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Evidence-based Algorithms for Management of Differentiated Thyroid Cancer and Lymph Node Metastasis

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Disclosure

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Objectives

- Review the epidemiology of thyroid cancer.
- Outline the management of thyroid cancer.
 - Primary
 - Nodal metastasis
 - Locally advanced



Sonographic Features of Thyroid Nodule

Table 1. Sonographic Patterns, Risk of Malignancy, and FNA Guidance for Thyroid Nodules in the 2015 American Thyroid Association Guidelines

Sonographic pattern	US features	Estimated risk of malignancy, %	FNA size cutoff (largest dimension)
High suspicion	Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule with one or more of the following features: irregular margins (infiltrative, microlobulated), microcalcifications, taller than wide shape, rim calcifications with small extrusive soft tissue component, evidence of ETE	> 70–90 ^a	Recommend FNA at ≥ 1 cm
Intermediate suspicion	Hypoechoic solid nodule with smooth margins without microcalcifications, ETE, or taller than wide shape	10–20	Recommend FNA at ≥ 1 cm
Low suspicion	Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, without microcalcification, irregular margin or ETE, or taller than wide shape	5–10	Recommend FNA at ≥ 1.5 cm
Very low suspicion	Spongiform or partially cystic nodules without any of the sonographic features described in low, intermediate, or high suspicion patterns	< 3	Consider FNA at ≥ 2 cm observation without FNA is also a reasonable option
Benign	Purely cystic nodules (no solid component)	< 1	No biopsy ^b

Adapted from Haugen et al., with permission from Mary Ann Liebert, Inc. [3].

FNA, fine needle aspiration; US, ultrasonography; ETE, extrathyroidal extension.

^aThe estimate is derived from high volume centers, the overall risk of malignancy may be lower given the interobserver variability in sonography; ^bAspiration of the cyst may be considered for symptomatic or cosmetic drainage.



Bethesda Classification

2017 Bethesda System for Reporting Thyroid Cytopathology

Diagnostic Category	ROM if NIFTP not cancer	ROM if NIFTP is cancer	Management
Nondiagnostic/unsatisfactory Cyst fluid only Acellular specimen Other: Obscuring factors	5–10%	5–10%	Repeat fine needle aspiration under ultrasound guidance
Benign Benign follicular nodule Chronic lymphocytic (Hashimoto) thyroiditis, in proper clinical setting Granulomatous (subacute) thyroiditis	0–3%	0–3%	Clinical and US follow-up until two negative
Atypia of undetermined significance/ follicular lesion of undetermined significance	6–18%	10–30%	Repeat FNA, molecular testing, or lobectomy
Follicular neoplasm/ suspicious for a follicular neoplasm (Specify if Hürthle cell type)	10–40%	25–40%	Molecular testing, lobectomy
Suspicious for malignancy	45–60%	50–75%	Lobectomy or near-total thyroidectomy
Malignant Papillary thyroid carcinoma Medullary thyroid carcinoma Poorly differentiated carcinoma Undifferentiated (anaplastic) carcinoma Squamous cell carcinoma Carcinoma with mixed features Metastatic malignancy Non-Hodgkin lymphoma Other	94–96%	97–99%	Lobectomy or near-total thyroidectomy



Cancer Statistics

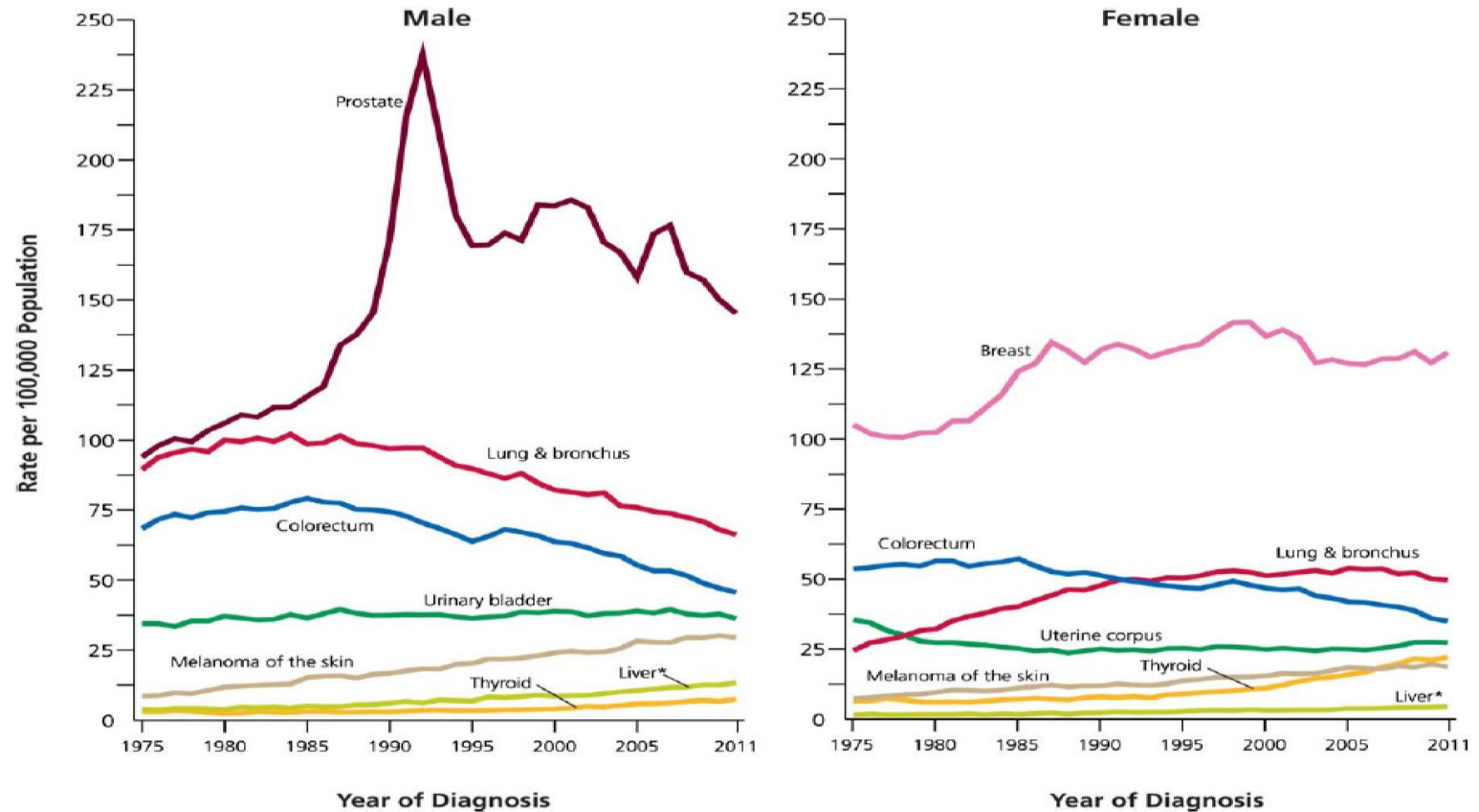


FIGURE 3. Trends in Incidence Rates for Selected Cancers by Sex, United States, 1975 to 2011.

Rates are age adjusted to the 2000 US standard population and adjusted for delays in reporting.

*Includes intrahepatic bile duct.

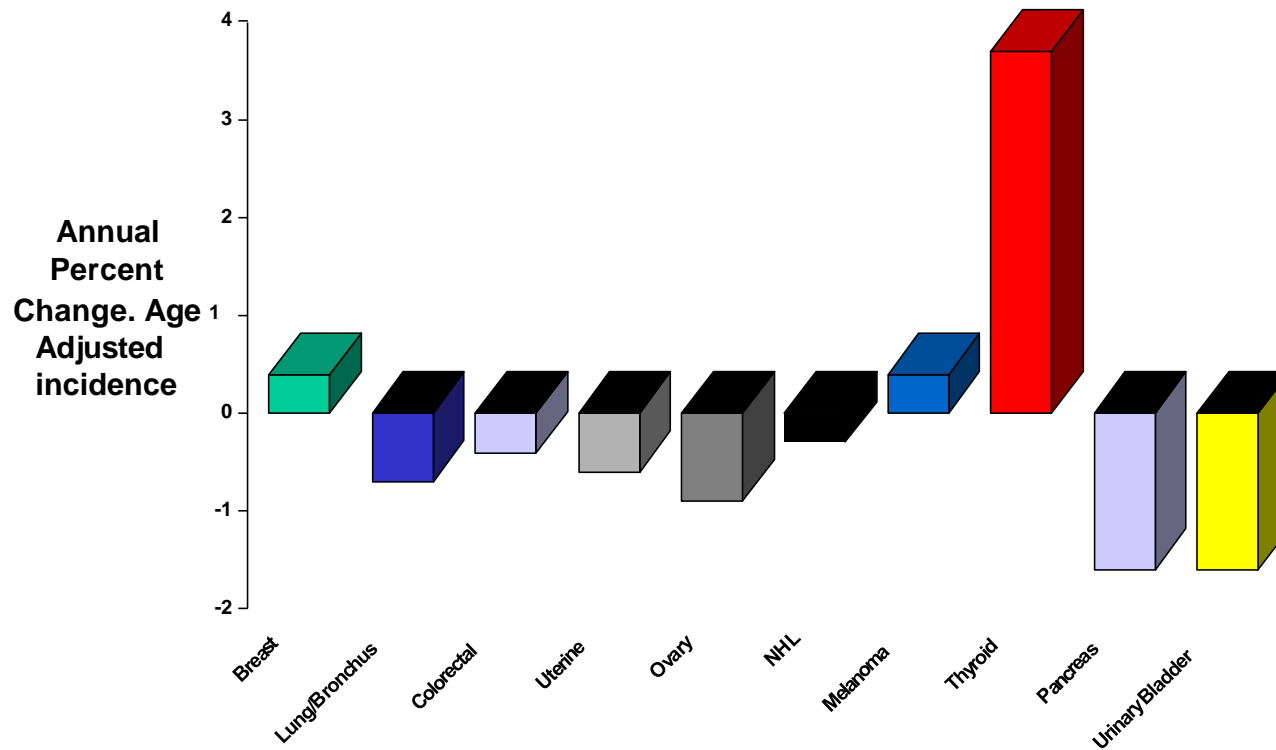
Siegel et al. Cancer Statistics. 2015.



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Thyroid Nodule and Thyroid Cancer

Cancer in Women



<http://seer.cancer.gov>

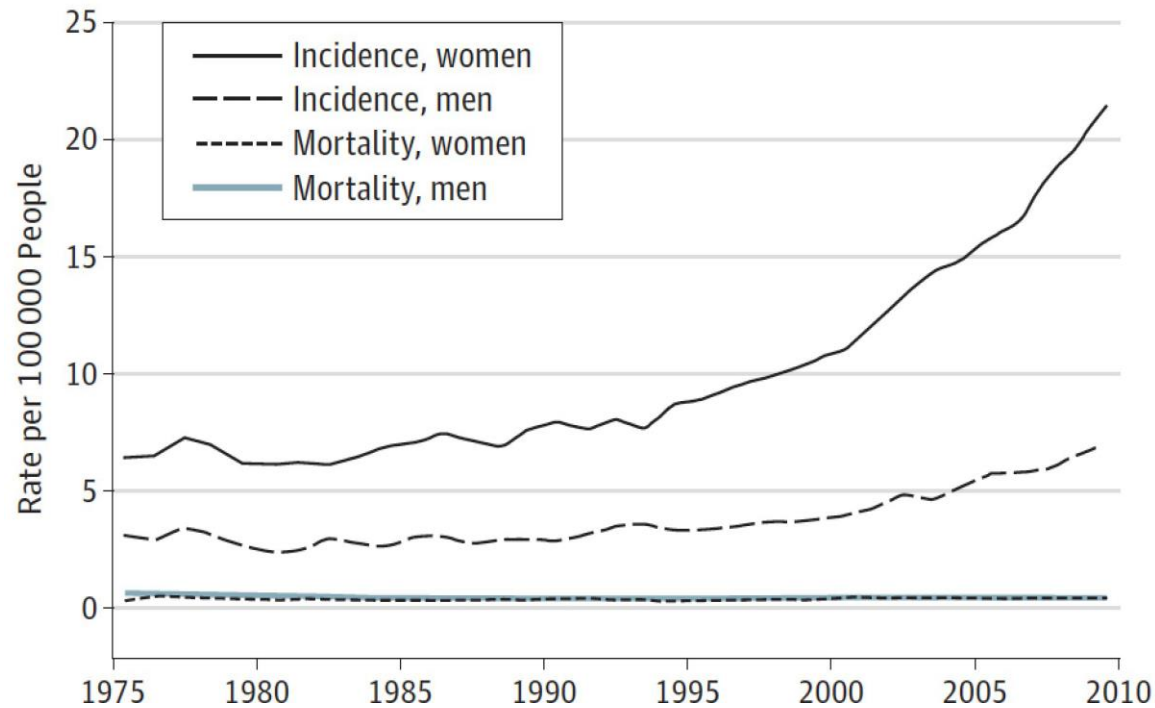


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Thyroid Nodule and Thyroid Cancer

Incidence

Figure 3. Thyroid Cancer Incidence and Mortality by Sex, 1975 to 2009



Davies et al.



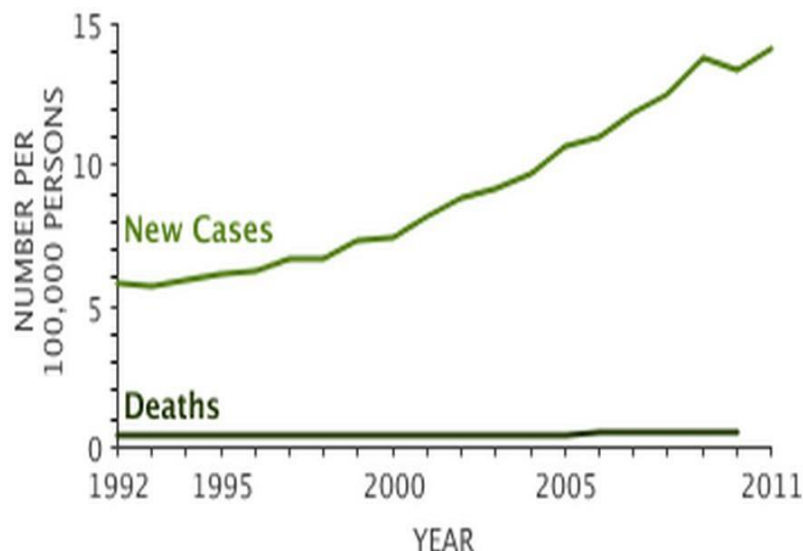
> At a Glance

Estimated New Cases in 2014	62,980
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% of All New Cancer Cases	3.8%
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Estimated Deaths in 2014	1,890
--------------------------	-------

% of All Cancer Deaths	0.3%
------------------------	------



Percent Surviving 5 Years

97.8%

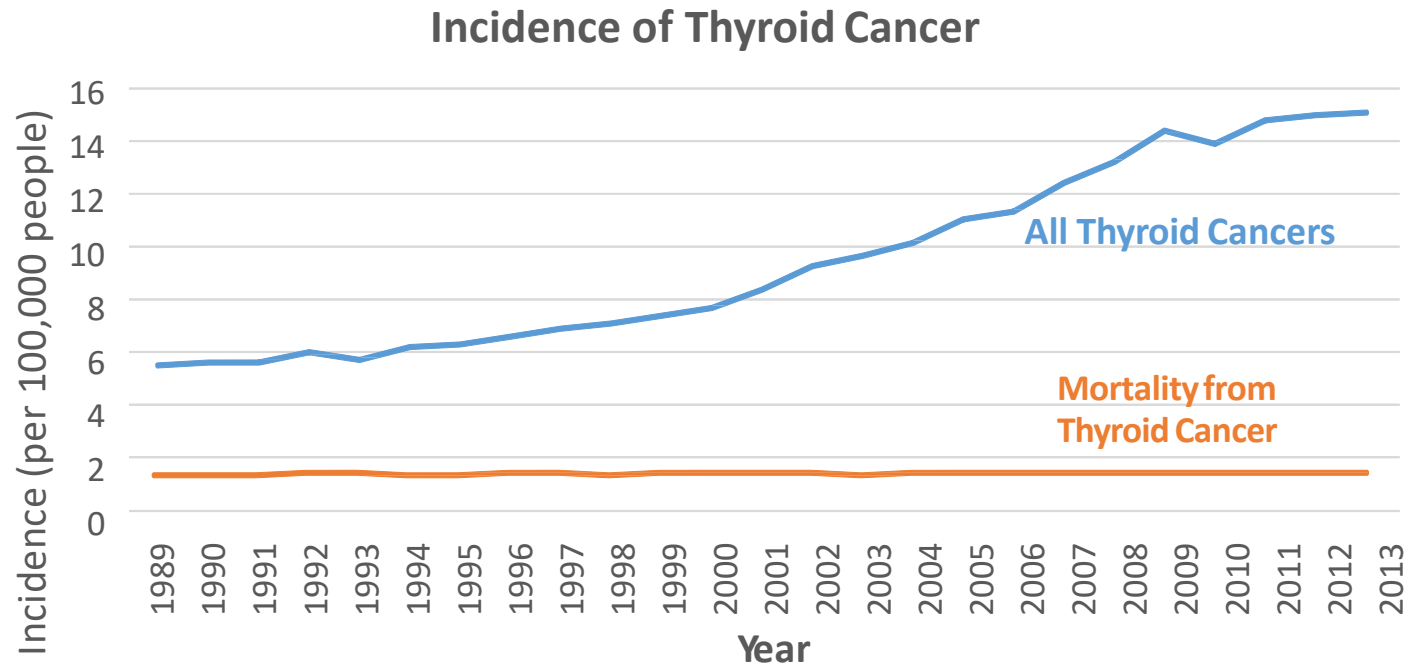
2004-2010

Number of New Cases and Deaths per 100,000: The number of new cases of thyroid cancer was 12.9 per 100,000 men and women per year. The number of deaths was 0.5 per 100,000 men and women per year. These rates are age-adjusted and based on 2007-2011 cases and 2006-2010 deaths.

<http://seer.cancer.gov>



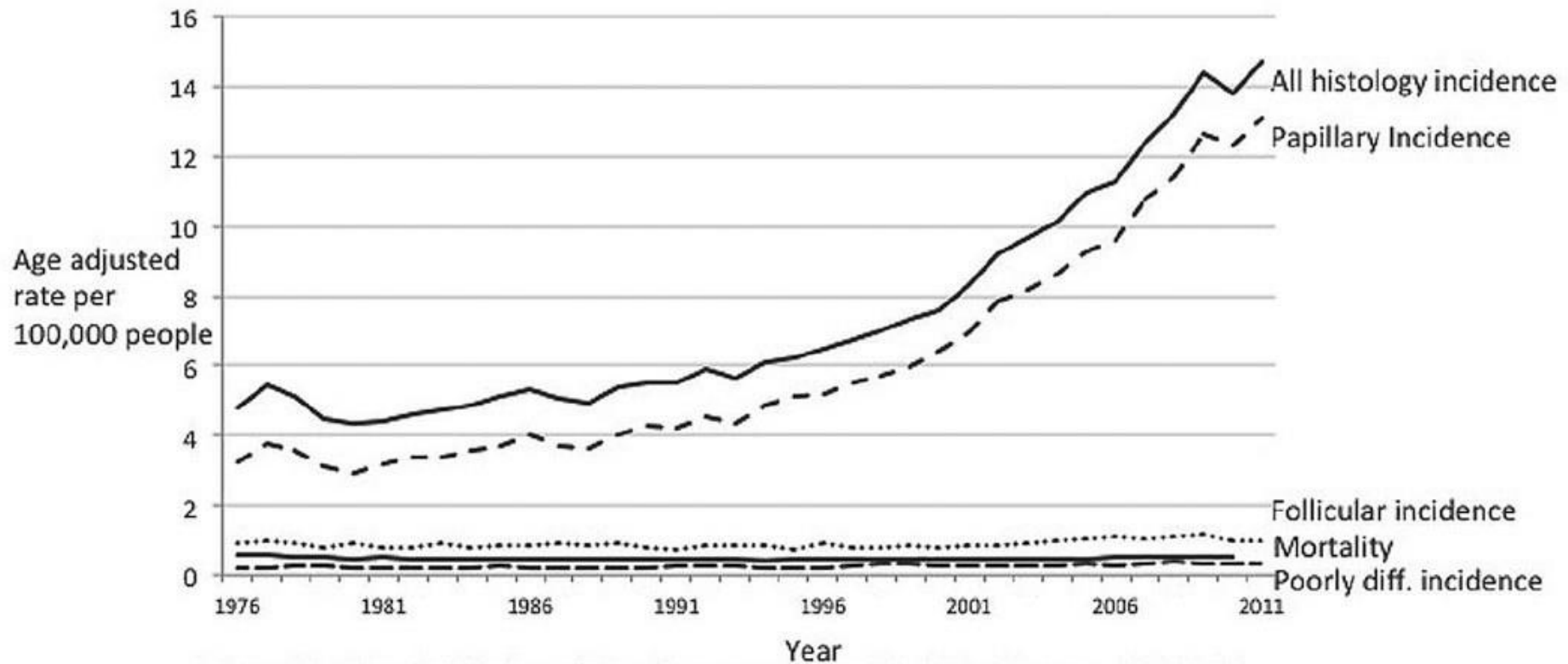
Incidence of Thyroid Cancer



Davies et al Endocrine Practice. 2015..



What Type of Thyroid Cancer is Driving the Increase in Incidence



Davies et al Endocrine Practice. 2015..



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Thyroid Nodule and Thyroid Cancer

Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)

JAMA Oncology | Original Investigation

Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma A Paradigm Shift to Reduce Overtreatment of Indolent Tumors

Yuri E. Nikiforov, MD, PhD; Raja R. Seethala, MD; Giovanni Tallini, MD; Zubair W. Baloch, MD, PhD;
Fulvio Basolo, MD; Lester D. R. Thompson, MD; Justine A. Barletta, MD; Bruce M. Wenig, MD; Abir Al Ghuzlan, MD;
Kennichi Kakudo, MD, PhD; Thomas J. Giordano, MD, PhD; Venancio A. Alves, MD, PhD;
Elham Khanafshar, MD, MS; Sylvia L. Asa, MD, PhD; Adel K. El-Naggar, MD; William E. Gooding, MS;
Steven P. Hodak, MD; Ricardo V. Lloyd, MD, PhD; Guy Maytal, MD; Ozgur Mete, MD; Marina N. Nikiforova, MD;
Vania Nosé, MD, PhD; Mauro Papotti, MD; David N. Poller, MB, ChB, MD, FRCPath; Peter M. Sadow, MD, PhD;
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Ronald A. Ghossein, MD



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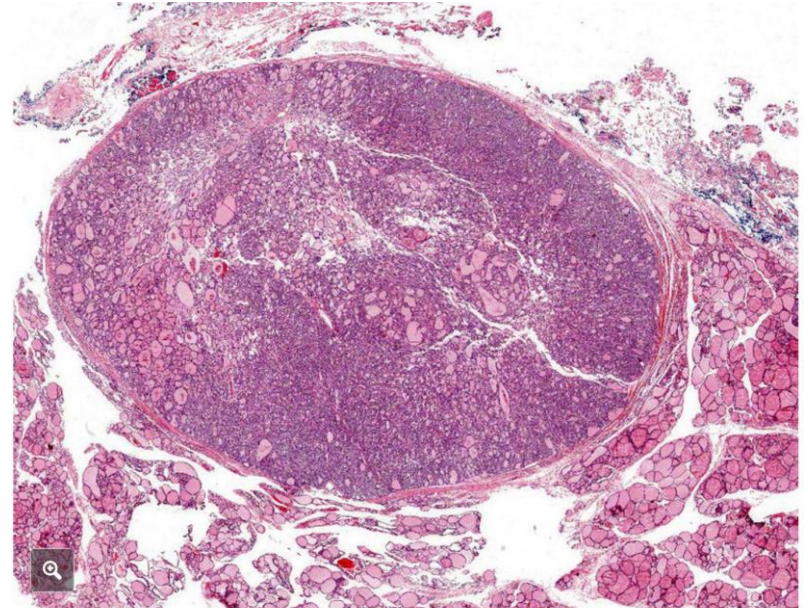
Thyroid Nodule and Thyroid Cancer

HEALTH

It's Not Cancer: Doctors Reclassify a Thyroid Tumor

By GINA KOLATA APRIL 14, 2016

The New York Times



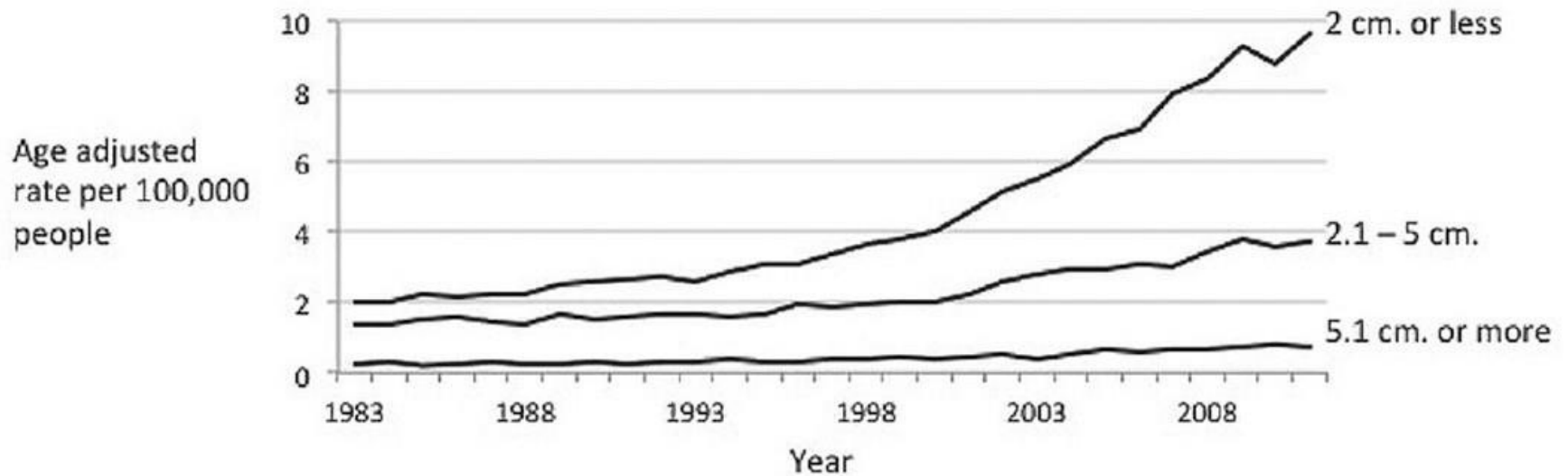
A noninvasive follicular thyroid neoplasm with papillary-like nuclear features, or Niftp, a type of tumor that was previously considered a kind of cancer, but has been downgraded by a panel of doctors. Yuri Nikiforov



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Thyroid Nodule and Thyroid Cancer

Small Cancers are Driving the Increasing Incidence



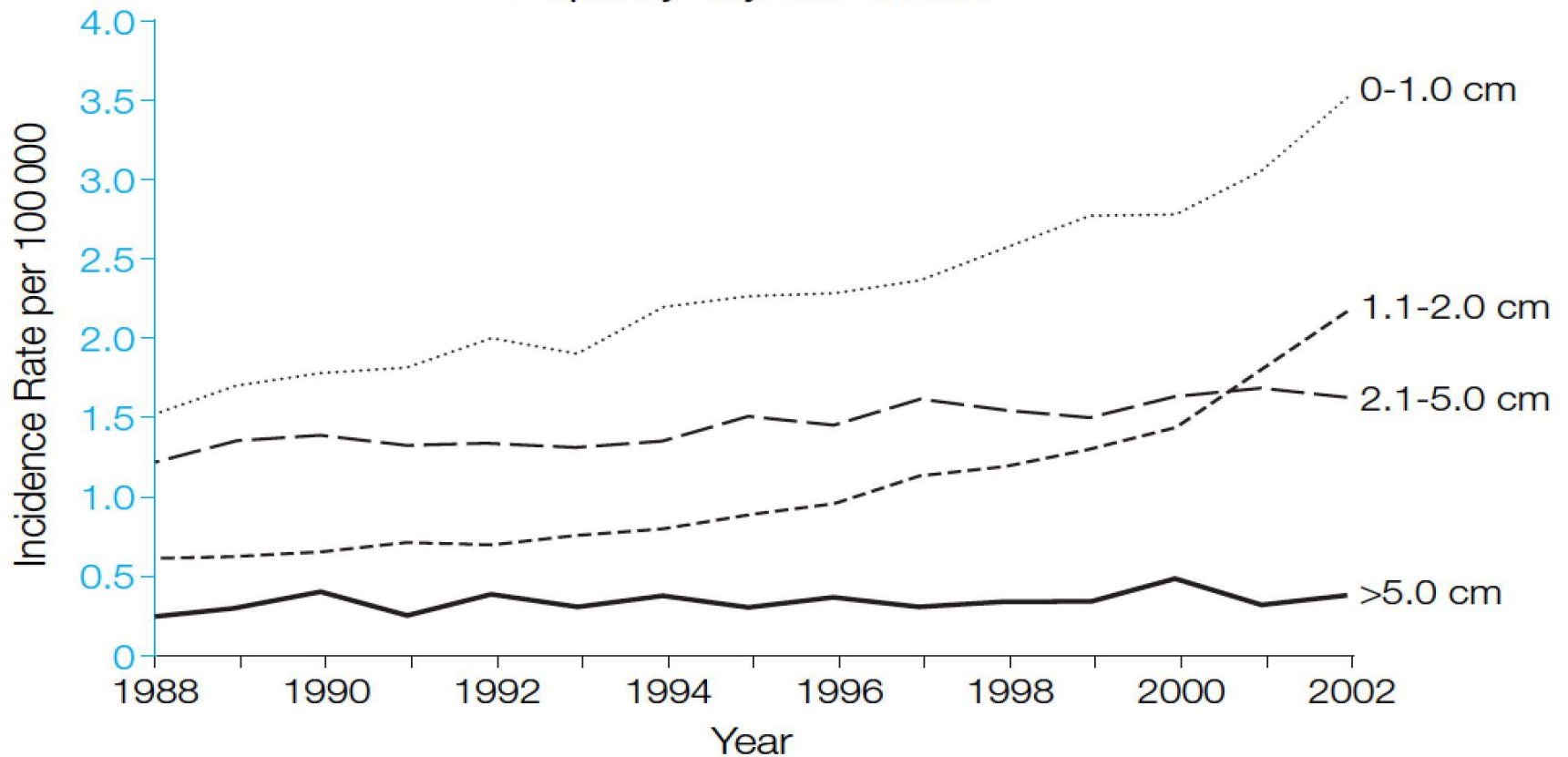
Davies et al Endocrine Practice. 2015.



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Thyroid Nodule and Thyroid Cancer

Papillary Thyroid Cancer



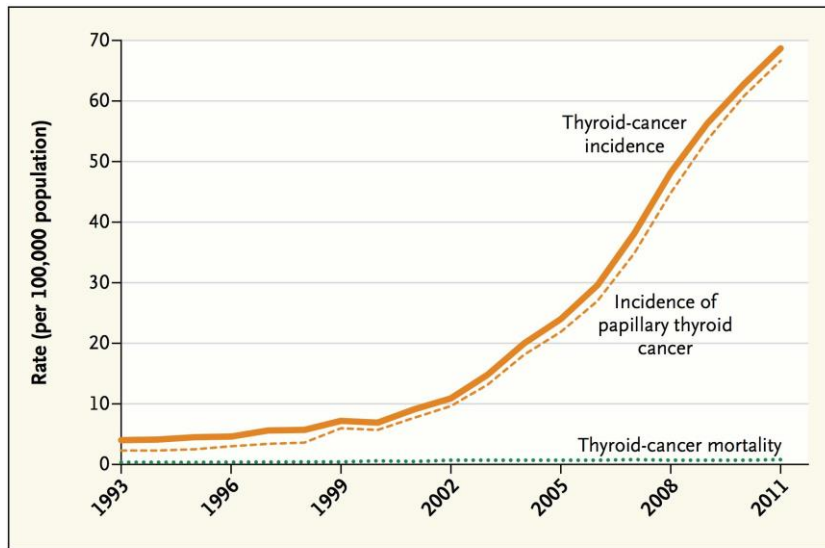
Davies et al JAMA. 2006.



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Thyroid Nodule and Thyroid Cancer

Korea' Epidemic: Screening



Thyroid-Cancer Incidence and Related Mortality in South Korea, 1993–2011.

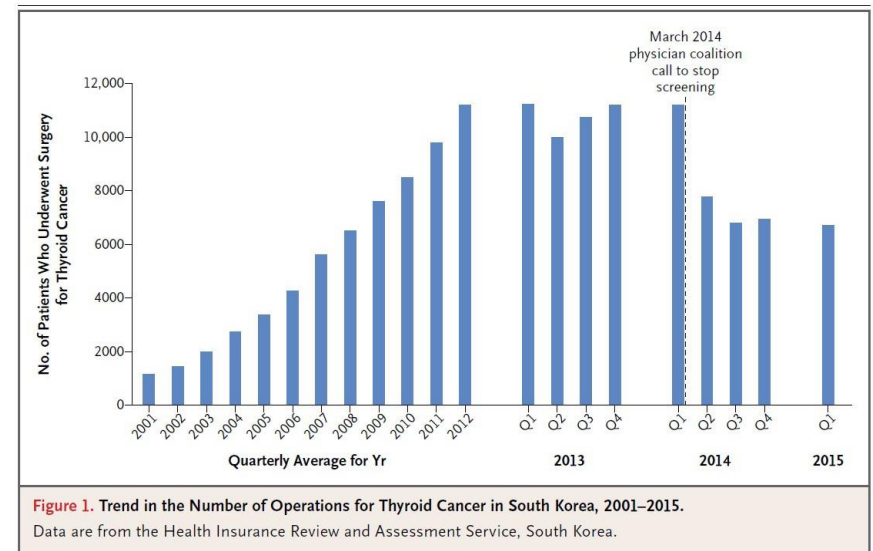


Figure 1. Trend in the Number of Operations for Thyroid Cancer in South Korea, 2001–2015.

Data are from the Health Insurance Review and Assessment Service, South Korea.

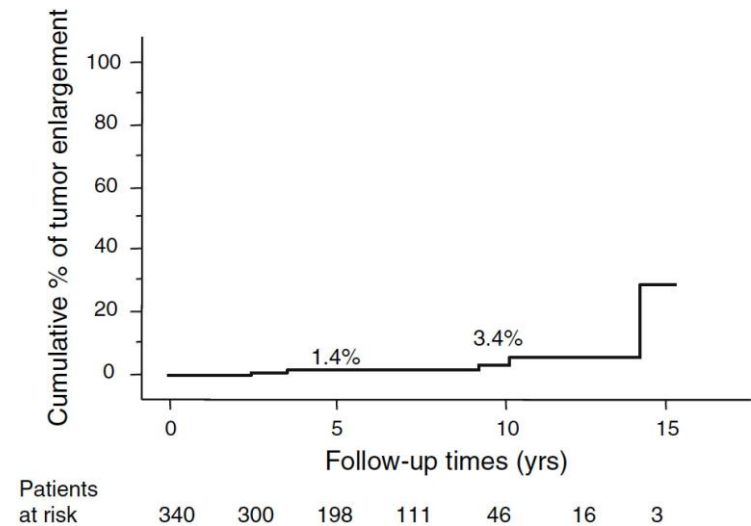
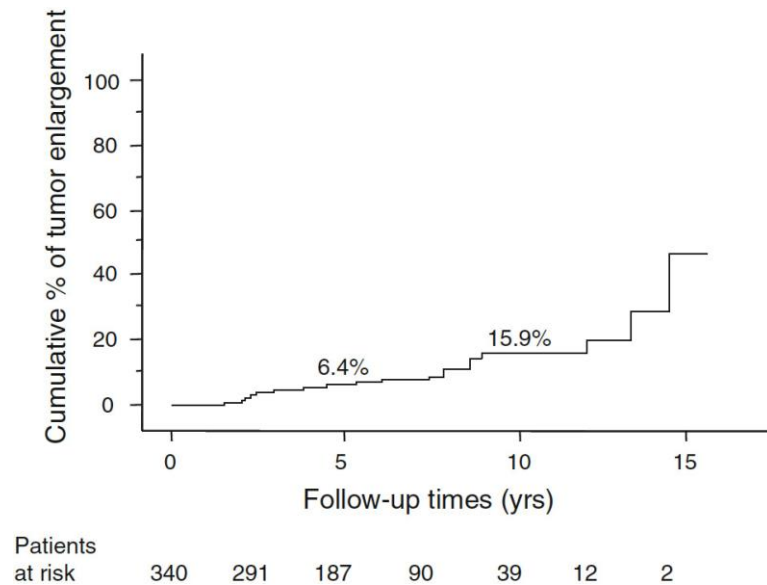
Ahn et al. NEJM. 2014.



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Thyroid Nodule and Thyroid Cancer

Treatment: Observation



Ito et al. World J Surg. 2010.



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Thyroid Nodule and Thyroid Cancer

Observation Trial

Japan Experience

After 22 years of follow up and observation in
~1200 patients (low risk papillary
microcarcinomas)

- 8% size increase >3mm
- 4% regional metastasis

Miyauchi et al. World J Surg. 2016.



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Thyroid Nodule and Thyroid Cancer

Observation Criteria

- Tumor factors
 - <1 cm
 - Within thyroid parenchyma
 - No lymphadenopathy
 - Not multifocal
- Patient factors
 - Older
 - Motivated
 - Able to tolerate long term follow up



Extent of Surgery

- Thyroid lobectomy and isthmusectomy
- Total thyroidectomy



Thyroid Lobectomy and Isthmusectomy

- Thyroid cancer < 2 cm
- No extra-thyroidal extension
- No clinical evidence of lymph node metastasis



Saving Thyroids — Overtreatment of Small Papillary Cancers

H. Gilbert Welch, M.D., M.P.H., and Gerard M. Doherty, M.D.

This year, more than 50,000 people in the United States will be diagnosed with thyroid cancer.¹ Three quarters of these diagnoses will be in women; their median age at diagnosis will be about 50 years (for context, the median age at the time of breast cancer diagnosis is 62). Thyroid cancer has become an increasingly common diagnosis for Americans: over the past 25 years, its incidence has tripled — largely reflecting the detection of small papillary thyroid cancers.²

Despite this dramatic rise in incidence, mortality due to thyroid cancer has remained stable, which suggests that there is widespread overdiagnosis — de-

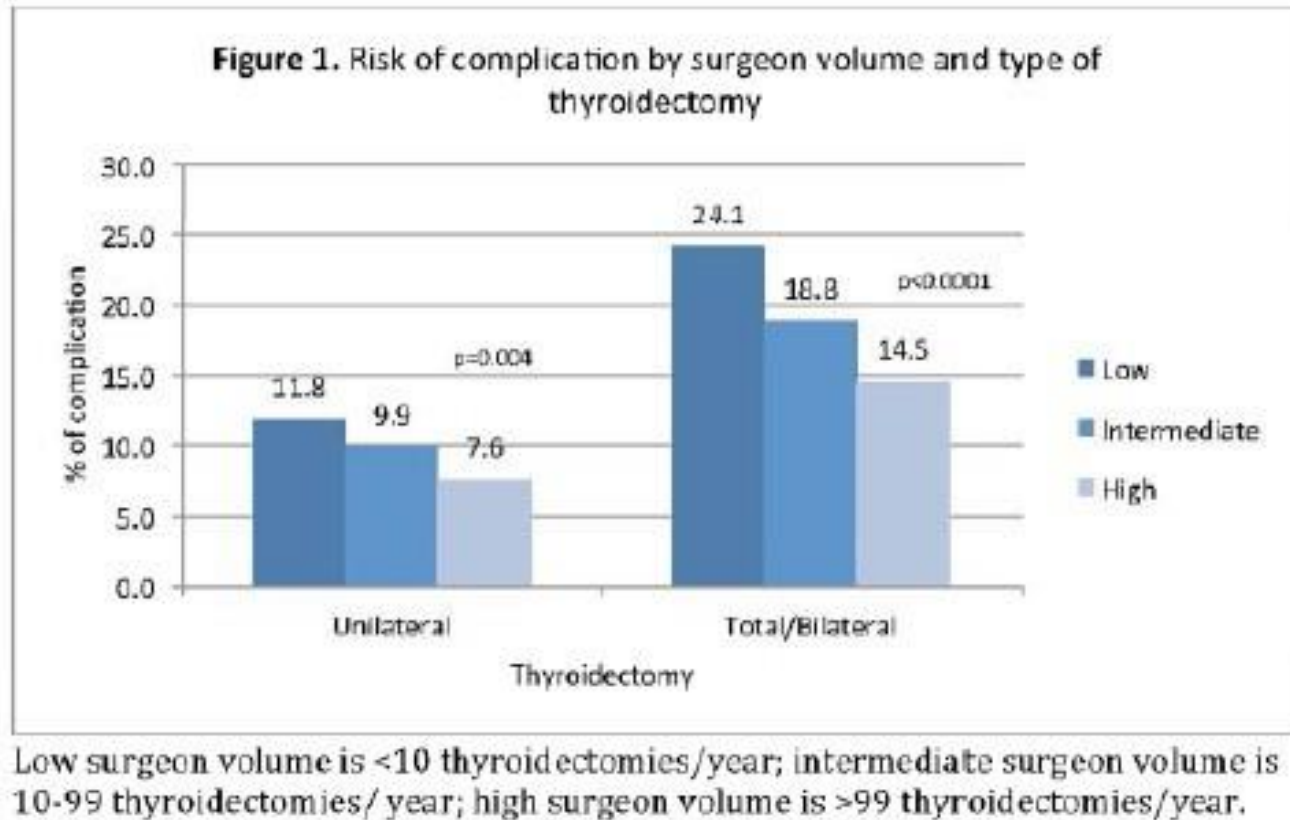
tomy. It carries a risk of injury to either recurrent laryngeal nerve (or, rarely, both of them) and a risk of hypoparathyroidism due to damage to all four parathyroid glands; it also necessitates lifelong thyroid hormone replacement. The less extensive operation is thyroid lobectomy, or removal of about half the thyroid gland. This surgery carries a lower risk of nerve damage, avoids the risk of hypoparathyroidism altogether, and preserves thyroid tissue — for many patients, obviating the need for permanent thyroid hormone-replacement therapy. Adjuvant therapy with radioactive iodine (RAI) must be preceded by total thyroidectomy.

Given the additional harms of total thyroidectomy, one would expect that the recognition of similar effectiveness would lead lobectomy to become the dominant procedure, especially given the increasing detection of small tumors. But instead, the opposite has happened. The lower graph shows that the rate of total thyroidectomy is, in fact, accelerating faster than the rate of lobectomy. Currently, about 80% of patients who have surgery for localized papillary thyroid cancer (≤ 2 cm in diameter) undergo a total thyroidectomy.

Why are physicians subjecting patients to the additional risks of hypoparathyroidism and recurrent

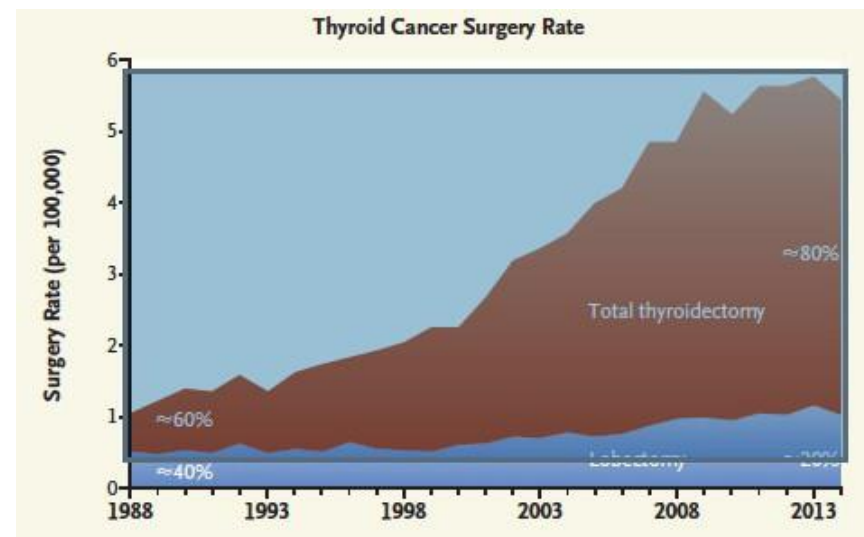
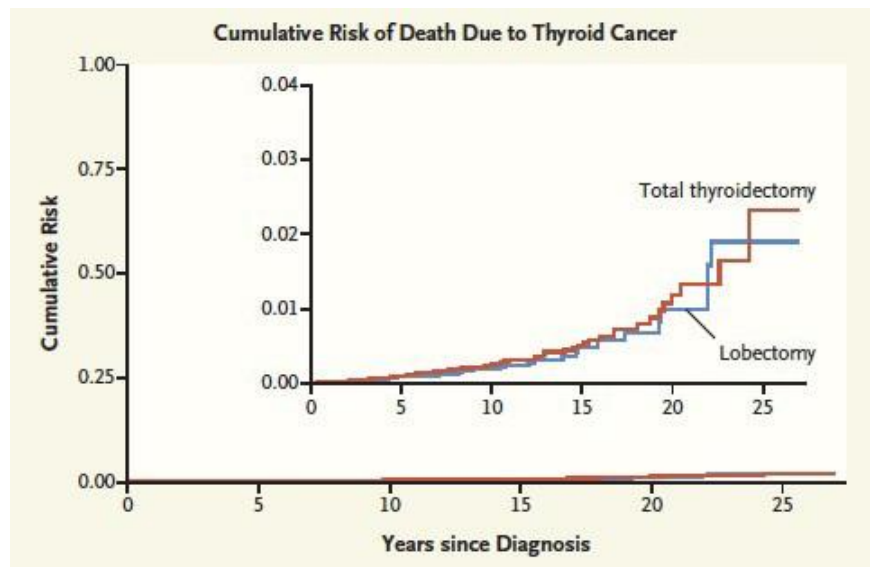


Risks



Hauch et al. SSO. 2014.





Welch et al. NEJM. 2018.



Thyroid Lobectomy versus Total Thyroidectomy

- Thyroid cancer > 2 cm and < 4 cm
- No extra-thyroidal extension
- No clinical evidence lymph node metastasis
- Multi-disciplinary team
 - Enable RAI
 - Enhance follow-up (Tg is more specific)
- Patient preference
- Thyroid cancer > 2 cm and < 4 cm
- No extra-thyroidal extension
- No clinical evidence lymph node metastasis



Total Thyroidectomy

- Thyroid cancer > 4 cm
- Gross extra-thyroidal extension
- Clinically apparent metastatic disease
- Metastatic disease to distant sites



Neck Dissection

- Indication
 - Therapeutic (cN1)
 - Clinically apparent based on pre-operative assessment or intra-operative findings
 - Prophylactic (cN0)
- Extent
 - Central neck dissection
 - Lateral neck dissection



Indications and extent of central neck dissection for papillary thyroid cancer: An American Head and Neck Society Consensus Statement

Nishant Agrawal, MD,^{1*} Maria R. Evasovich, MD,² Emad Kandil, MD,³ Salem I. Noureldine, MD,⁴ Erin A. Felger, MD,⁵ Ralph P. Tufano, MD, MBA,⁶ Dennis H. Kraus, MD,⁷ Lisa A. Orloff, MD,⁸ Raymon Grogan, MD,⁹ Peter Angelos, MD, PhD,⁹ Brendan C. Stack Jr, MD,¹⁰ Bryan McIver, MD,¹¹ Gregory W. Randolph, MD¹²

2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

The American Thyroid Association Guidelines Task Force
on Thyroid Nodules and Differentiated Thyroid Cancer

Bryan R. Haugen,^{1,*} Erik K. Alexander,² Keith C. Bible,³ Gerard M. Doherty,⁴ Susan J. Mandel,⁵ Yuri E. Nikiforov,⁶ Furio Pacini,⁷ Gregory W. Randolph,⁸ Anna M. Sawka,⁹ Martin Schlumberger,¹⁰ Kathryn G. Schuff,¹¹ Steven I. Sherman,¹² Julie Ann Sosa,¹³ David L. Steward,¹⁴ R. Michael Tuttle,¹⁵ and Leonard Wartofsky¹⁶



Pre-operative and Intraoperative Vigilance

Vigilant assessment is required both preoperatively (central and lateral) and intraoperatively (central) to accurately detect cN1 disease requiring dissection.

Agrawal et al. Head and Neck. 2017.



- Recommendation
 - Preoperative neck US for cervical (central and especially lateral neck compartments) lymph nodes is recommended for all patients undergoing thyroidectomy for malignant or suspicious for malignancy cytologic or molecular findings. (Strong recommendation, Moderate-quality evidence)
 - US-guided FNA of sonographically suspicious lymph nodes ≥ 8 –10mm in the smallest diameter should be performed to confirm malignancy if this would change management. (Strong recommendation, Moderate-quality evidence)



Cross-sectional Imaging

AHNS CONSENSUS STATEMENT: CONTROL NECK DISSECTION FOR PTC

TABLE 2. Cross-sectional imaging with CT or MRI plays a supplemental role in preoperative imaging for thyroid cancer, especially in the following clinical scenario.

-
- Clinical or ultrasound evidence of an invasive primary thyroid malignancy (ie, irregular margins between the primary tumor and the aerodigestive tract or major vessels of the neck)
 - Presence of a large primary tumor
 - Presence of bulky (>3 cm) nodal disease incompletely imaged with ultrasound (posteriorly or inferiorly located)
 - Presence or extension of nodal disease into the mediastinum, retrotracheal, or parapharyngeal and retropharyngeal regions, incompletely imaged with ultrasound
 - Suspicion of RLN tumor invasion (ie, vocal fold paralysis)
 - Mass fixation to surrounding structures
 - Absence of an experienced ultrasound practitioner in evaluating cervical lymph nodes
-

Abbreviation: RLN, recurrent laryngeal nerve.



Intraoperative Vigilance

Even in the absence of preoperatively apparent cN1 disease, surgeons must assess all of the central neck subcompartments intraoperatively through visualization, inspection, and palpation to make sure that macroscopic nodal disease is appropriately detected and therefore resected.



Prognostic Significance of Lymph Node Metastases in DTC

- Clinically apparent LN's in 35% presenting with PTC
- Cervical LN's involved in up to 20-80% of patients
 - Up to 80% of patients with cN0 disease (physical examination, imaging, intra-operative inspection) may harbor microscopically positive nodes
 - Most common compartment is the central neck
 - Lateral compartment metastases occur less frequently and usually subsequent to central compartment
 - Skip metastases to lateral compartment can occur in up to 18% of patients
- The impact of lymph node metastasis on prognosis in patients with PTC is unclear
 - Survival
 - Recurrence
 - Clinically apparent nodal disease and not in microscopic nodal disease

Randolph et al. Thyroid 2012; Cranshaw et al. Surg Oncol 2008; Schlumberger et al. NEJM. 1998; Noguchi et al. Surg Clin North Am 1987; ATA2015.



Risk of Recurrence Based on Nodal Status on Presentation

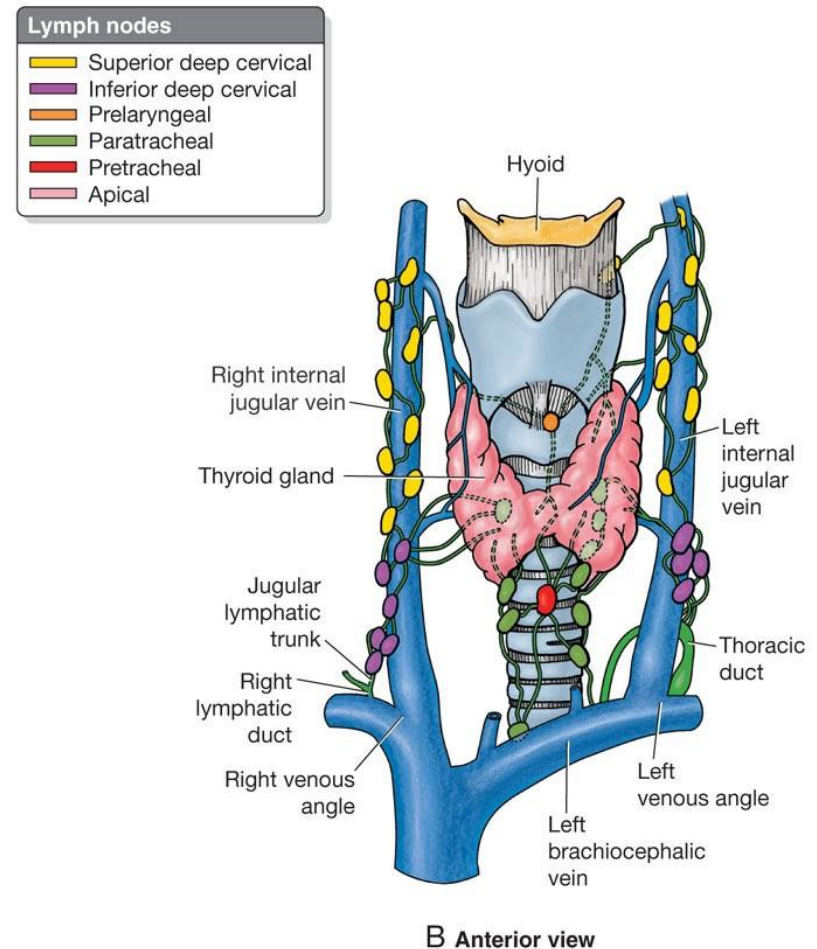
- Clinical N0
 - Range 0-9%, Average 4%
- Clinical N0, Pathology N1 (micro-mets and small volume nodal mets {0.2 to 1cm})
 - Range 4-11.5%, Average 6%
- Clinical N1, Pathology N1 (clinically apparent)
 - Range 10-42%, Average 22%

Wang et al. Ann Surg Oncol 2013; Shan et al. Laryngoscope 2012; Cranshaw et al Surg Oncology 2008; Bardet et al Eur J Endo 2008; So et al Surgery 2010; Wada et al Ann Surg 2003



Central Neck Dissection

- Level 6 LN's
 - Prelaryngeal (Delphian) nodes
 - Pretracheal nodes
 - Paratracheal nodes located in the tracheoesophageal groove (left and right)
- Level 7 LN's:
 - Superior mediastinal nodes/brachiocephalic nodes



Carty et al. Thyroid. 2009.

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Thyroid Nodule and Thyroid Cancer

Central Neck Dissection

- CND: comprehensive removal of prelaryngeal, pretracheal and **at least one paratracheal** nodal basin
- Designate unilateral vs. bilateral
- Formalize boundaries of dissection and document in operative note
 - Define the specific regions and nodal packets
 - Indication should be defined as therapeutic or prophylactic



Therapeutic Central Neck Dissection

- Yes!
- Based on pre-operative radiographic evaluation and intra-operative inspection
- RECOMMENDATION 36
 - Therapeutic central-compartment (level VI) neck dissection for patients with clinically involved central nodes should accompany total thyroidectomy to provide clearance of disease from the central neck. (Strong recommendation, Moderate-quality evidence)
- The extent of CND can be either unilateral or bilateral
 - Bilateral dissection is required when cN1 disease is present in both paratracheal regions
 - Definite benefit given the potential for hypoparathyroidism and bilateral RLN injury
 - Unilateral CND is preferred when disease is confined to one paratracheal region to avoid these risks



Prophylactic Central Neck Dissection

- Controversial!
- No randomized controlled trial
- No improvement in long-term patient outcome
- Increased risk of hypoparathyroidism and RLN injury
- Recommendations 36
 - Thyroidectomy without prophylactic central neck dissection is appropriate for small (T1 or T2), noninvasive, clinically node-negative PTC (cN0) and for most follicular cancers. (Strong recommendation, Moderate-quality evidence)
 - Prophylactic central-compartment neck dissection (ipsilateral or bilateral) should be considered in patients with papillary thyroid carcinoma with clinically uninvolved central neck lymph nodes (cN0) who have **advanced primary tumors (T3 or T4)** or **clinically involved lateral neck nodes (cN1b)**, or if the information will be used to plan further steps in therapy. (Weak recommendation, Low-quality evidence)
- The decision to perform pCND requires a multidisciplinary team decision-making process that includes the patient, surgeon, and endocrinologist weighing the risks and benefits individually in each case

Moreno et al. Thyroid 2012; Wang et al. Ann Surg Oncol 2012; Chisholm et al. Laryngoscope 2009; Roh et al. Ann Surg 2007; Raffaelli et al. Surgery 2012; Yoo et al. World J Surg 2012; Ywata de Carvalho et al. JAMA Oto 2015; Pacini et al. Eur J Endo 2006.



Exception

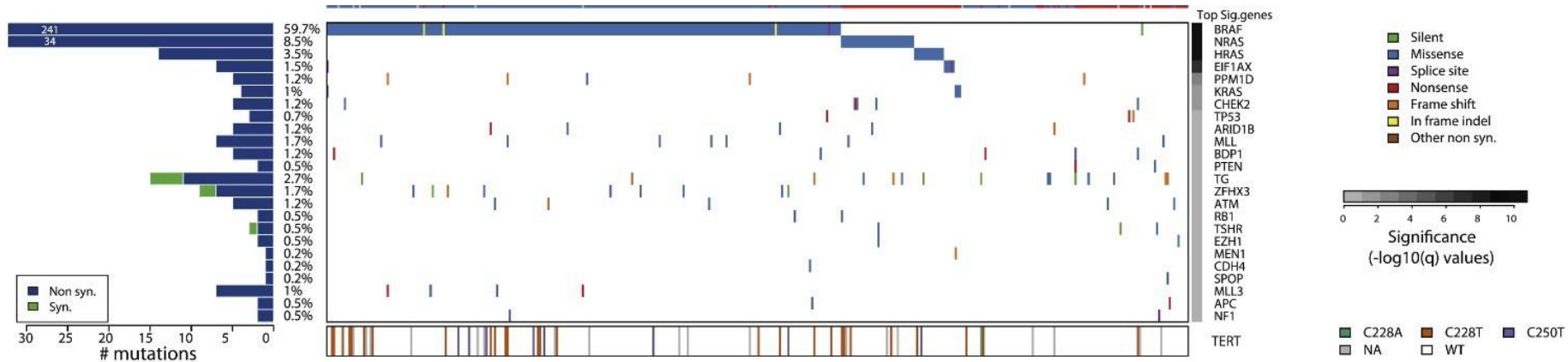
- If lateral neck disease present (N1b)
 - High likelihood of central neck metastases (80%)
 - Skip metastases 18%
 - Prophylactic central neck dissection may be considered
- Medullary thyroid cancer
 - Elective CND

Khafif et al. Head Neck 2008; Noguchi et al. Surg Clin North Am 1987.



Molecular Markers

C



None of the current molecular markers, including BRAF, have been demonstrated to be clear, independent prognostic indicators; therefore they should not impact the decision for pCND.

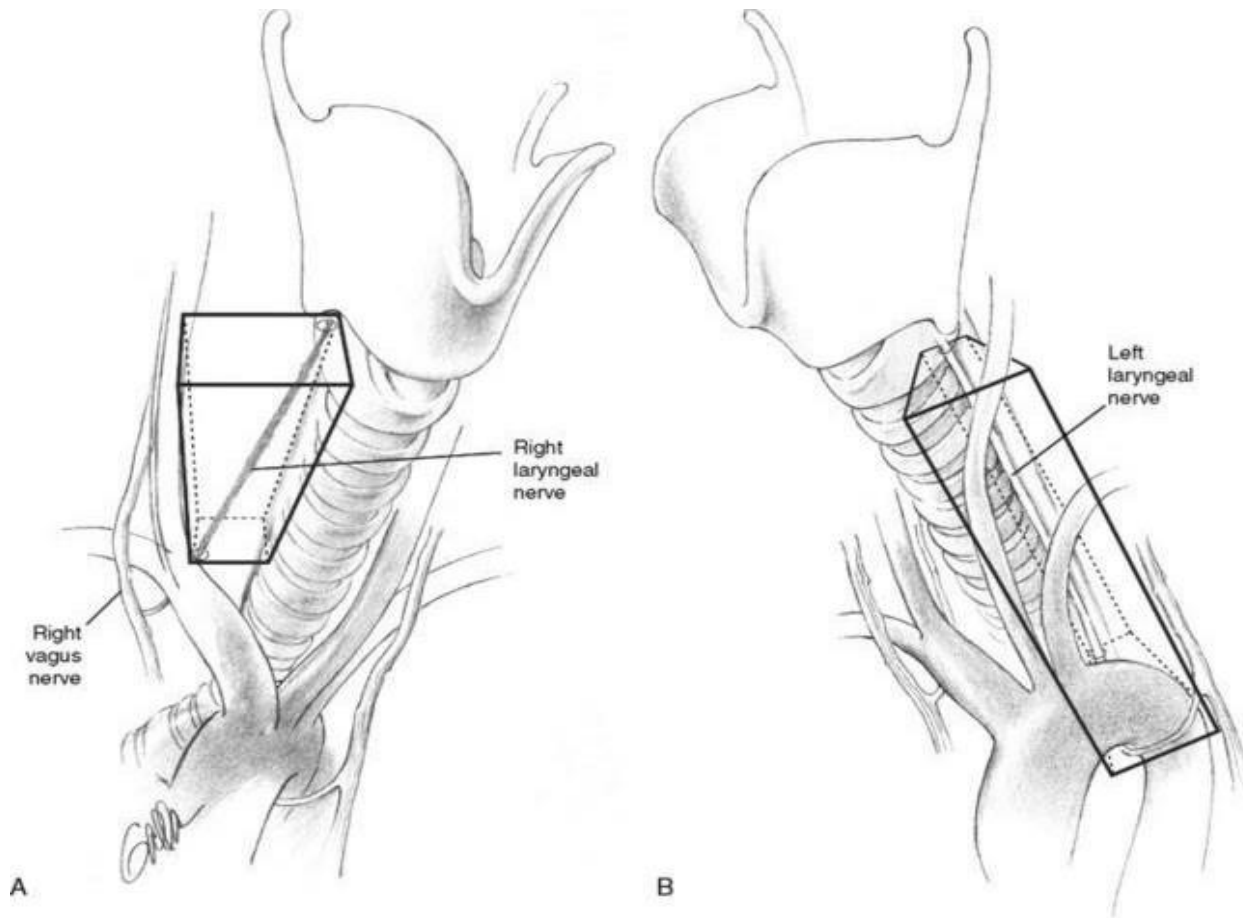
TCGA. Cell. 2014.



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Thyroid Nodule and Thyroid Cancer

Central Neck Dissection: Anatomy



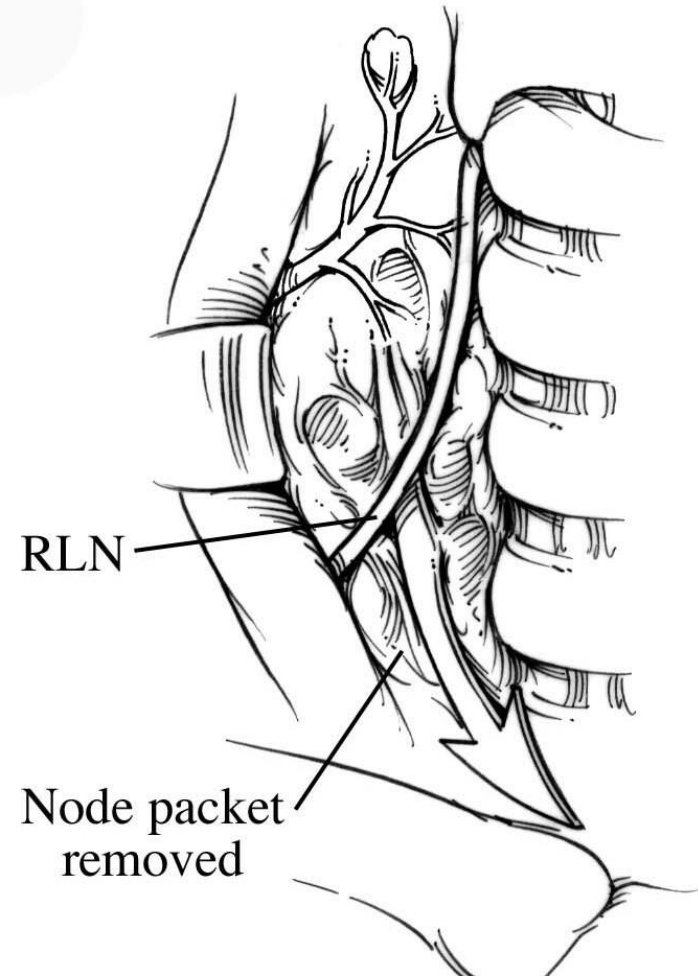
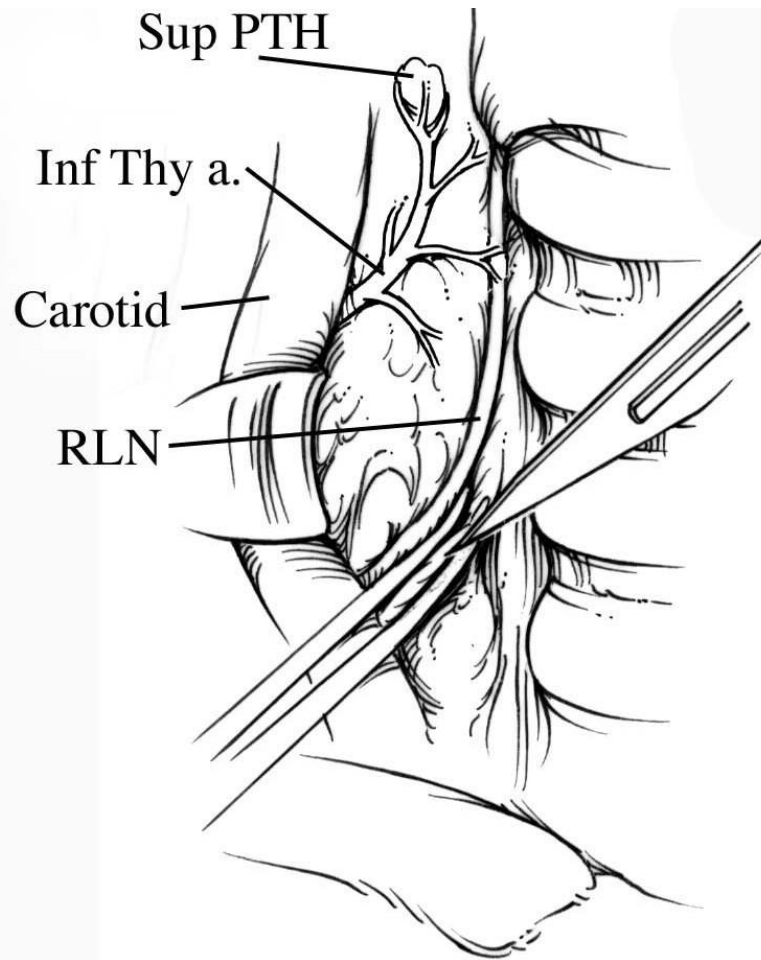
Randolph. Surgery of Thyroid and Parathyroid Glands, 2nd Edition.



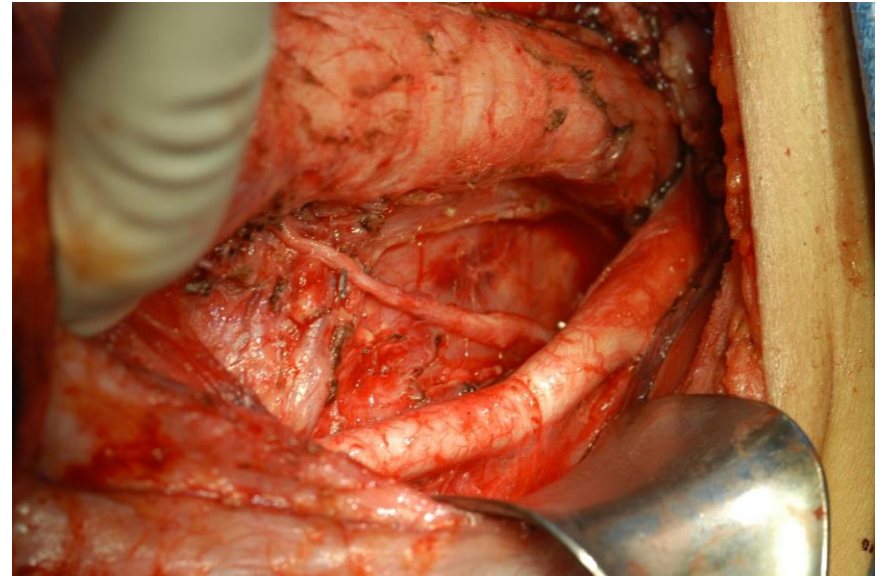
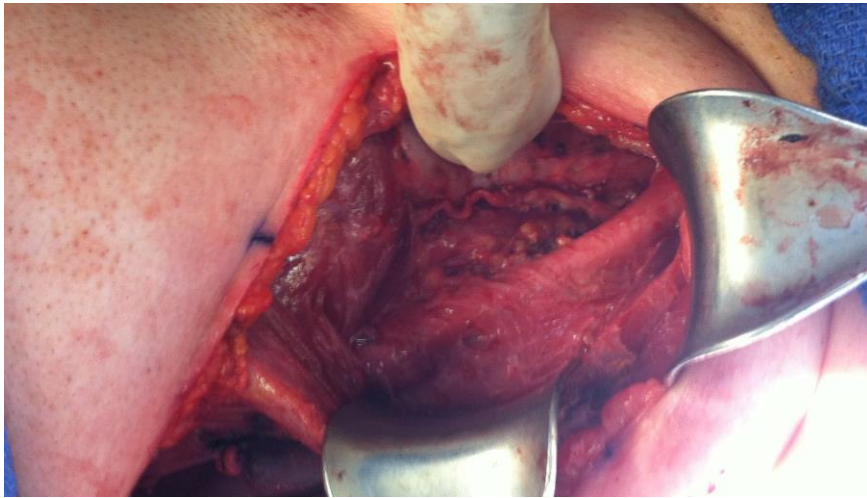
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Thyroid Nodule and Thyroid Cancer

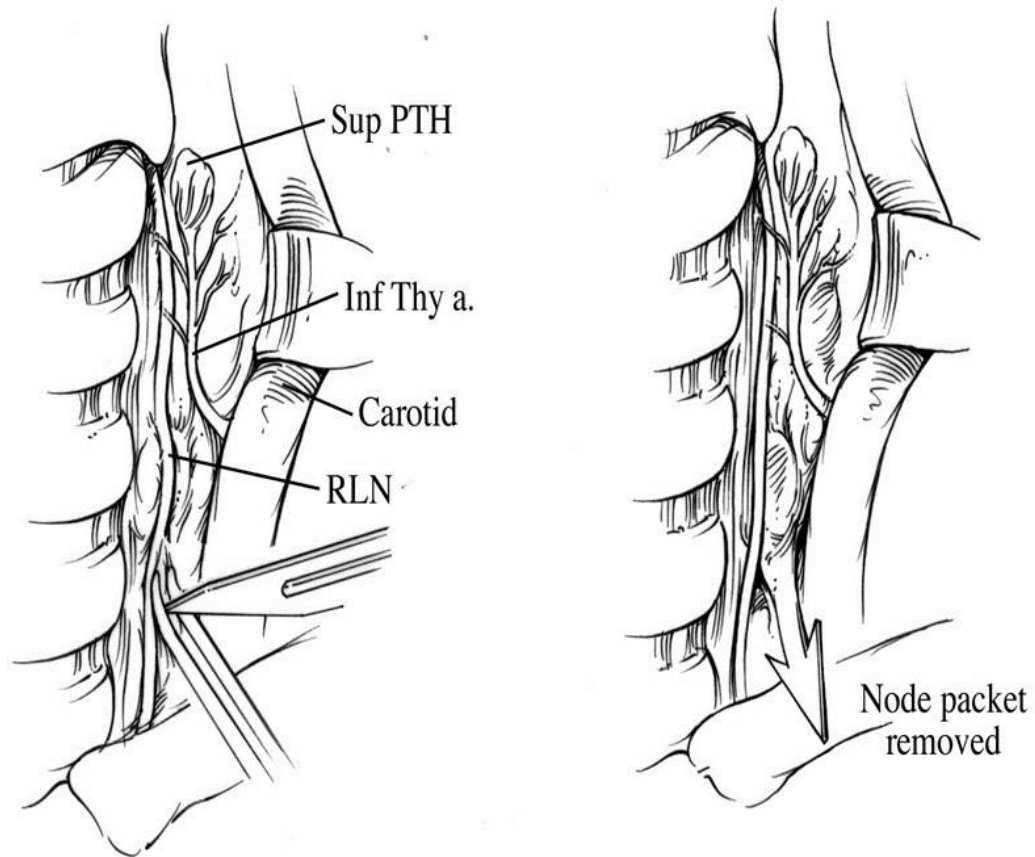
Central Neck Dissection: Right Paratracheal



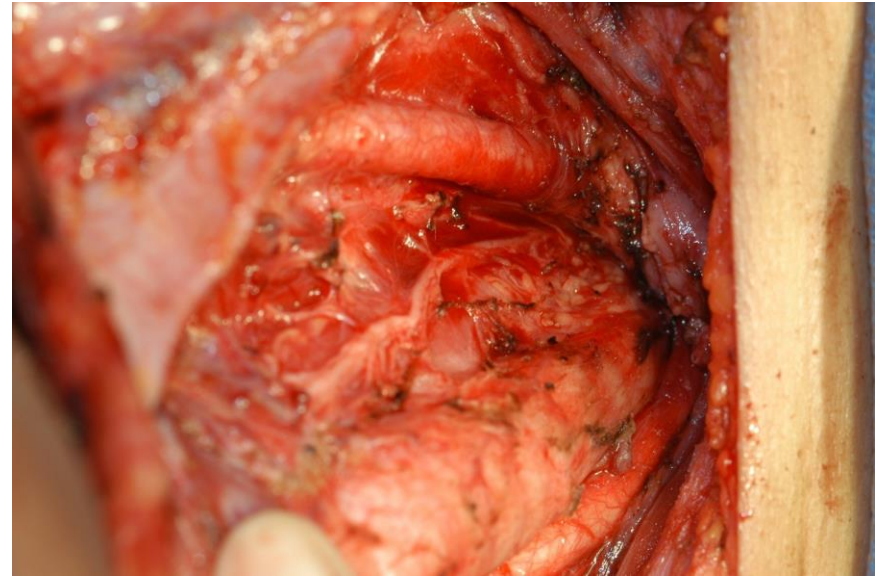
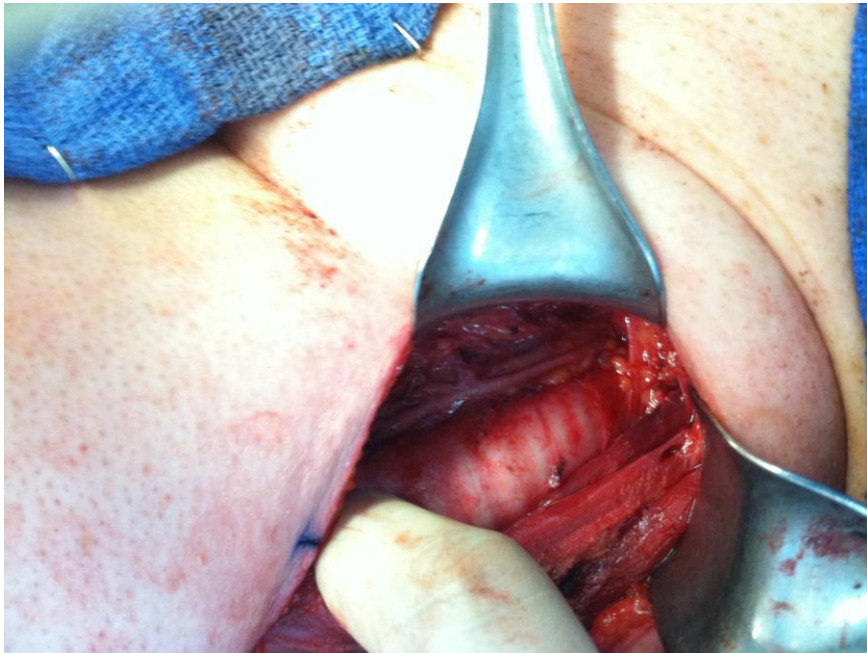
Central Neck Dissection: Right Paratracheal



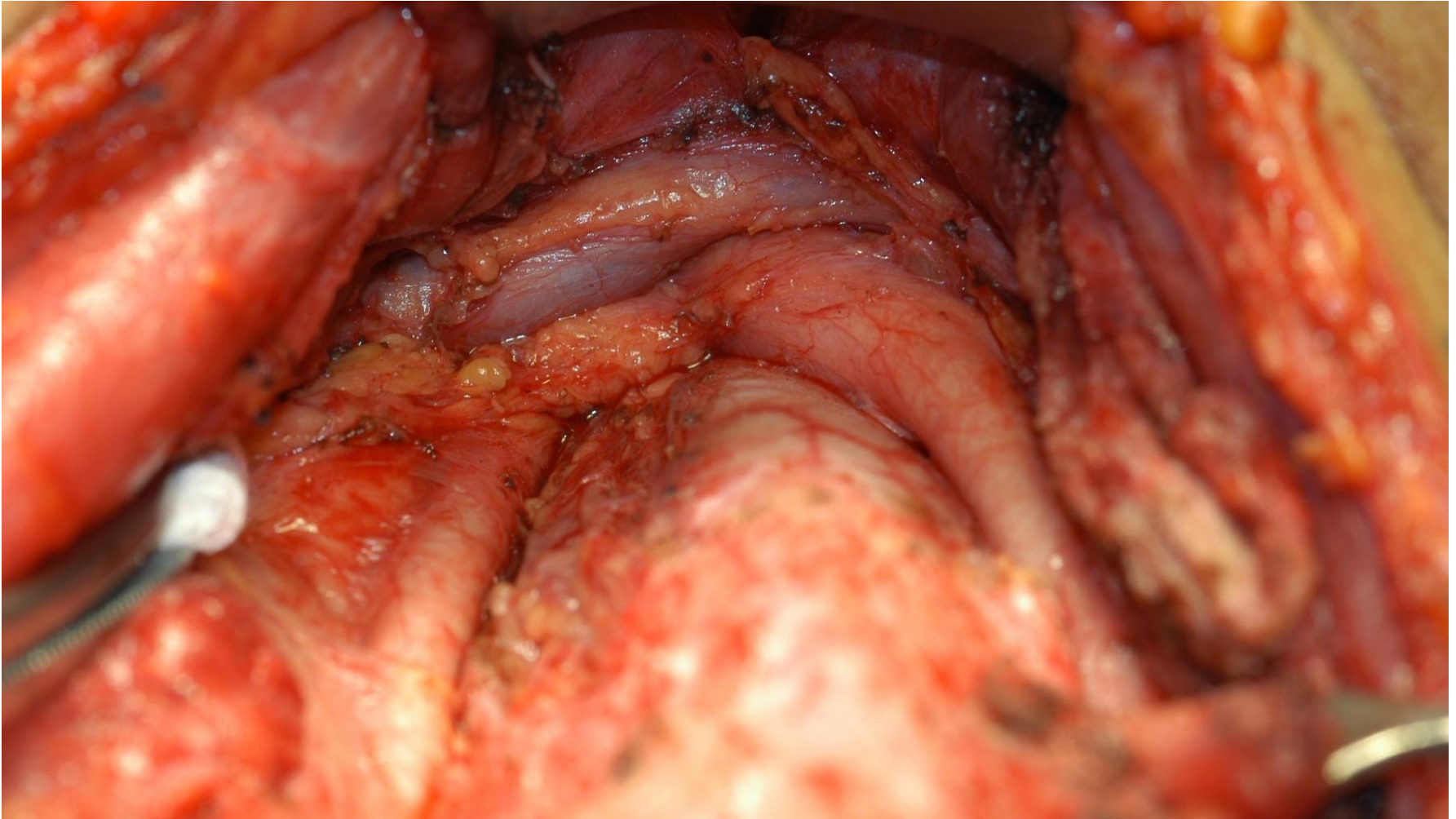
Central Neck Dissection: Left Paratracheal



Central Neck Dissection: Left Paratracheal



Central Neck Dissection



Nerve Monitoring

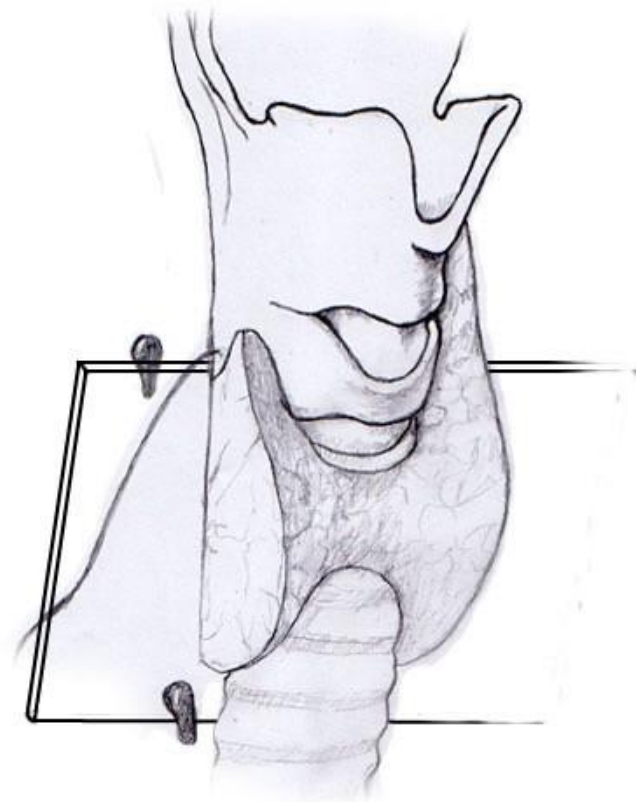
Intraoperative nerve monitoring (IONM) is useful during CND given its ability to:

1. Map and localize the RLN and the external branch of the superior laryngeal nerve (EBSLN).
2. Aid in dissection once the nerves are identified, and in elucidation of presence, mechanism and site of nerve injury.
3. To prognosticate postoperative nerve function allowing for intraoperative surgical decision changes to minimize the chances of bilateral nerve paralysis.



Parathyroid Glands

- Parathyroid glands should be preserved whenever possible during CND, especially the superior parathyroid glands
- Superior
 - Posterolateral aspect of the superior pole of the thyroid gland at the cricothyroidal cartilage junction
 - Most commonly found 1 cm above the intersection of the inferior thyroid artery and the recurrent laryngeal nerve
- Inferior
 - The inferior parathyroid glands are more variable in location
 - Most commonly found near the lower thyroid pole of the thyroid



Therapeutic Lateral Neck Dissection

- Yes!
- RECOMMENDATION 37
 - Therapeutic lateral neck compartmental lymph node dissection should be performed for patients with biopsy-proven metastatic lateral cervical lymphadenopathy.(Strong recommendation, Moderate-quality evidence)
- Functional compartmental dissection is favored over “berry picking”
 - Associated with higher rates of recurrence



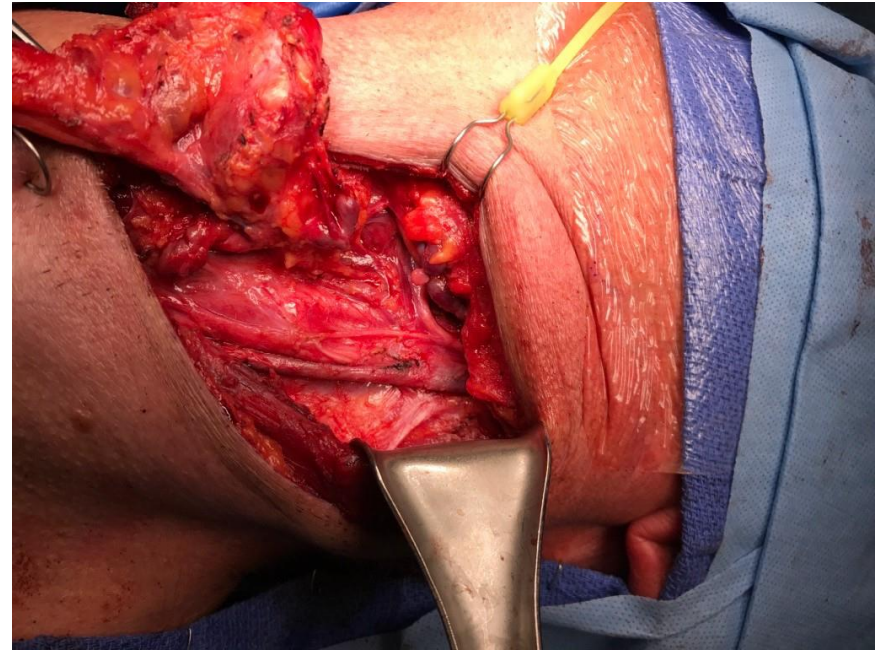
Prophylactic Lateral Neck Dissection

- NO!



Lateral Neck Dissection Extent

- Level 2: 52-60%
 - Elective 2b dissection when 2a is involved
- Level 3: 57-72%
- Level 4: 41-52%
- Level 5: 12-40%
 - Level 5b should be included routinely
- Multiple lymph nodes in multiple levels tend to be involved



Kupferman et al. Head and Neck 2004; Koo et al. Ann Surg Onc 2009; Tufano et al. World J of Surg 2009



Neck Dissection

Focal “Berry picking” of only clinically involved lymph nodes without a compartmental dissection leads to higher rates of recurrence and should be abandoned.



Lymph Node Management

- Therapeutic central neck dissection
 - Yes
- Prophylactic central neck dissection
 - Controversial
- Therapeutic lateral neck dissection
 - Yes
- Prophylactic lateral neck dissection
 - No
- Multidisciplinary team decision-making process that includes the patient, surgeon, and endocrinologist weighing the risks and benefits individually in each case



Multi-disciplinary Team

Communication of intraoperative findings and postoperative care from the surgeon to the other multidisciplinary collaborators of the patient's thyroid cancer care team is critical for individualized risk stratification, subsequent therapy, and monitoring approaches that are often jointly managed in the postoperative setting.

Agrawal et al. Head and Neck. 2017.



Conclusion

- More thyroid cancer
 - NIFTP
- Less surgery
 - Observation is an option
 - Lobectomy is a (preferred) option
- Appropriate Surgery





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