DL, Doppman JL. Radiology 1991; 178:37-47

18

IPSS outcomes

Procedural success
- Series of 327 patients
- Overall technical success rate 88% for bilateral cannulation
  - However, nearly 2/3 of technical failures had unilateral sampling that diagnosed CD
- Lateralization was accurate in only about 50% of patients
- Complications were rare, groin hematoma 2.5%

Deipolyi A et al. Journal of Neurointerventional Surgery 2017;9:196-199

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Inferior Petrosal Sinus Sampling (IPSS)

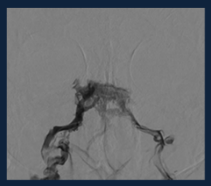
Additional potential complications:
- Venous thrombosis
- Hyponatremia due to DDAVP

20

Thank you for your attention.

Marc A. Lazzaro, MD

Associate Professor of Neurology and Neurosurgery
Medical College of Wisconsin



21

ENDOCRINE SURGERY
MEDICAL COLLEGE OF WISCONSIN

Surgical Approaches for Adrenalectomy

Tracy S. Wang, MD, MPH, FACS, FSSO
Professor of Surgery
Vice-Chair of Strategic and Professional Development

Endocrine Surgery Symposium – April 1, 2023

MCW Surgery
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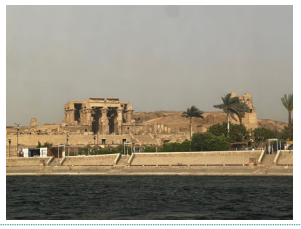
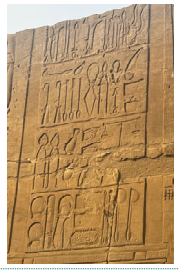
1

DISCLOSURES

No financial disclosures





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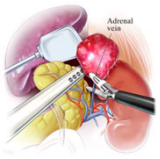
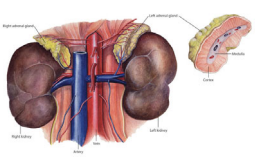
Objectives

- Discuss operative approaches for adrenalectomy
- Factors to consider in decision-making
  - Minimally invasive vs. open approach
  - Transabdominal vs. Posterior retroperitoneal





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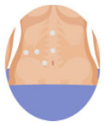
Surgical Options

- The surgical paradigm for the treatment of benign primary or metastatic adrenal neoplasms has shifted.
- Traditional: Open adrenalectomy
  - Larger incisions, more post-operative pain, longer hospital stays
- Present day gold standard: Minimally invasive adrenalectomy
  - Has proven to be both cost-effective (laparoscopic) and safe.
- Multiple choices for approach:
  - Transabdominal (anterior) vs. posterior retroperitoneoscopic adrenalectomy
  - Laparoscopic vs. robotic-assisted



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Figures from Bartz-Kurycki et al. Reviews in Endocrine and Metabolic Disorders 2022 Jul;1:1-14.

4

Indications for Surgery

Functional tumors

- All patients with a cortisol-producing adenoma (overt hypercortisolism).
- In patients with MACS…indication for surgery is more controversial.
- All patients with pheochromocytomas
- All patients with primary aldosteronism and a unilateral source of aldosterone excess

Malignant tumors (concern for malignancy)

- Any adrenal mass with concerning radiographic characteristics and most lesions ≥4 cm
- Adrenal metastasectomy should be considered in the case of an isolated adrenal metastatic lesion.

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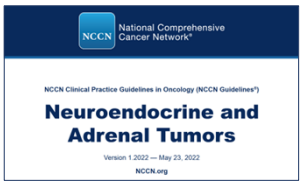
Bancos I. JCEM 2021;106(11):3331-3353
Yip et al. JAMA Surg 2022;157(10):870-877

5

Guidelines



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NCCN 2022
Yip et al. JAMA Surg 2022;157(10):870-877

6

OPEN vs. MINIMALLY INVASIVE adrenalectomy

AAES Adrenalectomy Guidelines

- R7.1. **When patient and tumor characteristics are appropriate, we recommend minimally invasive adrenalectomy over open adrenalectomy** because of improved perioperative morbidity. (Strong recommendation, low-quality evidence).
- R4.2. Regardless of operative approach, we recommend en bloc radical resection with an intact capsule to microscopicially negative R0 margins because of improved survival. Although **open resection is preferred when ACC is suspected,** the choice of operative approach should be based on the certainty of a complete R0 resection without tumor disruption (Strong recommendation, low-quality evidence

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Yip et al. JAMA Surg 2022;157(10):870-877

7

OPEN vs. MINIMALLY INVASIVE adrenalectomy

- AAES Adrenalectomy Guidelines
- NCCN (2022 guidelines):

Indication	Surgical Approach
Primary aldosteronism (unilateral disease, presumed benign)	Adrenalectomy, minimally invasive preferred
Hypercortisolism <4cm >4cm or malignant imaging characteristics	 Adrenalectomy Adrenalectomy*
Pheochromocytoma	Adrenalectomy, minimally invasive preferred when safe and feasible
Suspected adrenocortical carcinoma	Adrenalectomy, open recommended

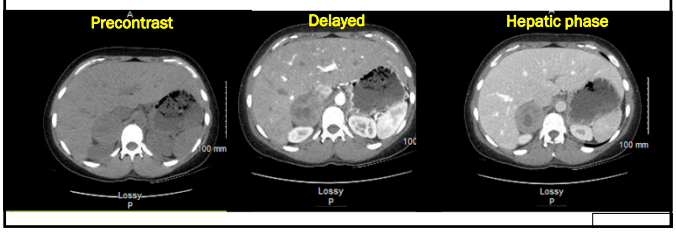
* If size is resectable by laparoscopy, may explore using a minimally invasive approach with planned conversion for evidence of local invasion. The decision for open vs. minimally invasive surgery is based on tumor size and degree of concern regarding potential malignancy, and local surgical expertise.

8

34-year old woman
At referring institution for Raynaud's syndrome and left upper extremity claudication
Had an incidental right adrenal mass identified (on echocardiogram) – CT performed with concern for liver invasion

Measured 6.9 cm, indeterminate in appearance, washout 14.3% (no HU reported)

Biopsy (referring institution): Pheochromocytoma

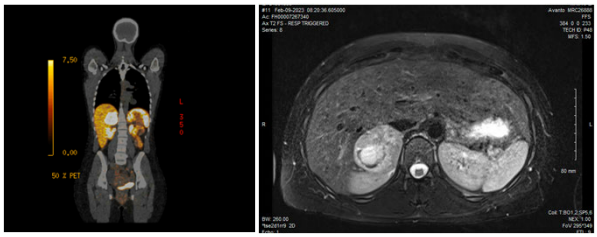


9

34-year old woman with incidentally identified large right adrenal mass

Upon referral, confirmed with biochemical evaluation
Metanephrine: 11.85 (normal, 0.00 - 0.49)
Normetanephrine: 3.44 (normal, 0.00 – 0.89)

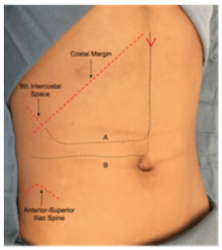
Referred to genetics: no mutation identified



10

Open adrenalectomy

- Options for surgical incision
  - Midline
  - Subcostal
  - Modified Makuuchi (right) / Reverse Makuuchi (left)
  - Thoracoabdominal
- Potential advantages for Makuuchi incision:
  - Exposure to upper quadrants and retroperitoneum
    - Left: splenic attachments
    - Right: posterior and lateral aspects of triangular ligament
  - Ruffolo et al. study: no significant diff in hernia rates or postoperative pain management



Ruffolo LI et al. Surgery 2018;164:1372-1376

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Minimally invasive adrenalectomy

Which approach?

Laparoscopic or Robotic

Transabdominal (TA) or Posterior retroperitoneoscopic (PRA)

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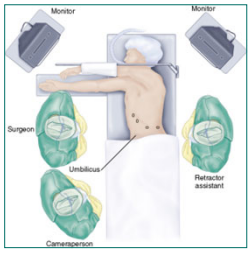
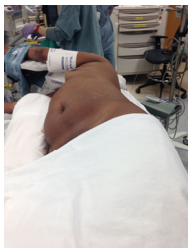
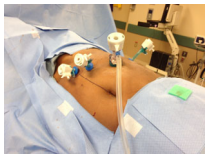
Transabdominal LEFT Adrenalectomy







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Duh, Atlas of Endocrine Surgical Techniques, 2009

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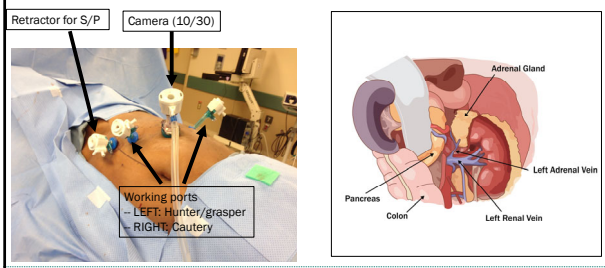
Transabdominal LEFT adrenalectomy



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Hangge, Johnson, Wang. Shackelford's Atlas, in press.

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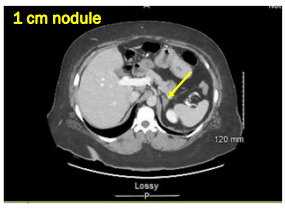
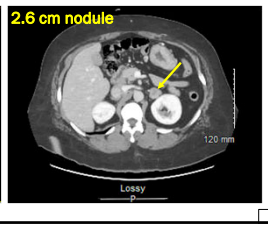
47-year-old woman with incidental adrenal nodules (CT chest during evaluation with COVID symptoms)
Two left adrenal nodules: 2.6 cm (17, 78, and 29 HU on pre-, early post- and delayed contrast images) and 1.0 cm (8-10 HU) – both consistent with adenoma

Normal metanephrines and normetanephrines
1mg DST: Cortisol 1.9, ACTH 2.0, dexamethasone 258
Repeat 1 mg DST: cortisol 2.2, ACTH <1.5, dexamethasone 232
Salivary cortisol: 5.3, 11.9





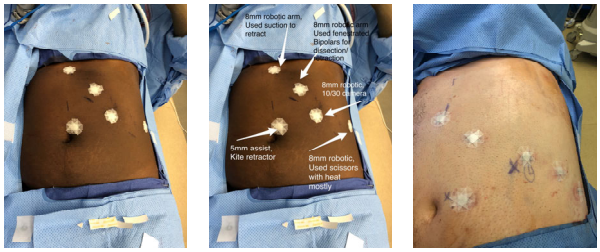
15

Left robotic-assisted transabdominal adrenalectomy

- Patient with incidental 2.6 cm left adrenal nodule
- Biochemical evidence of hypercortisolism secondary to mild autonomous cortisol excess (MACE)

16

Transabdominal LEFT adrenalectomy - ROBOTIC



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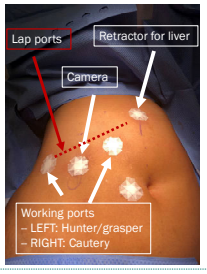
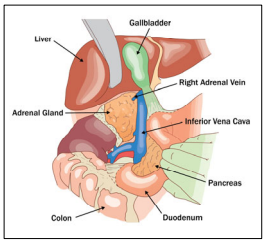
Transabdominal RIGHT adrenalectomy





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Hangge, Johnson, Wang. Shackelford's Atlas, in press

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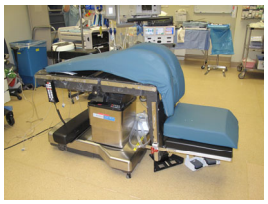
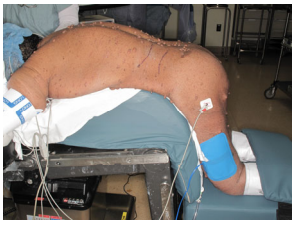
Posterior Retroperitoneoscopic Adrenalectomy





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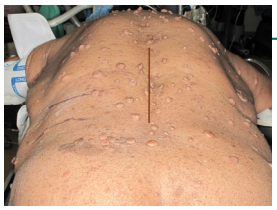

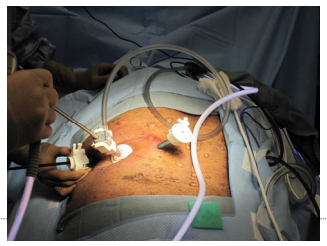

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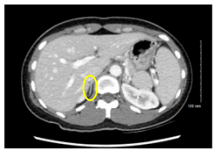
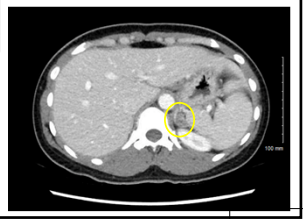
31-year old woman, an Afghan refugee to Wisconsin
History of hypertension for the past two years and was noted to have hypokalemia (as low as 2.2 mEq/L)
Aldosterone: 56.9
Plasma renin activity: <0.1
Adrenal CT: 2.0 cm LEFT adrenal nodule; right adrenal gland is normal
AVS performed, consistent with left-sided gradient

	IVC	Left AV	Right AV #1	Right AV #2
Aldosterone	103	11900	157	161
Cortisol	16.5	418	198	207
Dopamine	<20		<20	25
Epinephrine	10		1290	2144
Norepinephrine	301		704	604
A:C ratio		28.4	0.79	0.77





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Left laparoscopic posterior retroperitoneoscopic adrenalectomy

- Patient with history of hypertension and hypokalemia
- Biochemical evidence of primary aldosteronism
- 2.5 cm left adrenal mass identified on imaging
- Adrenal vein sampling with left-sided gradient and aldosterone excess

22

31-year old woman, an Afghan refugee to Wisconsin
History of hypertension for the past two years and was noted to have hypokalemia (as low as 2.2 mEq/L)
Aldosterone: 56.9
Plasma renin activity: <0.1
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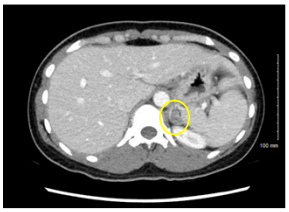

POSTOPERATIVE FOLLOW-UP:
No longer required antihypertensive medications
OR potassium supplementation

Aldosterone: <4.0

23

Which approach – TA vs. PRA

	TA	PRA
Advantages	• Ability to evaluate abdomen • Larger working space for larger tumors • Easier to teach	• Early visualization of the adrenal vein • Less postoperative pain • Improved cosmesis • No need to reposition patient for bilateral adrenalectomy
Disadvantages	• Risk of incisional hernia • Possibility of increased difficulty in patient with previous abdominal operation • Reposition patient for bilateral adrenalectomy	• Smaller workplace • High retroperitoneal insufflation pressures, may increase intraocular pressure and decrease cardiac return
Contraindications	• High likelihood of malignancy	• Inability to tolerate prone position • High likelihood of malignancy

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Which approach – TA vs. PRA

	CONSIDERATIONS
Surgeon Factors	• Which technique does the surgeon know how to do / is the surgeon most comfortable with? • Working relationship with operative team (Anesthesia)
Patient Factors	• Patient BMI (particularly at extremes) • Inability to tolerate prone position • Previous abdominal surgery • Posterior adiposity index • Depth of subcutaneous adipose tissue and distance between ribs and pelvis
Tumor/Disease Characteristics	• Adrenal pathology / type of hormone secretion • Tumor size • Relationship of tumor to renal vasculature, vena cava, or aorta • Anterior/posterior location of the adrenal relative to the kidney

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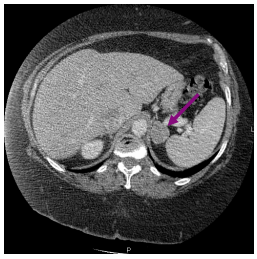
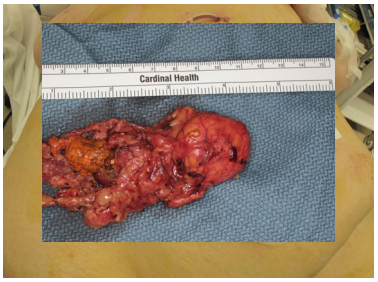
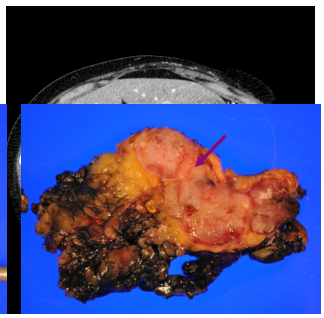
60 year old woman
- Cushing's syndrome
- No previous abdominal surgery
- 3.1 cm left adrenal nodule
- BUT: BMI 47.3





26

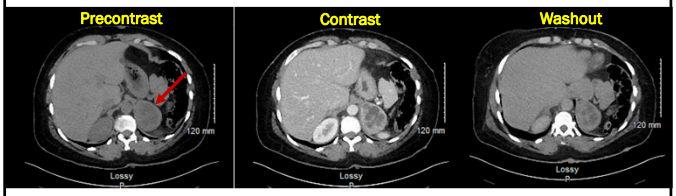
48 year old woman with metastatic breast cancer
- Brain, CNS, lung metastases
- Previous reconstruction (TRAM)
- Previous hysterectomy
- Adrenal nodule: 2.5 cm
  - 1.4 cm one year ago



27

41-year old woman
At referring institution for chest pain – incidental adrenal mass identified
Adrenal CT: 6.7 cm mass, abuts kidney, but no concern for direct extension
Nonenhanced images: 20 HU
Absolute washout: 43%; relative washout: 28%

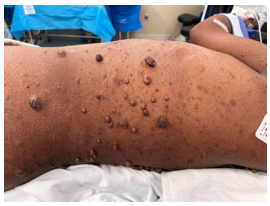
Metanephrines: 10.80 (normal 0.00 – 0.49 nmol/L)
Normetanephrines: 15.6 (normal 0.00 – 0.89 nmol/L)

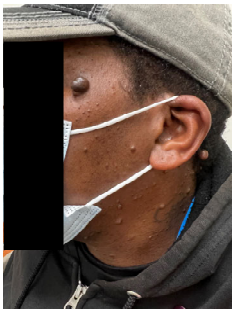


28

41-year old woman
At referring institution for chest pain – incidental adrenal mass identified
Adrenal CT: 6.7 cm mass
Nonenhanced images: 20 HU
Absolute washout: 43%; relative washout: 28%

Metanephrines: 10.80 (normal 0.00 – 0.49 nmol/L)
Normetanephrines: 15.6 (normal 0.00 – 0.89 nmol/L)



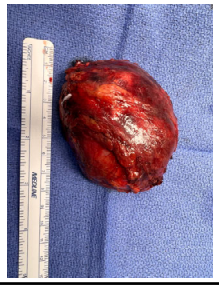


29

41-year old woman
At referring institution for chest pain – incidental adrenal mass identified
Adrenal CT: 6.7 cm mass

Had genetic evaluation – NF1 mutation identified
Currently undergoing evaluation with Neuro-Oncology

Transabdominal adrenalectomy – benign pheochromocytoma



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Robotic adrenalectomy

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Robotic adrenalectomy

Laparoscopic versus robotic adrenalectomy: A comprehensive meta-analysis

Konstantinos P. Economopoulos [a, b, *], Konstantinos S. Mylonas [b, c], Aliki A. Stamou [b, d], Vasileios Theocharidis [b, d], Theodoros N. Sergentanis [b, e], Theodora Psaltopoulou [e], Melanie L. Richards [f]

Table 2
Results of the meta-analyses examining the differences between robotic and laparoscopic adrenalectomy. Bold cells denote statistically significant associations.

Categorical outcomes	n°	Events (rate, %)		OR (95%CI)	Heterogeneity I^2, p-value	Publication bias, p-value
		RA	LA			
Intraoperative complications	5	5.8	5.3	1.20 (0.33–4.38)	14.6%, 0.321	NC
Postoperative complications	8	6.8	9.8	0.69 (0.36–1.31)	0.0%, 0.646	NC
Mortality	3	0.0	2.0	0.42 (0.07–2.72)	0.0%, 0.980	NC
Conversion to laparotomy	7	2.2	5.6	0.51 (0.21–1.23)	0.0%, 0.981	NC
Conversion to laparoscopy/laparotomy	8	3.9	5.3	0.73 (0.32–1.69)	0.0%, 0.566	NC
Continuous outcomes		Events (mean)				
Operative time (minutes)	13	171.80	162.40	**+15.60 (+2.12 to +29.08)**	77.4%, <0.001	0.284
Length of hospital stay (days)	11	2.38	2.88	**−0.40 (−0.64 to −0.17)**	78.3%, <0.001	0.945
Blood loss (ml)	9	45.7	74.8	−9.78 (−22.10 to +2.53)	0.0%, 0.612	NC

[a] Number of study arms; RA: robotic adrenalectomy, LA: laparoscopic adrenalectomy, NC: not calculable; **bold** letters denote statistical significance.

International Journal of Surgery 2017;38:95-104.

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Adoption of Robotic Adrenalectomy: A Two Institution Study of Surgeon Learning Curve

Reagan A. Collins, BA, Tracy S. Wang, MD MPH, Sophie Dream, MD, Carmen C. Solórzano, MD, Colleen M. Kiernan, MD MPH

SSO2023

Background:

- Robotic adrenalectomy (RA) is feasible and safe yet concerns over increased costs, operative times, and the learning curve (LC) have limited its adoption.
- **Aim**: Assess the LC of the transition to RA for two senior (Surgeons A and B) and two junior surgeons (Surgeons C and D)

Methods:

2 institutions 2007-2022

4 surgeons*

457 adrenalectomies

182 (40%) laparoscopic

275 (60%) robotic

*one senior and one junior surgeon at each institution

Figures:

Figure 1. Operative time trends during the transition from laparoscopic adrenalectomy (LA) to RA for senior surgeons (A and B).

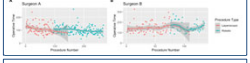
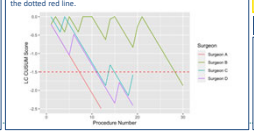


Figure 2. LC trend for RA setting the operative threshold at >180 minutes. Surgeon A achieves proficiency after 8 cases, Surgeon B after 29 cases, Surgeon C after 12 cases, and Surgeon D after 11 cases. The surgeon has overcome the learning curve after crossing the dotted red line.



Results:

RA outcomes (Senior* vs. Junior):

- **Operative Time** (*106 vs. 106 min)
- **Complications** (*7.1% vs. 2.0%)
- **Conversions to Open** (*1% vs. 0%)

Learning curve of 8-29 procedures to achieve operative proficiency for RA

Conclusions:

- Improved outcomes and operative time with RA at 2 high-volume centers with 4 high-volume surgeons.
- Short LC regardless of prior robotic experience in a structured team learning environment with proctoring and mentoring.

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Robotic Adrenalectomy: My thoughts

- ADVANTAGES
  - Aspects of the surgery are less challenging because of the degrees of freedom and articulation of the instruments and robotic arms
    - RIGHT: mobilization of the triangular ligament, superior extension of the adrenal gland
    - LEFT: inferior border of the adrenal gland
  - 3D visualization and magnification
  - Surgeon ergonomics –
- DISADVANTAGE
  - Have to be mindful of the costs of instruments and what instruments you utilize
  - Availability of surgical assistants to allow for teaching at the console
    - Bedside assistants
    - Dual consoles

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Conclusions

- Optimal operative approach will vary based on surgeon and each patient
  - Use the approach you are most comfortable with
  - Be willing to consider use of new technologies!

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MCW Endocrine Surgery

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