



Thyroid and Parathyroid Disease

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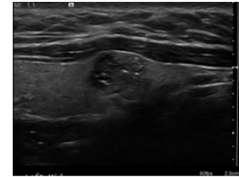
MedNet21
Center for Continuing Medical Education

 **THE OHIO STATE UNIVERSITY**
WEXNER MEDICAL CENTER

No Disclosures

Agenda

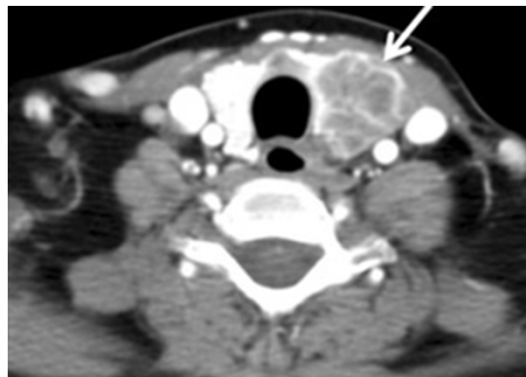
- Thyroid nodules and cancer
 - Imaging
 - Indications for FNA
 - Common FNA results
 - Extent of surgery
- PHPT
 - Definition of “Asymptomatic” PHPT
 - Indications for Parathyroidectomy
 - Benefits of Parathyroidectomy



BAD
to the
BONE

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%

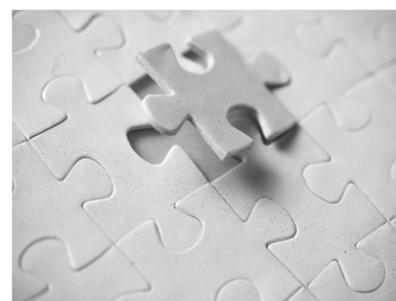
Golden SH., et al. J Clin Endo Metab 2009; 94:1853-78
 Mazzaferri M. New England Journal Medicine 1993; 328:553-558
 Guth S., et al. Eur J Clin Invest 2009; 39:699-706

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Thyroid nodules - background

- Up to 15% of nodules are cancer

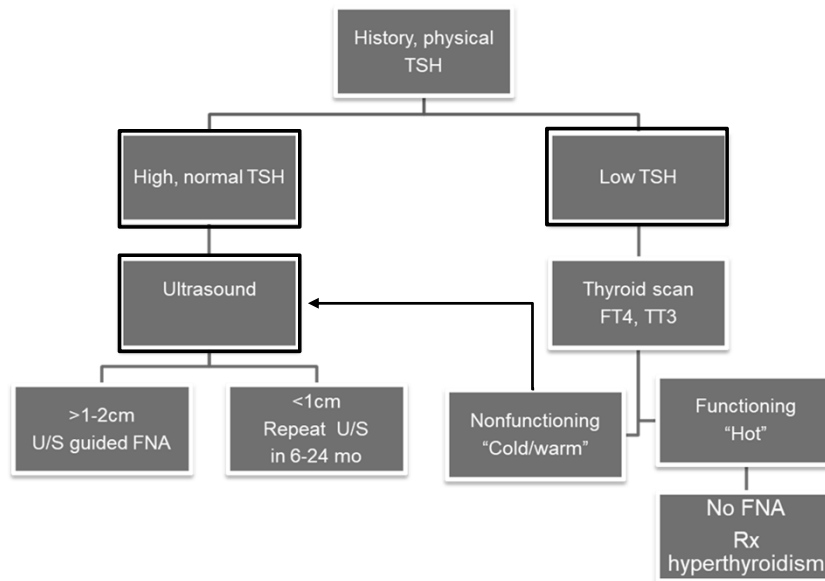
Study	Number of Biopsies	Malignant (%)
Yassa 2007	3589	14%
Theoharis 2009	3207	15%
Yang 2007	4703	7.6%



- 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

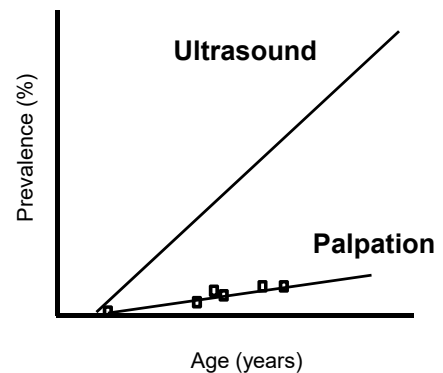
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Thyroid nodules - background

- 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

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American Thyroid Association Guidelines

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

Strong recommendation, high-quality evidence



Haugen 2016 Thyroid

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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

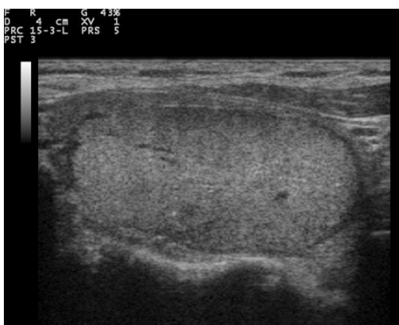
Evaluation of a New Thyroid Nodule - Imaging

- 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

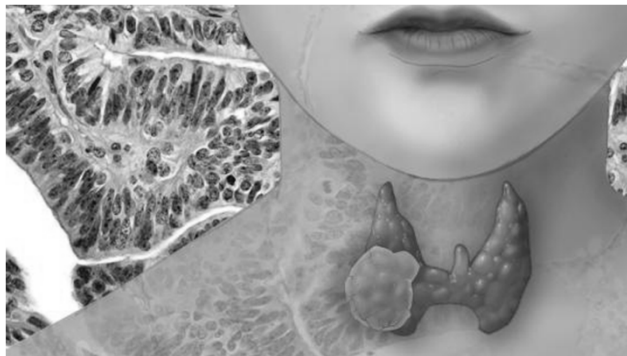
Thyroid ultrasound



- 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

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

Haugen et al 2015 Thyroid

American College of Radiology TI-RADS

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

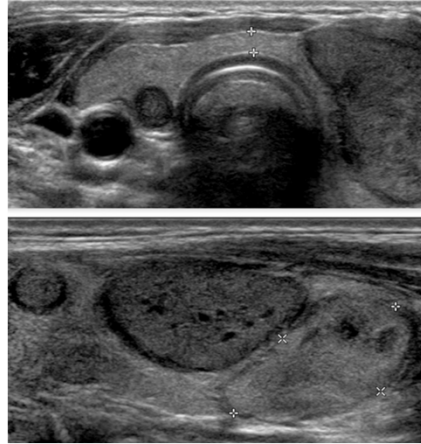
Add points from all categories to determine TIRADS level

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

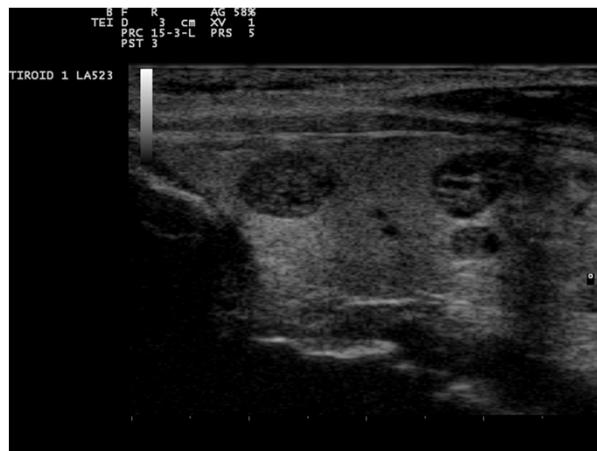
Tessler et al 2017 J Am Coll Radiol 14: 587-95

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

FNA performed on	Number of nodules >1cm		
	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

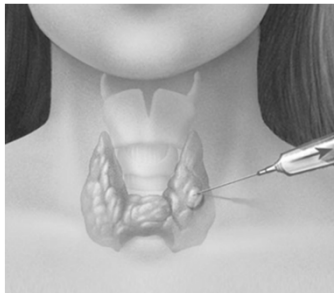
Considerations for FNA

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

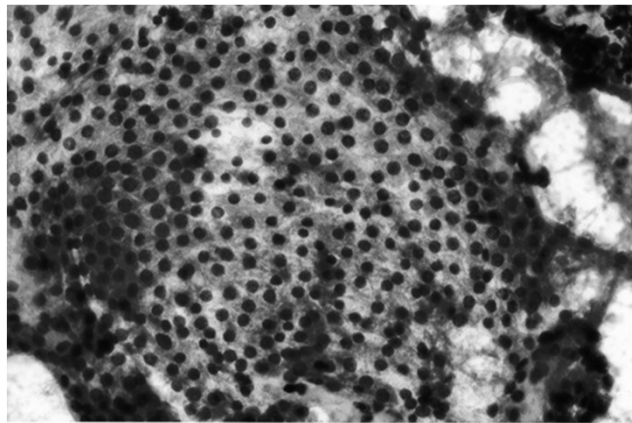


Follow-Up for Nodules Not Meeting Initial Criteria for FNA

- 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 (%)	← Varies by institution
Nondiagnostic or Unsatisfactory		1-4	
Benign		0-3%	
Indeterminate	Atypia of Undetermined Significance <u>or</u> Follicular Lesion of Undetermined Significance	~ 5-15%**	
	Follicular Neoplasm <u>or</u> Suspicious for a Follicular Neoplasm	15-30%	
	Suspicious for Malignancy	60-75%	
Malignant		97-99%	

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FNA - non-diagnostic result

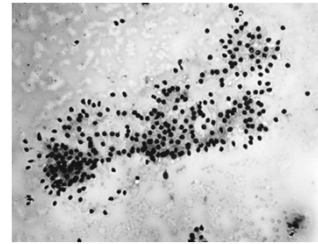
- NO interpretation can be made
- Incidence varies based on technique and experience (5-15%)
- Repeated in 6 weeks
- If repeated biopsies are non-diagnostic consider surgical excision



Hypocellular specimen

FNA - benign

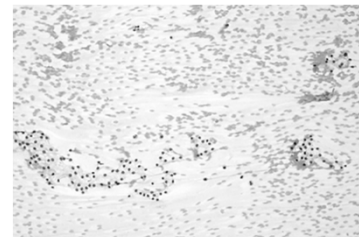
- High suspicion US pattern
 - Repeat US and FNA in 6-12 months
- Low to Intermediate suspicion US pattern
 - Repeat US in 12-24 months
 - Repeat FNA if...
 - If 20% growth in 2 dimensions, 50% increase in nodule volume or development of new suspicious sonographic features
- Very Low suspicion US pattern
 - 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



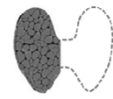
Haugen et al 2015 Thyroid

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

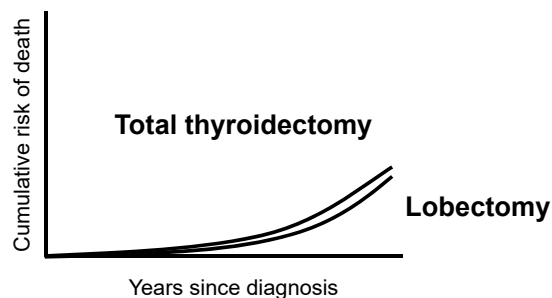
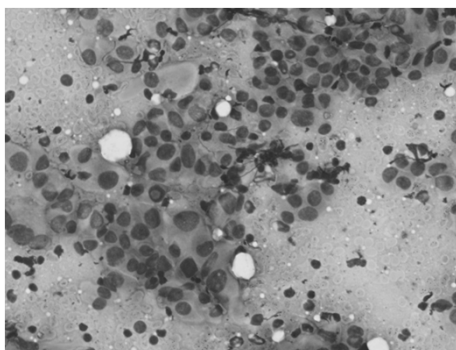
- Afirma
 - Previously “rule-out”
 - Benign >96% NPV, safe to leave in
 - Xpression Atlas → extent of surgery
- Thyroseq
 - Previously “rule-in”
 - v3 is similar to Afirma



[https://commons.wikimedia.org/wiki/File:Preparation_of_the_RT-PCR_Reaction_\(05811009\)_\(49869473991\).jpg](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 ($\leq 1\text{cm}$, very low risk)
- Lobectomy vs total thyroidectomy ($<4\text{cm}$, low risk)
- Total thyroidectomy and nodal dissection based on US



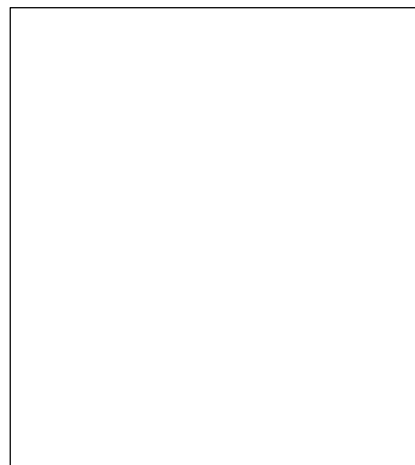
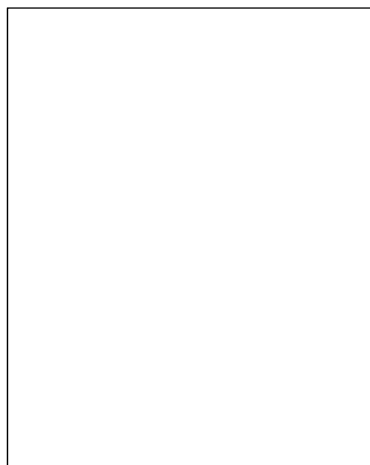
Welch and Doherty 2018 NEJM 379: 310-312

Extent of Initial Surgery

Thyroid lobectomy



- $< 4\text{cm}$
- 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

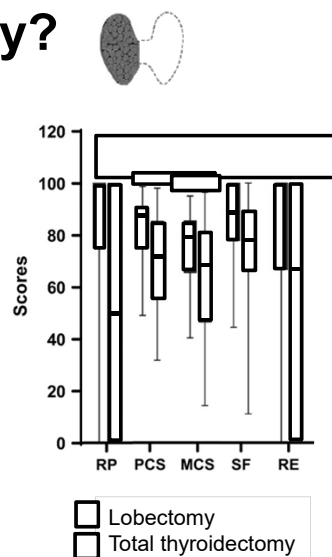
Why consider thyroid lobectomy?

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

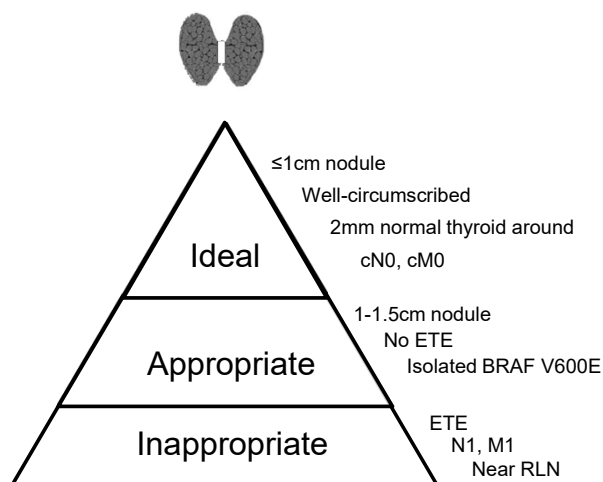
Active surveillance

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

BAD

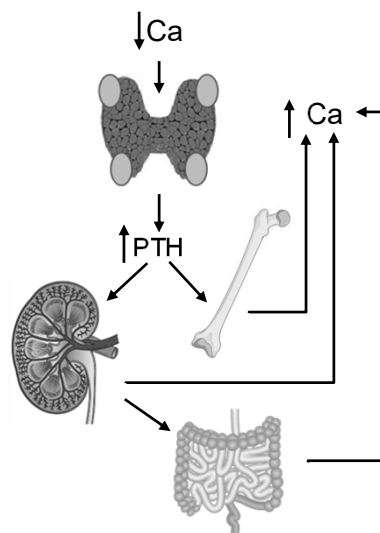
BONE

And other things!

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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>

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Background

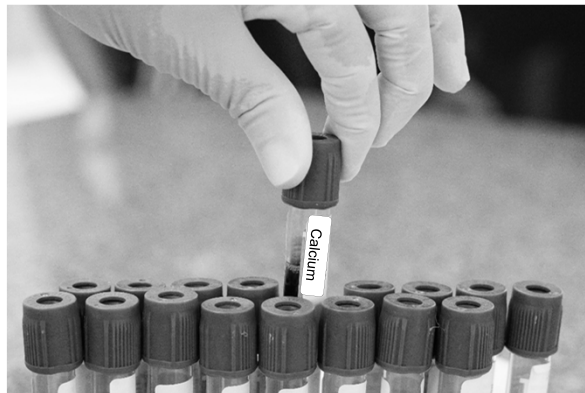
- 4 parathyroid glands
- 85% single adenoma
- 15% four-gland hyperplasia



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Diagnosis

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



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Diagnosis

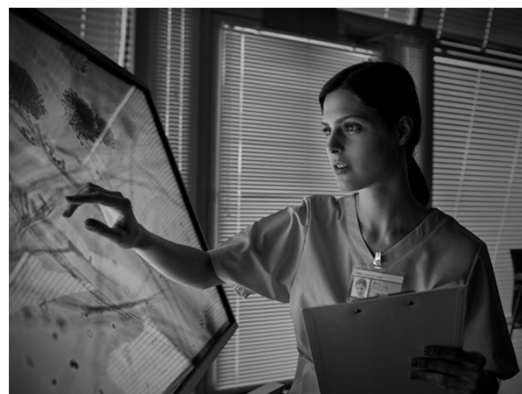
- High/normal serum calcium
- Inappropriate (high/normal) parathyroid hormone
- Absence of secondary causes
 - Thiazide diuretics
 - Lithium
 - Chronic kidney disease
 - Vitamin D deficiency



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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

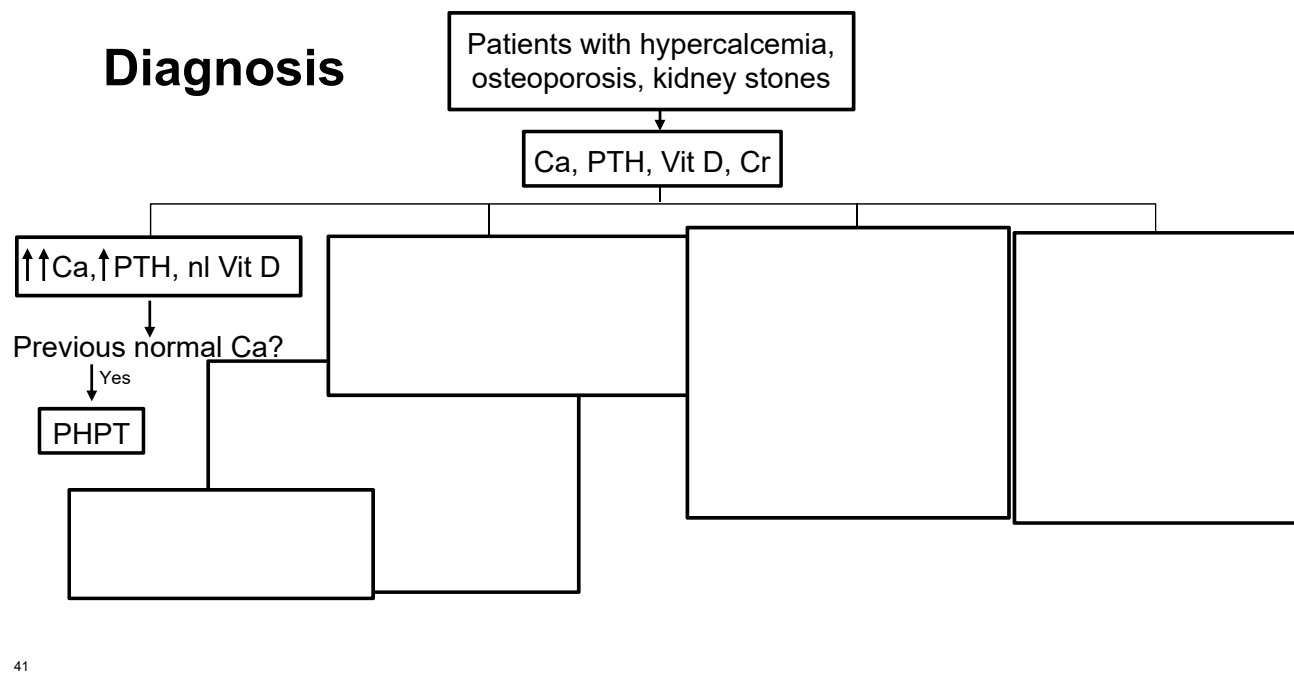


↑ ↑ Ca + ↑ ↑ PTH + nl Vit D + past normal Ca

Igsogna, NEJM 2018.

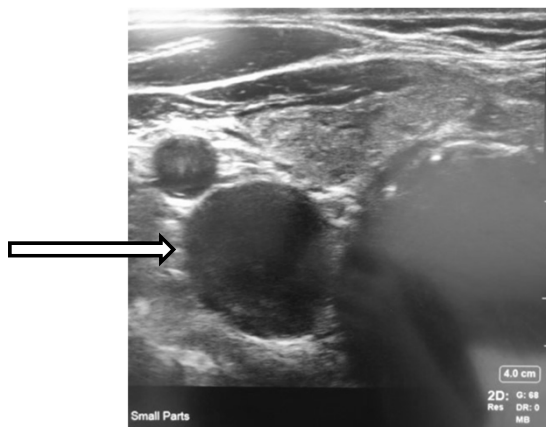
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Diagnosis



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Imaging is not necessary for diagnosis



Usually negative in 4 gland hyperplasia

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You made the diagnosis!

Now what?



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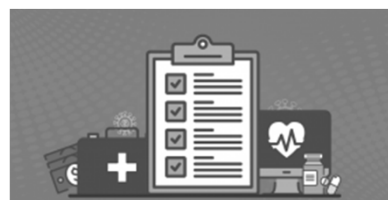
Treatment options

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, \$\$\$

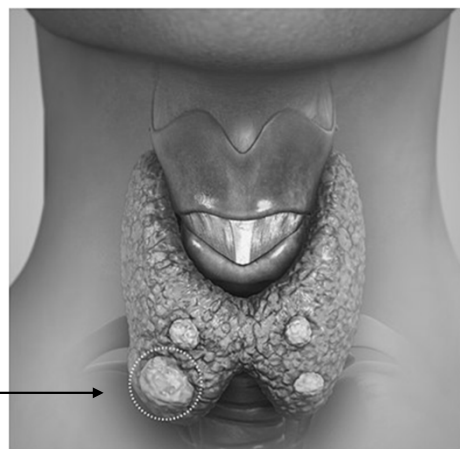


3. Surgery

- Only definitive treatment : 95-98% cure rate

Khan, Osteo Int. 2016.

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Parathyroid
adenoma

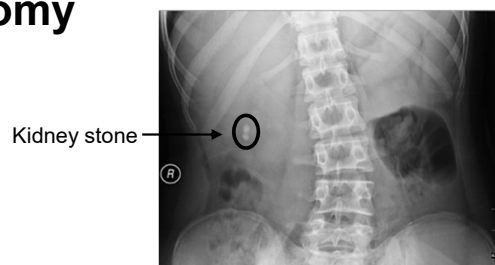
Adapted from <https://www.scientificanimations.com/wiki-images/>

Who should get parathyroidectomy?

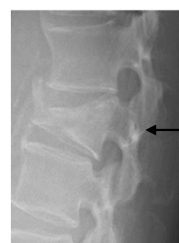
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NIH Guidelines for Parathyroidectomy

- 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



Kidney stone



Vertebral fracture

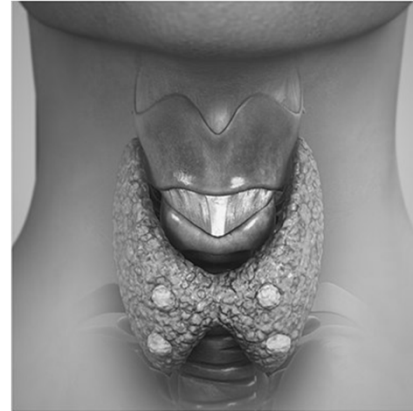
Bilezikian, J Endocrinol Metab 2009.
Caillard, Surgery 2007.
Eigelberger, Ann Surg 2004.

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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



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

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**Symptomatic improvement
after parathyroidectomy**

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

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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.

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

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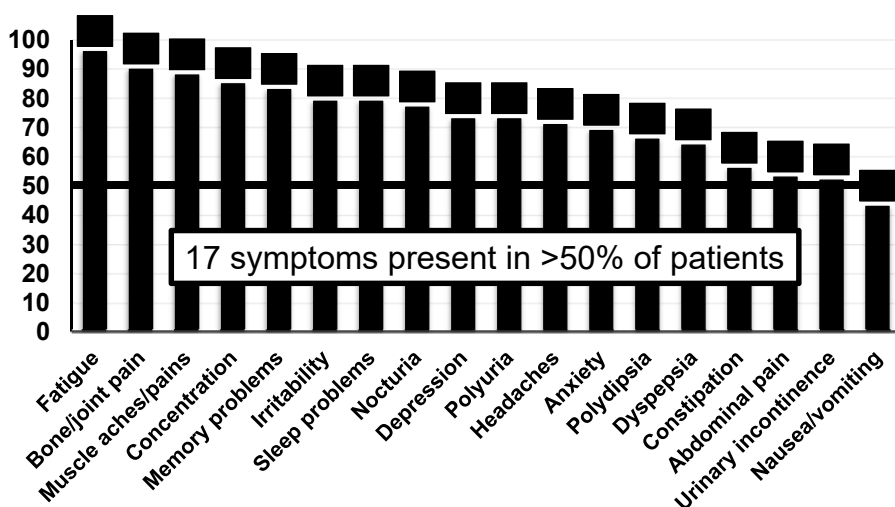
<https://pixabay.com/en/woman-old-age-retirement-home-65675/> archive copy

“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

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Symptoms in patients with PHPT



No patient in this cohort was truly asymptomatic!

Murray, Surgery 2013.

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**Does calcium level
predict symptoms?**

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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.

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

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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.

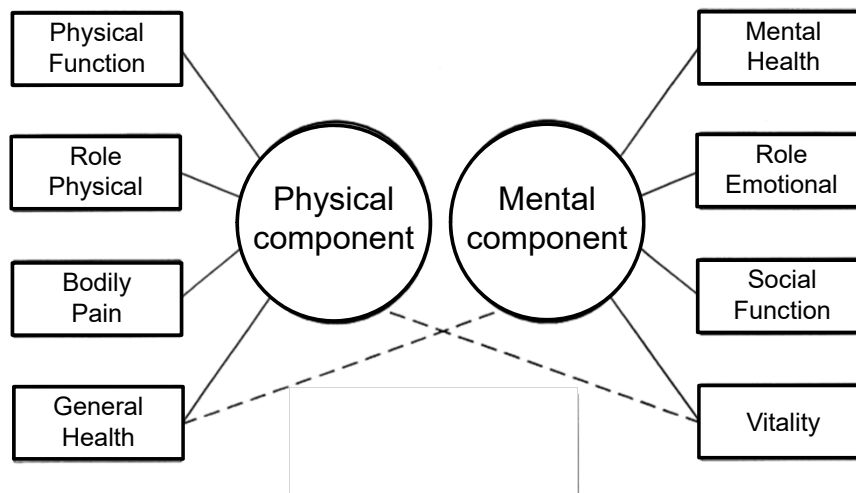
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**Does parathyroidectomy
improve quality of life?**

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SF-36 quality of life assessment



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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.

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Too good to be true?



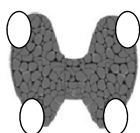
http://www.marines.mil/unit/mcascherrypoint/PublishingImages/2009/IMG_8542.JPG

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Symptomatic improvement is not a placebo effect



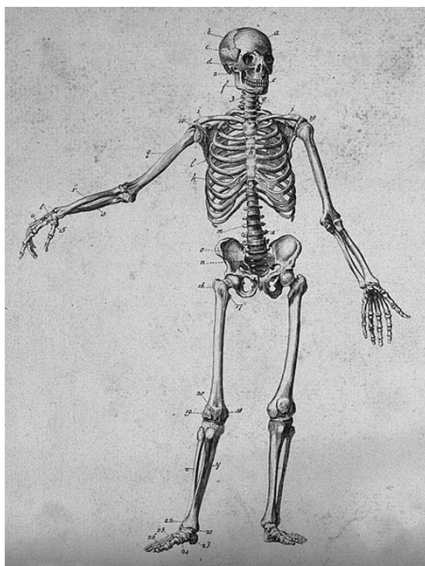
▪ VS.



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.

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Wellcome Images

Bone disease improvement after parathyroidectomy

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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.

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



**What about patients
without osteoporosis?**

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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.

65

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

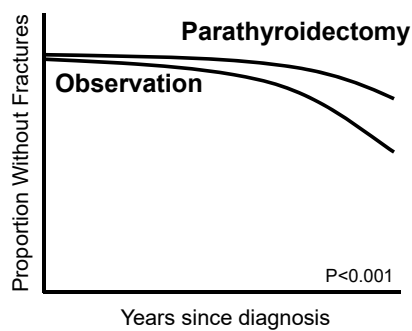


https://commons.wikimedia.org/wiki/File:Fracture_both_bones_of_the_left_arm.jpg

**Does parathyroidectomy
improve risk of fractures?**

66

Parathyroidectomy improves fracture risk



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

VanderWalde, Arch Surg 2006.

67

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.

68

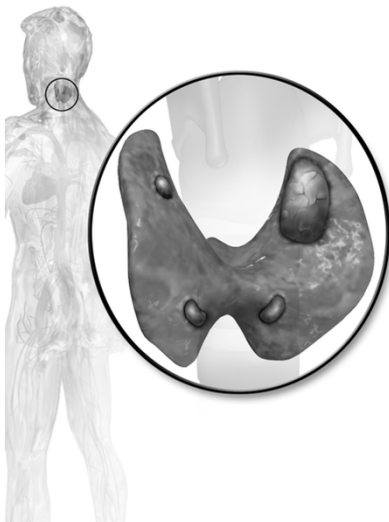
https://commons.wikimedia.org/wiki/File:202007_A_patient_undergoing_fracture_treatment_illustration.svg

Bone health after parathyroidectomy

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



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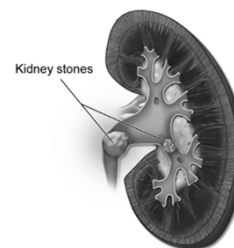
Medical gallery of Blausen Medical 2014

**Renal, cardiovascular, and
mortality benefits after
parathyroidectomy**

70

Decreased kidney stones after parathyroidectomy

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

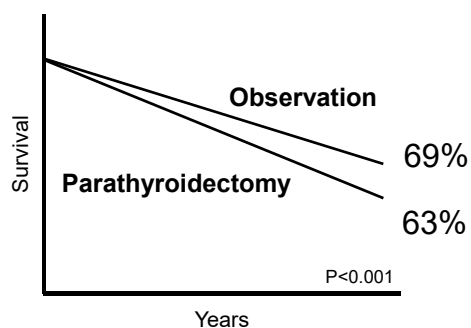


[Medical gallery of Blausen Medical 2014](#)

Mollerup, BMJ 2002.

71

Improved mortality after parathyroidectomy



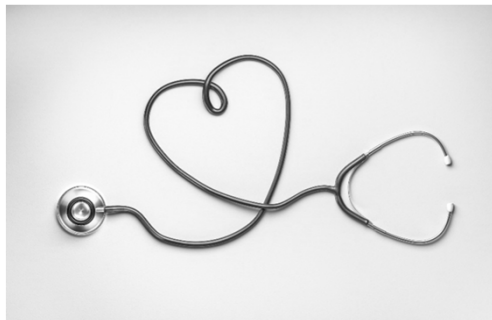
Obsevation =
hazard ratio of
1.54, which is
similar to
untreated HTN!

Vestergaard, BMJ 2003.

72

Renal, CV health after parathyroidectomy

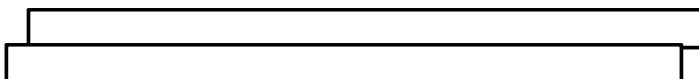
- Risk of kidney stones is reduced after parathyroidectomy
- Risk of atherosclerotic CV disease is reduced after parathyroidectomy
- Survival is improved



73

Disease progression in 5 years

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

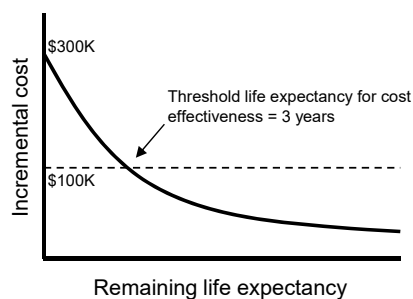


The majority of patients will meet criteria for parathyroidectomy in 5 years

Rubin JCEM 2008
Assadipour. Surgery 2019.

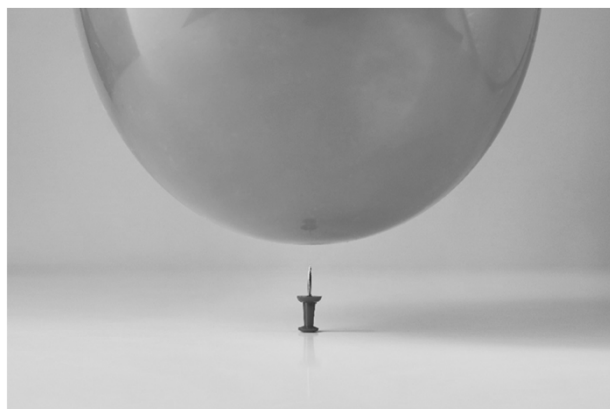
74

Parathyroidectomy is cost-effective



Zanocco. Surgery 2017.

75



Isn't surgery risky?

76

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



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Operations

- Focused parathyroidectomy
- Four gland exploration



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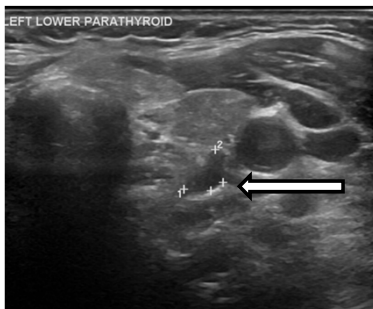
Focused parathyroidectomy

- 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

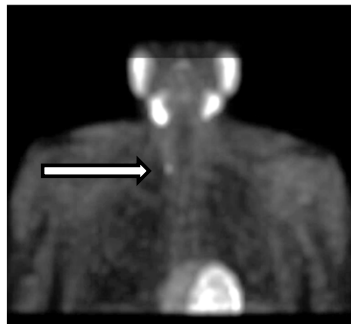


79

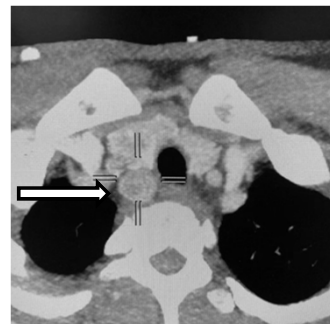
Preoperative localization



Ultrasound



Sestamibi



4D CT

80

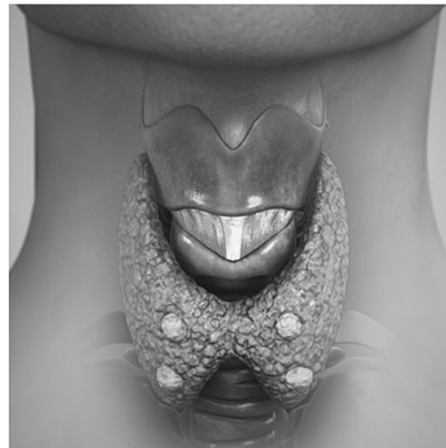


**What if preoperative
localization is negative?**

81

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/>

82

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.

83

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



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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.”

85

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
BAD

BONE

And other things!

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