Thyroid and Parathyroid Disease

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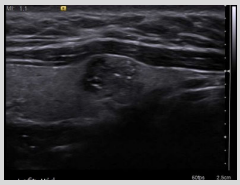
No Disclosures

2

Agenda

- Thyroid nodules and cancer
  - Imaging
  - Indications for FNA
  - Common FNA results
  - Extent of surgery
- PHPT
  - Definition of “Asymptomatic” PHPT
  - Indications for Parathyroidectomy
  - Benefits of Parathyroidectomy



https://commons.wikimedia.org/wiki/File:Papillary_Thyroid_carcinoma_Ultrasound_37F_20160005.jpg

A patient was found to have a possible thyroid nodule on CT scan…

Adapted from DOI:10.1007/s13244-016-0506-5. ISSN 1869-4101

Thyroid nodules are common

Endocrine Condition	Prevalence
Thyroid nodules	30-70%
Metabolic syndrome	35-40%
Obesity	25-50%
Hyperlipidemia	15-20%
Diabetes	5-25%
Osteoporosis	7%

Golden SH., et al. J Clin Endo Metab 2009; 94:1853-78
Mazzaferri M. New England Journal Medicine 1993; 328:553-558
Guth S., et al. Eur J Clin Invest 2009; 39:699-706

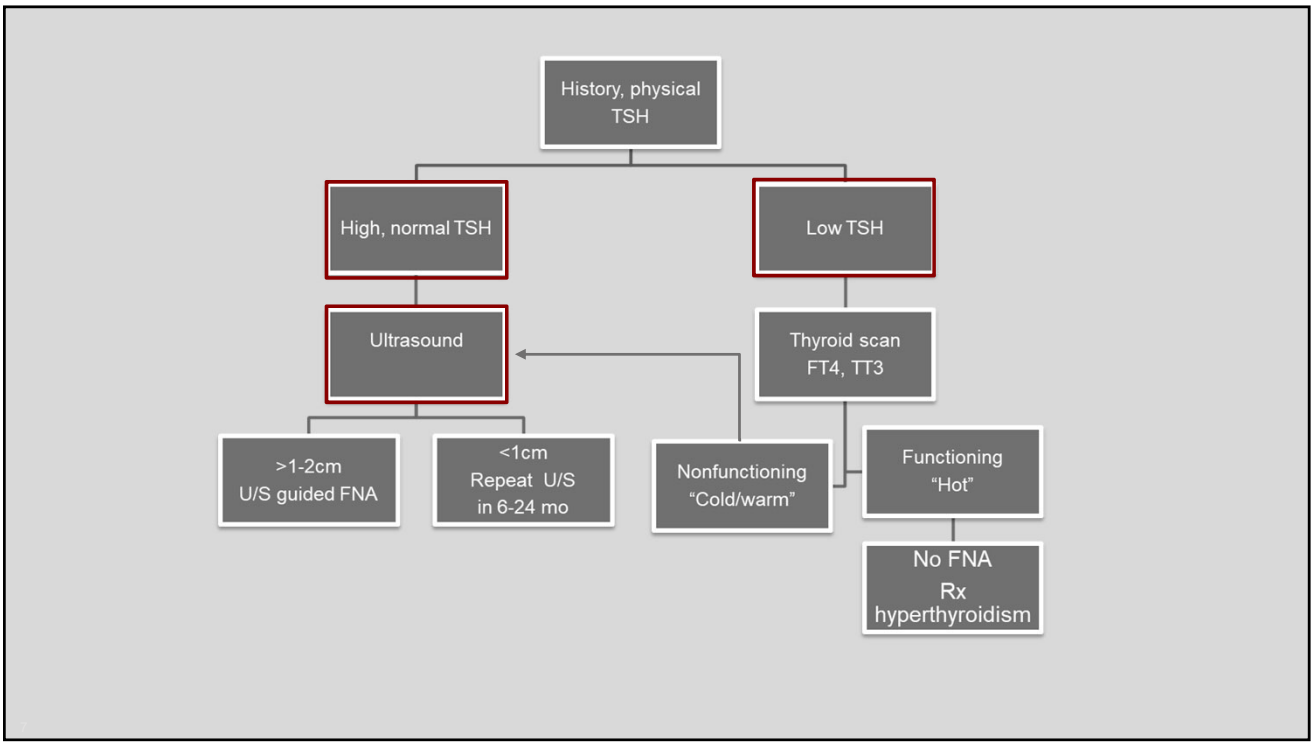
Thyroid nodules - background

- Up to 15% of nodules are cancer

Study	Number of Biopsies	Malignant (%)
Yassa 2007	3589	14%
Theoharis 2009	3207	15%
Yang 2007	4703	7.6%

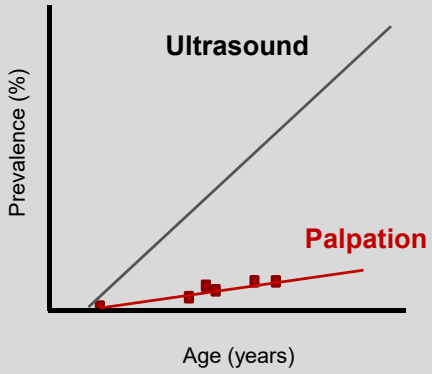
- **Which ones to resect?**

Yassa L., et al. Cancer Cytopathology 2007; 111(6):508-16
Theoharis, C., et al. Thyroid 2009; 19(11):1215-23
Yang J., et al. Cancer Cytopathology 2007; 111(5):306-15



Thyroid nodules - background

- 5% prevalence in general population
- Up to 67% prevalence by ultrasound!
- Increases with age, female sex, iodine deficiency, radiation exposure



Mazzaferri M. New England Journal Medicine 1993; 328:553-558

American Thyroid Association Guidelines

Thyroid sonography should be performed in all patients with known or suspected thyroid nodules.

Strong recommendation, high-quality evidence

AMERICAN THYROID ASSOCIATION
FOUNDED 1923

Haugen 2016 Thyroid

A patient was found to have a possible thyroid nodule on CT scan…

Get TSH and an ultrasound!

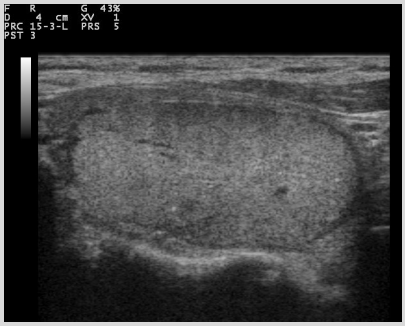
https://commons.wikimedia.org/wiki/File:Ultrasound_Scan_ND_110207151454_1519090.jpg

Evaluation of a New Thyroid Nodule - Imaging

- Ultrasound
  - Most useful, only test needed for most
- Thyroid Scintigraphy
  - Reserved for hyperthyroid work-up
- CT
  - Rarely indicated
  - Substernal extension
  - Extensive nodal disease
  - Suspicion of MTC or ATC

https://commons.wikimedia.org/wiki/File:Neck_ultrasound.jpg

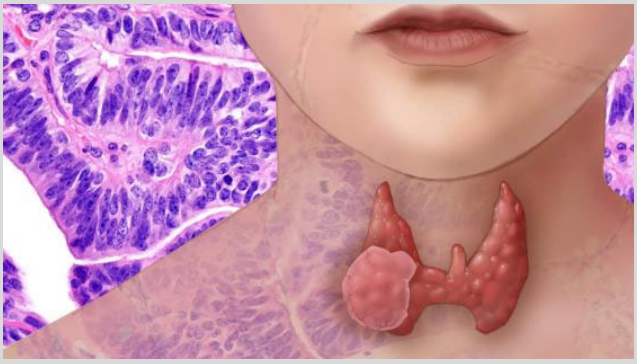
Thyroid ultrasound



- Nodule
  - Size
  - Location
  - Composition
  - Echogenicity
  - Margins
  - Presence of calcifications
  - Taller than wide
  - Vascularity
- Lymph node
  - Size and shape
  - Loss of hilum
  - Calcifications
  - Echogenicity

https://commons.wikimedia.org/wiki/File:Thyroid_ultrasound_110322134324_1353480.jpg

Which nodules should we biopsy?



Increasing malignancy risk with increasing nodule diameter

Nodule diameter, cm	Multivariate analysis, OR (95% CI)	p Value
1.0-1.9	1 (reference)	
2.0-2.9	1.30 (1.14-1.49)	<0.0001
3.0-3.9	1.58 (1.34-1.88)	<0.0001
≥4.0	1.70 (1.42-2.04)	<0.0001

- ATA nodule risk stratification system
- Thyroid Imaging Reporting and Data System (TI-RADS)

Angell T 2019 JCEM 104: 5665-5672

ATA nodule risk stratification

More suspicious

Category	Risk of malignancy	US Description	FNA Threshold
Benign	0%	Simple cyst	n/a
Very low suspicion	<3%	Spongiform, partially cystic with no suspicious features	≥2cm
Low suspicion	5-10%	Isoechoic solid with regular margin Partially cystic with eccentric solid	≥1.5cm
Intermediate suspicion	10-20%	Hypoechoic, solid, regular margin	≥1cm
High suspicion	>70-90%	Hypoechoic, solid with: irregular margins microcalcifications taller than wide extrathyroidal extension suspicious lymph nodes	≥1cm

Smaller size threshhold

Haugen et al 2015 Thyroid

American College of Radiology TI-RADS

Composition		Echogenicity		Shape		Margin		Echogenic foci	
• Cystic	0	• Anechoic	0	• Wider than tall	0	• Smooth	0	• None	0
• Spongiform	0	• Hyper/iso	1	• Taller than wide	3	• Ill-defined	0	• Comet-tails	0
• Mixed	1	• Hypo	2			• Lobulated/irregular	2	• Macro	1
• Solid	2	• Very hypo	3			• ETE	3	• Peripheral/rim	2
								• Punctate	3

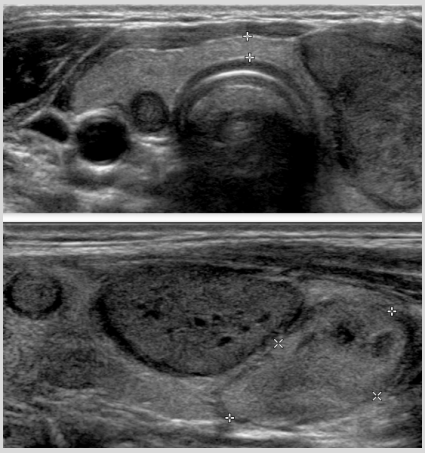
Add points from all categories to determine TIRADS level

0 points	2 points	3 points	4-6 points	≥7 points
TR1 Benign No FNA	**TR2** Not suspicious No FNA	**TR3** Mildly suspicious FNA ≥ 2.5cm Follow ≥ 1.5cm	**TR4** Moderately suspicious FNA ≥ 1.5cm Follow ≥ 1.0cm	**TR5** Highly suspicious FNA ≥ 1.0cm Follow ≥ 0.5cm

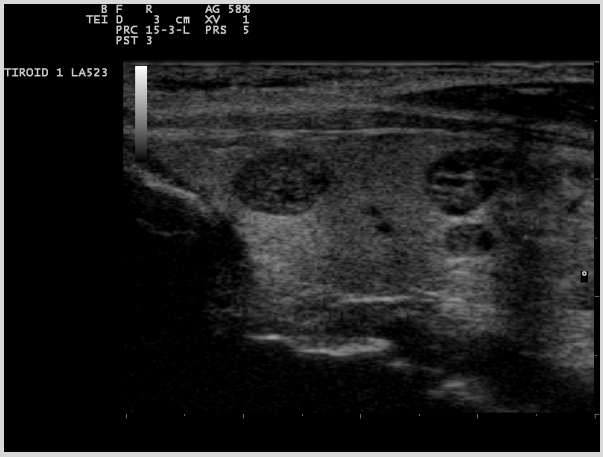
Tessler et al 2017 J Am Coll Radiol 14: 587-95

Risk stratification of thyroid nodules

- All reduce unnecessary biopsies
- High concordance rates for classifying nodules as intermediate or high suspicion



What about multiple nodules?



https://commons.wikimedia.org/wiki/File:Ultrasound_Scan_ND_0107091941_0928470.png

Missed cancer with biopsy of only largest nodule

- 1985 patients with FNA of 3483 nodules

	Number of nodules >1cm		
FNA performed on	**2 nodules (n = 73)**	**3 nodules (n = 27)**	**≥ 4 nodules (n = 20)**
Largest nodule	86.3%	51.8%	55%
Largest 2 nodules	100%	81.5%	85%
Largest 3 nodules		100	95%
Largest 4 nodules			100%
Missed cancers when only 1 nodule is biopsied	**13.7%**	**48.2%**	**45%**

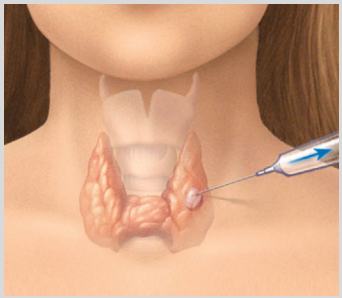
Frates et al 2006 JCEM 91: 3411-17

Considerations for FNA

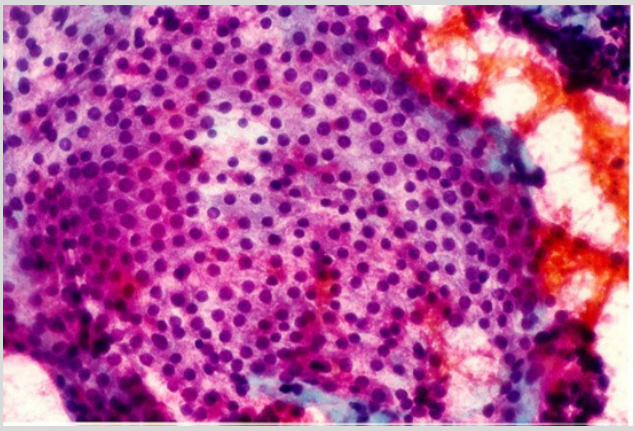
- Lower threshold for FNA
  - Concerning clinical features
  - PET avid
  - Young age
- Higher threshold for FNA
  - Older age without concerning clinical features
  - Significant comorbidities

Follow-Up for Nodules Not Meeting Initial Criteria for FNA

- US in 6-12 months for high suspicion nodules
- US in 12-24 months for low/intermediate suspicion nodules
- US >24 months if at all for very low suspicion nodules/cystic lesions



What happens after FNA?



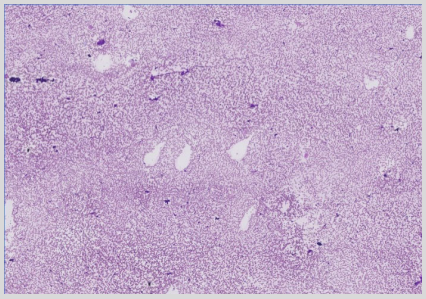
FNA Results

	Diagnostic Category	Risk of Malignancy (%)
	Nondiagnostic or Unsatisfactory	1-4
	Benign	0-3%
Indeterminate	Atypia of Undetermined Significance *or* Follicular Lesion of Undetermined Significance	~ 5-15%**
Indeterminate	Follicular Neoplasm *or* Suspicious for a Follicular Neoplasm	15-30%
Indeterminate	Suspicious for Malignancy	60-75%
	Malignant	97-99%

← Varies by institution

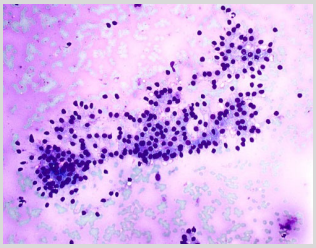
FNA - non-diagnostic result

- NO interpretation can be made
- Incidence varies based on technique and experience (5-15%)
- Repeated in 6 weeks
- If repeated biopsies are non-diagnostic consider surgical excision



Hypocellular specimen

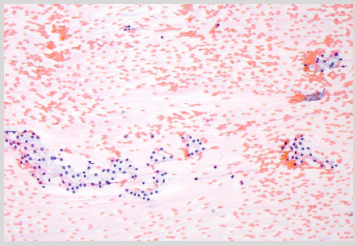
FNA - benign



- High suspicion US pattern
  - Repeat US and FNA in 6-12 months
- Low to Intermediate suspicion US pattern
  - Repeat US in 12-24 months
  - Repeat FNA if…
    - If 20% growth in 2 dimensions, 50% increase in nodule volume or development of new suspicious sonographic features
- Very Low suspicion US pattern
  - Utility of repeat US limited, no follow-up necessary
  - If US repeated, should be in ≥ 24 months

Haugen et al 2015 Thyroid

FNA - benign



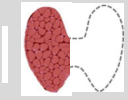
- 2nd benign cytology and no growth, US every 3-5 years
- Growing nodule should be monitored
- Surgery if…
  - Large (> 4 cm)
  - Compressive symptoms
  - Other clinical concerns

Haugen et al 2015 Thyroid

FNA – indeterminate

- Molecular testing
  - Genomic and transcriptional profiles that identify risk of malignancy
  - Good option for average patient
- Diagnostic lobectomy
  - Consider if your institution has high malignancy rate for indeterminate FNA biopsy
  - Consider in patients with increased risk

Molecular testing



Lobectomy

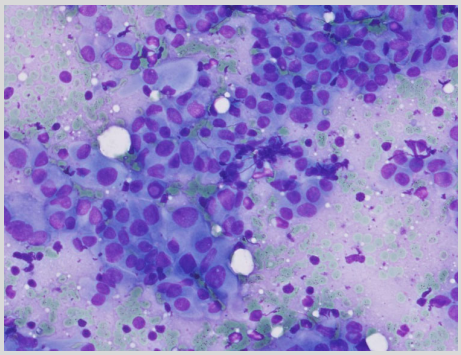
Molecular testing

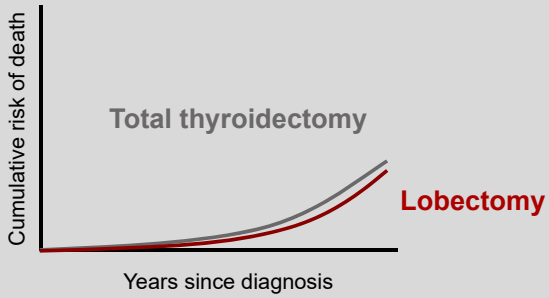
- Afirma
  - Previously “rule-out”
  - Benign >96% NPV, safe to leave in
  - Xpression Atlas → extent of surgery
- Thyroseq
  - Previously “rule-in”
  - v3 is similar to Afirma

https://commons.wikimedia.org/wiki/File:Preparation_of_the_RT-PCR_Reaction_(05811009)_(49869473991).jpg

FNA – malignant or suspicious for malignancy

- Active surveillance vs lobectomy (≤ 1cm, very low risk)
- Lobectomy vs total thyroidectomy (<4cm, low risk)
- Total thyroidectomy and nodal dissection based on US

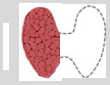




Welch and Doherty 2018 NEJM 379: 310-312

Extent of Initial Surgery

Thyroid lobectomy

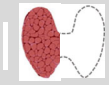


- < 4cm
- No extrathyroidal extension
- No suspicious lymph nodes

Welch and Doherty 2018 NEJM 379: 310-312

Confirmation of malignancy

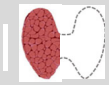
- Low risk well-differentiated thyroid cancer
  - Lobectomy is sufficient
  - RAI is not necessary



- Intermediate/high risk well-differentiated thyroid cancer
  - Completion thyroidectomy should be considered
  - RAI should be considered

Welch and Doherty 2018 NEJM 379: 310-312

Why consider thyroid lobectomy?

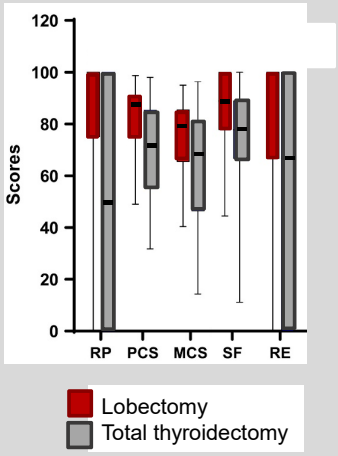


Advantages

- Decreased need for levothyroxine
- No risk of hypoparathyroidism
- Improved quality of life
  - Role physical (RP)
  - Social function (SF)
  - Role emotional (RE)
  - Physical component summary (PCS)
  - Mental component summary (MCS)

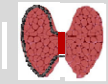
Disadvantages

- Potential completion thyroidectomy
- Difficulty with laboratory surveillance (Tg)



Lan Y., 2021, Cancer Medicine 10:1989-2002

Active surveillance

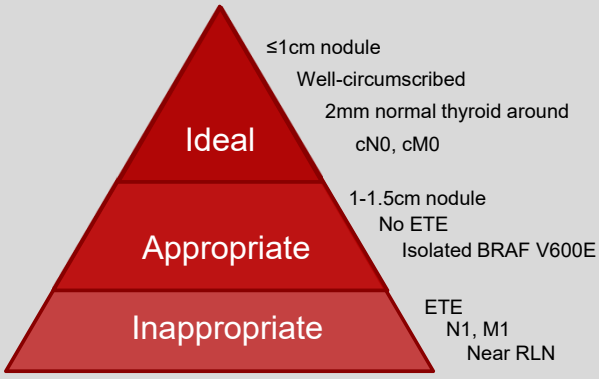


Indications for consideration

- Low risk PTC ≤ 10 mm
- Lack of high-risk features such as
  - Adjacent to RLN
  - Invasion
  - Clinically apparent LN
  - Distant metastases

Indications for surgery after AS

- Tumor diameter reaches 13 mm
- Appearance in LN metastases
- Change in patient preference
- Other thyroid/parathyroid disease requiring surgery



Sugitani I., 2021, Thyroid 21:183-192

Take Home

- Lower threshold for FNA in patients with higher risk of thyroid cancer
- Consider forgoing FNA in patients with significant comorbidities or poor prognosis cancer
- FNA cytopathology demonstrates significant variability which dictates management
- Consideration should be given for less aggressive treatment of low risk well-differentiated thyroid cancer

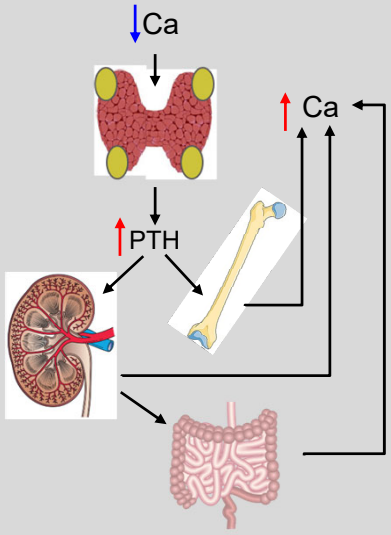
Primary hyperparathyroidism

And other things!

35

Background

- One or more of the parathyroid glands inappropriately makes PTH
- Prevalence 1% general population
  - 2-3.4% postmenopausal women
  - Underdiagnosed and undertreated
- Clinical diagnosis based solely on labs
  - Hypercalcemia with elevated or inappropriately normal PTH
  - Normocalcemia with elevated PTH



SMART-Servier Medical Art
http://open.umich.edu/education/med/resources/second-look-series/materials

Background

- 4 parathyroid glands
- 85% single adenoma
- 15% four-gland hyperplasia

Diagnosis

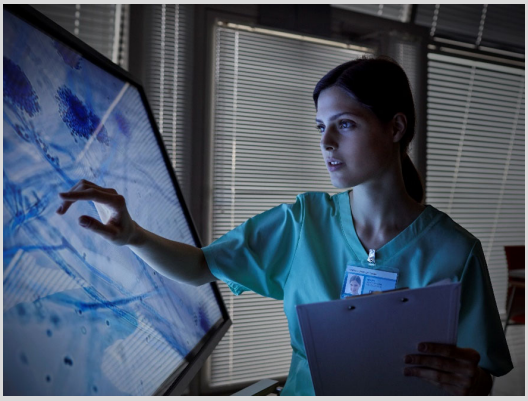
- Who should be tested?
  - Hypercalcemia
  - Osteoporosis
  - Kidney stones
- Labs
  - Calcium
  - PTH
  - 25-OH Vitamin D
  - Creatinine
  - Urine studies – Ca AND Cr

Diagnosis

- High/normal serum calcium
- Inappropriate (high/normal) parathyroid hormone
- Absence of secondary causes
  - Thiazide diuretics
  - Lithium
  - Chronic kidney disease
  - Vitamin D deficiency

Diagnosis

Finding	PHPT	FHH
Lifelong hypercalcemia	No	Yes
PTH	**High/normal**	**Normal**
Calcium	**High/normal**	**High**
25-OH Vit D	**Normal**	**Normal**
24h urine calcium	High/normal	Low
Calcium clearance	>0.02	<0.01



↑↑ Ca + ↑↑ PTH + nl Vit D + past normal Ca

Igsogna, NEJM 2018.

Diagnosis

Patients with hypercalcemia, osteoporosis, kidney stones

↓

Ca, PTH, Vit D, Cr

↑↑Ca, ↑PTH, nl Vit D

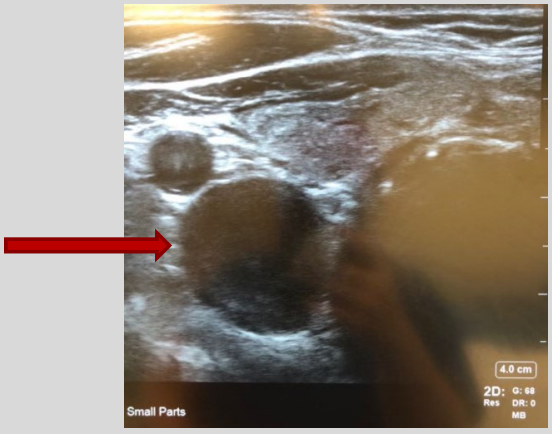
↓

Previous normal Ca?

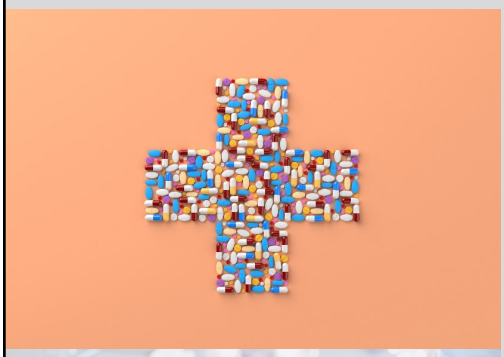
↓ Yes

PHPT

Imaging is not necessary for diagnosis



Usually negative in 4 gland hyperplasia



You made the diagnosis!

Now what?

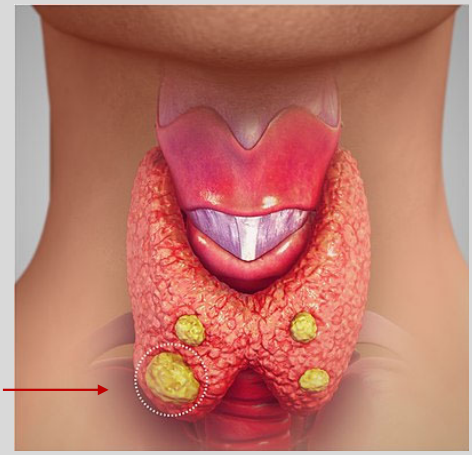
Treatment options

1. Observation
   - 29-62% chance of progression at 10 yrs
   - Hydration, normal calcium intake

2. Medical Therapy
   - Bisphosphonates – increased BMD *AND* fractures
   - Cinacalcet – improves hypercalcemia, but not BMD/fracture/QoL, may worsen kidney stones, $$$

3. Surgery
   - Only definitive treatment : 95-98% cure rate

Khan, Osteo Int. 2016.

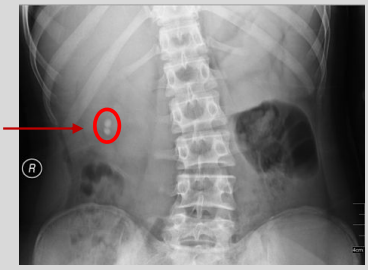


Adapted from https://www.scientificanimations.com/wiki-images/

Who should get parathyroidectomy?

NIH Guidelines for Parathyroidectomy

- Serum Calcium 1.0 mg/dl above normal
- Renal Criteria
  - Creatinine clearance <60 ml/min
  - 24-h urine calcium >400 mg/dl
  - Presence of nephrolithiasis or nephrocalcinosis
- Bone involvement
  - T score <-2.5 at lumbar spine, femoral neck, or distal 1/3rd radius
  - Vertebral fracture by imaging
- Age <50

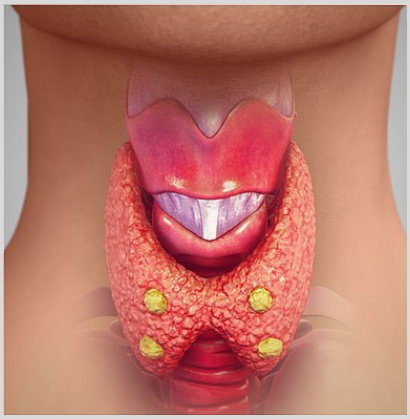


Bilezikian, J Endocrinol Metab 2009.
Caillard, Surgery 2007.
Eigelberger, Ann Surg 2004.

https://commons.wikimedia.org/wiki/File:Medical_X-Ray_imaging_BNP02_nevit.jpg
https://commons.wikimedia.org/wiki/File:Balloon_kyphoplasty_for_osteoporotic_vertebral_fracture.jpg

NIH Guidelines for Parathyroidectomy

- Ignores patients with subjective symptoms, age >50, and those with mild disease
- >90% of “asymptomatic” patients have significant symptoms that are likely related to PHPT



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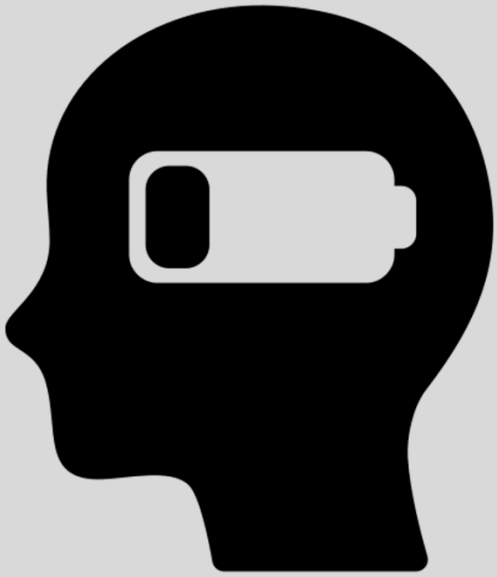


Symptomatic improvement after parathyroidectomy

https://thenounproject.com/victorulerz/collection/mental-health-and-disorder-outline/

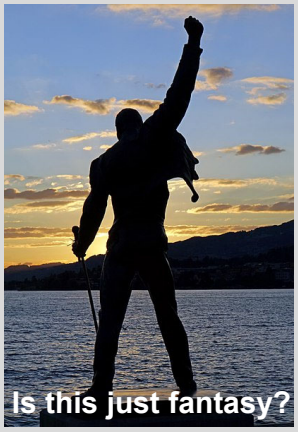
60 year-old woman with "asymptomatic" PHPT

- No kidney stones or fractures
- +Fatigue
- +Difficulty sleeping
- +Headaches
- +Difficulty concentrating
- +Irritability
- +Depression
- +Bone pain

Bilezikian. J Endocrinol Metab 2009.
Caillard. Surgery 2007.
Eigelberger. Ann Surg 2004.

60 year-old woman with "asymptomatic" PHPT

Lab	Value
Serum Calcium	11.0 (normal 8.5-10.5)
PTH	139 (normal 10-65)
Creatinine	0.97 (0.6-1.2)
Creatinine Clearance	>60
25-OH Vitamin D	28.6 (normal 30-100)
24-hour Urine Calcium	296 (normal 100-300)
T-score	-1.2



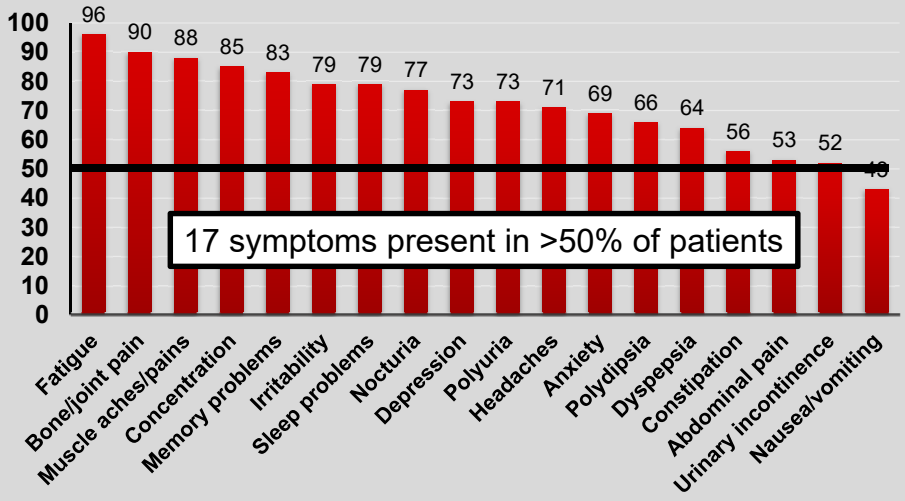
https://commons.wikimedia.org/wiki/File:Switzerland-03044_-_Freddie_Mercury_(Blue_Hour)_(22943513573).jpg

https://pixabay.com/en/woman-old-age-retirement-home-65675/ archive copy

"Primary hyperparathyroidism is like premature aging. The symptoms are what you expect to happen with older age – it just happens sooner than you think it should."

- Orlo Clark, M.D

Symptoms in patients with PHPT



No patient in this cohort was truly asymptomatic!

Murray, Surgery 2013.

Does calcium level predict symptoms?

Hypercalcemia does not predict symptoms

No difference	Increased with Ca <11.2	Increased with Ca ≥11.2
Fatigue	Bone / joint pain	Kidney stones
Weakness	Depression	
Difficulty concentrating	Constipation	
Memory problems		
Anxiety		
Abdominal pain		
Nausea/Vomiting		
Heartburn		
Polyuria/Nocturia		

Certain symptoms are more common with milder hypercalcemia

Bargren, JACS 2011.

Do patients who meet NIH guidelines have more symptom improvement after parathyroidectomy?

Non-NIH patients also see improvement in symptoms

No difference in symptom improvement between NIH and non-NIH

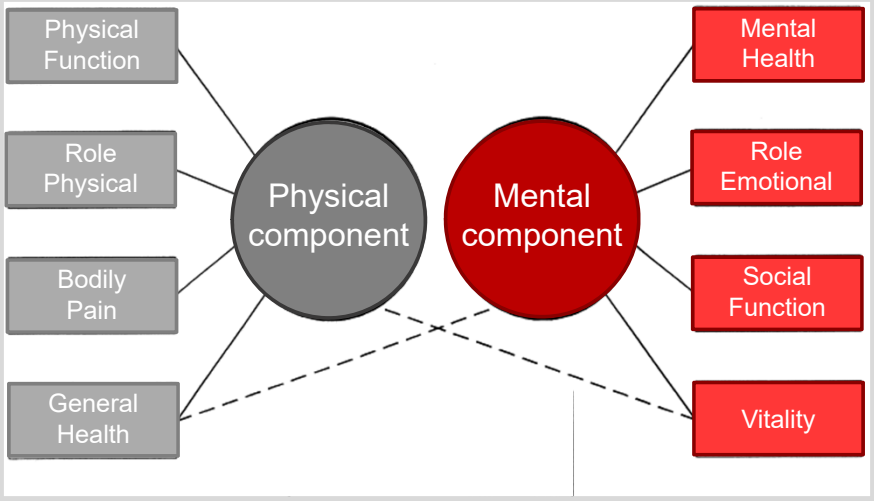
Fatigue	Constipation
Muscle aches	Dyspepsia
Back pain	Depression
Weakness	Memory loss
Polydipsia	Nausea

50% of patients have improvement in 10 symptoms!

Eigelberger, Ann Surg 2004.

Does parathyroidectomy improve quality of life?

SF-36 quality of life assessment



Parathyroidectomy Improves Quality of Life

Improvement at 6 months
Mental health

Improvements at 12 months
Mental Health
Bodily pain
Physical role function
General health

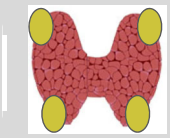
Ambrogini, J Clin Endocrinol Metab 2007.

Too good to be true?

http://www.marines.mil/unit/mcascherrypoint/PublishingImages/2009/IMG_8542.JPG

Symptomatic improvement is not a placebo effect

VS.



Improved with parathyroidectomy	No difference
Fatigue	Constipation
Muscle aches	Dyspepsia
Back pain	
Polydipsia	
Polyuria/Nocturia	
Depression	
Memory loss	
Nausea	
Polyuria/Nocturia	

Eigelberger, Ann Surg 2004.

Bone disease improvement after parathyroidectomy

Wellcome Images

Parathyroidectomy improves BMD in osteoporotic patients

	Parathyroidectomy	Observation	
Lumbar spine	5% increase in BMD	2% decrease in BMD	P<0.01
Total hip	2% increase in BMD	2% decrease in BMD	P<0.01

Ambrogini, J Clin Endocrinol Metab 2007.

https://commons.wikimedia.org/wiki/File:Ganzk%C3%B6rperDEXAscan2.jpg

What about patients without osteoporosis?

Parathyroidectomy improves BMD in normal patients

	Parathyroidectomy	Observation	
Lumbar spine	3.5% increase in BMD	1% decrease in BMD	P<0.01
Total hip	3.5% increase in BMD	1.5% decrease in BMD	P<0.01

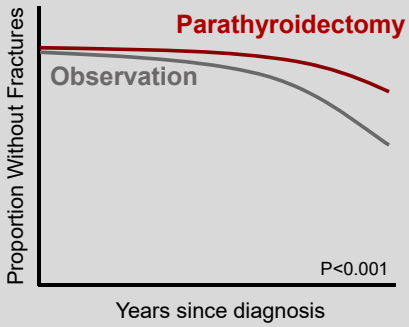
Ambrogini, J Clin Endocrinol Metab 2007.

https://commons.wikimedia.org/wiki/File:Ganzk%C3%B6rperDEXAscan2.jpg

https://commons.wikimedia.org/wiki/File:Fracture_both_bones_of_the_left_arm.jpg

Does parathyroidectomy improve risk of fractures?

Parathyroidectomy improves fracture risk



At 10 yrs 41% have fx with observation vs 27% with PTX

VanderWalde, Arch Surg 2006.

Fracture risk is lowest after parathyroidectomy

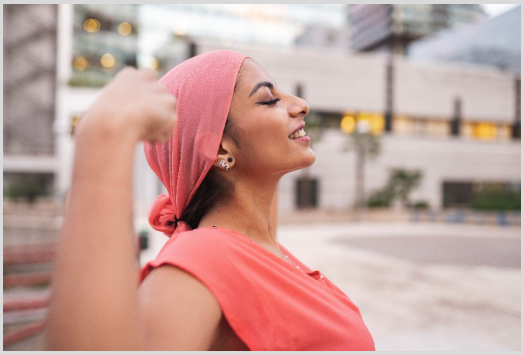
	Parathyroidectomy	Observation	Bisphosphonates
Hip fracture			
2-year	-2.8 events	10.2	+5.9
5-year	-16.0	24.9	+14.0
10-year	-35.5	55.9	+29.7

- Risk for any fracture is 3-10x higher
- Parathyroidectomy is associated with ↓ fracture risk
- Bisphosphonates is associated with ↑ fracture risk

Yeh. Ann Int Med 2016.

Bone health after parathyroidectomy

- BMD improves after parathyroidectomy
- Fracture risk improves after parathyroidectomy
- Bisphosphonates worsen fracture risk

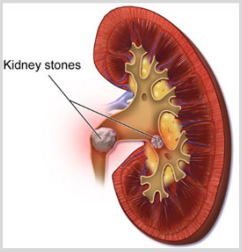


Medical gallery of Blausen Medical 2014

Renal, cardiovascular, and mortality benefits after parathyroidectomy

Decreased kidney stones after parathyroidectomy

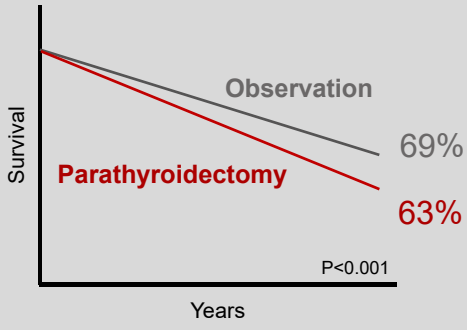
	Before Parathyroidectomy	After Parathyroidectomy	
Incidence rate ratio of stones	40.6%	16.9%	P<0.01



Medical gallery of Blausen Medical 2014

Mollerup, BMJ 2002.

Improved mortality after parathyroidectomy

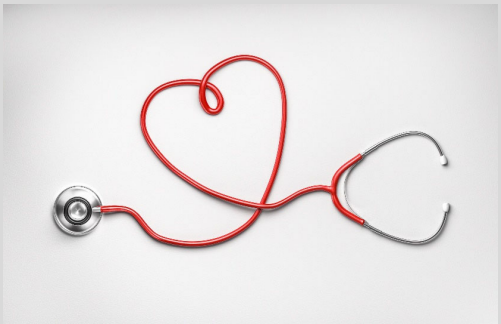


Obsevation = hazard ratio of 1.54, which is similar to untreated HTN!

Vestergaard, BMJ 2003.

Renal, CV health after parathyroidectomy

- Risk of kidney stones is reduced after parathyroidectomy
- Risk of atherosclerotic CV disease is reduced after parathyroidectomy
- Survival is improved



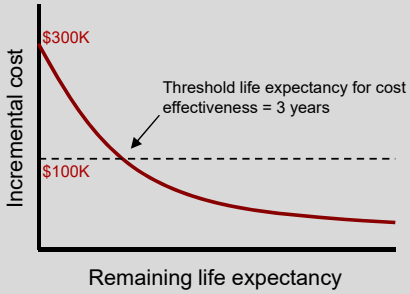
Disease progression in 5 years

Disease manifestation	% (n=6182)
Osteoporosis	12%
Nephrolithiasis	3%
Decrease in renal function	15%
Hypercalciuria	2%

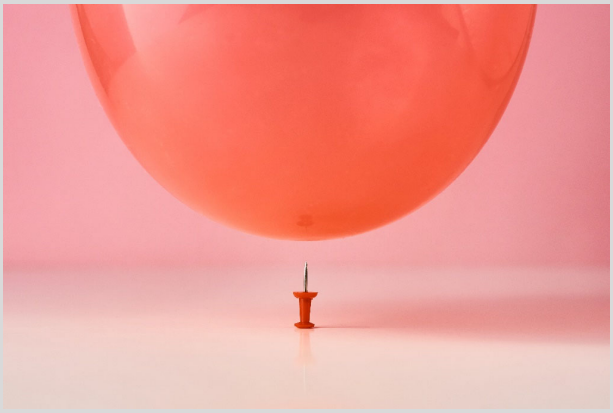
The majority of patients will meet criteria for parathyroidectomy in 5 years

Rubin JCEM 2008
Assadipour. Surgery 2019.

Parathyroidectomy is cost-effective



Zanocco. Surgery 2017.



Isn't surgery risky?

Surgical treatment

- Decision to operate is based on labs
  - Positive imaging is NOT required for surgery
  - Negative imaging in 20-30% of patients
  - Imaging can guide surgical plan
- Goals at surgery
  - Distinguish between adenoma vs. multi-gland disease
  - Clear neck at first operation

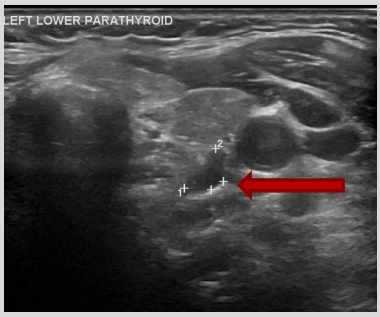
Operations

- Focused parathyroidectomy
- Four gland exploration

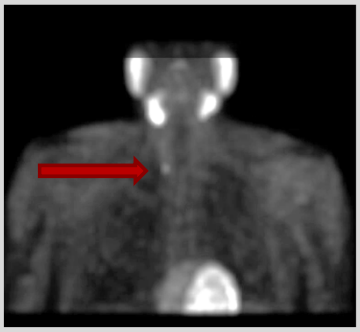
Focused parathyroidectomy

- Pre-operative localization
- Intra-operative PTH to confirm cure
  - Half-life is 4 minutes
- Advantages
  - Small incision size (2-3 cm)
  - Decreased operative time
  - Done as an outpatient
  - Less transient hypocalcemia

Preoperative localization



Ultrasound



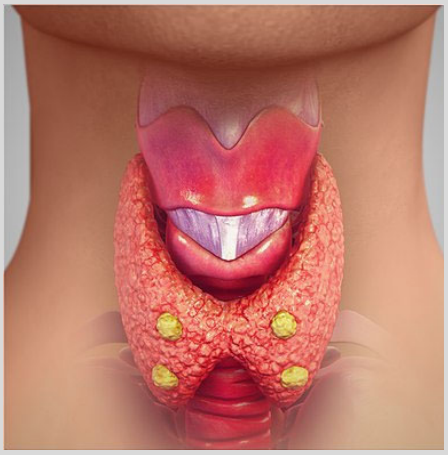
Sestamibi

4D CT

What if preoperative localization is negative?

Four gland exploration

- All parathyroids are identified
- Only abnormal parathyroids are resected
  - 3.5 glands resected for 4 gland hyperplasia
- >95% success when performed by an experienced parathyroid surgeon
- Done as an outpatient



Adapted from
https://www.scientificanimations.com/wiki-images/

Complications

- Failure to cure 1-5%
- Transient hypocalcemia
- Less than 1%
  - Hematoma
  - Recurrent laryngeal nerve injury
  - Wound infection
- Complications in elderly 5.1%
  - Cardiovascular complications 0.003%
  - Recurrent laryngeal nerve injury 0.005%

Adapted from https://commons.wikimedia.org/wiki/File:Risk_menecment.jpg

Morris, The Oncologist, 2010.

60 year-old woman with “asymptomatic” PHPT

- Underwent parathyroidectomy
  - 2-3 cm incision
  - Resection left inferior parathyroid
- Baseline PTH 200
- Post excision PTH 16
- Discharged on POD0

60 year-old woman with "asymptomatic" PHPT

"…improved recall of memory"

"It's the first time I can walk up the stairs without having to stop because of pain."

"I not only have a much better quality of life, I also have the gift of being able to be me."

"I can fall asleep faster & wake up not stiff"

"I am amazed I don't have to search for my words to communicate my ideas to others."

Summary and conclusions

- PHPT is common
- Most patients are symptomatic
- Parathyroidectomy can:
  - Improve symptoms and QoL
  - Increase BMD/decrease fracture risk
  - Decrease cardiovascular risk and overall mortality
- Complication rates for parathyroidectomy are low
- Vast majority of patients benefit from parathyroidectomy

PHPT

And other things!