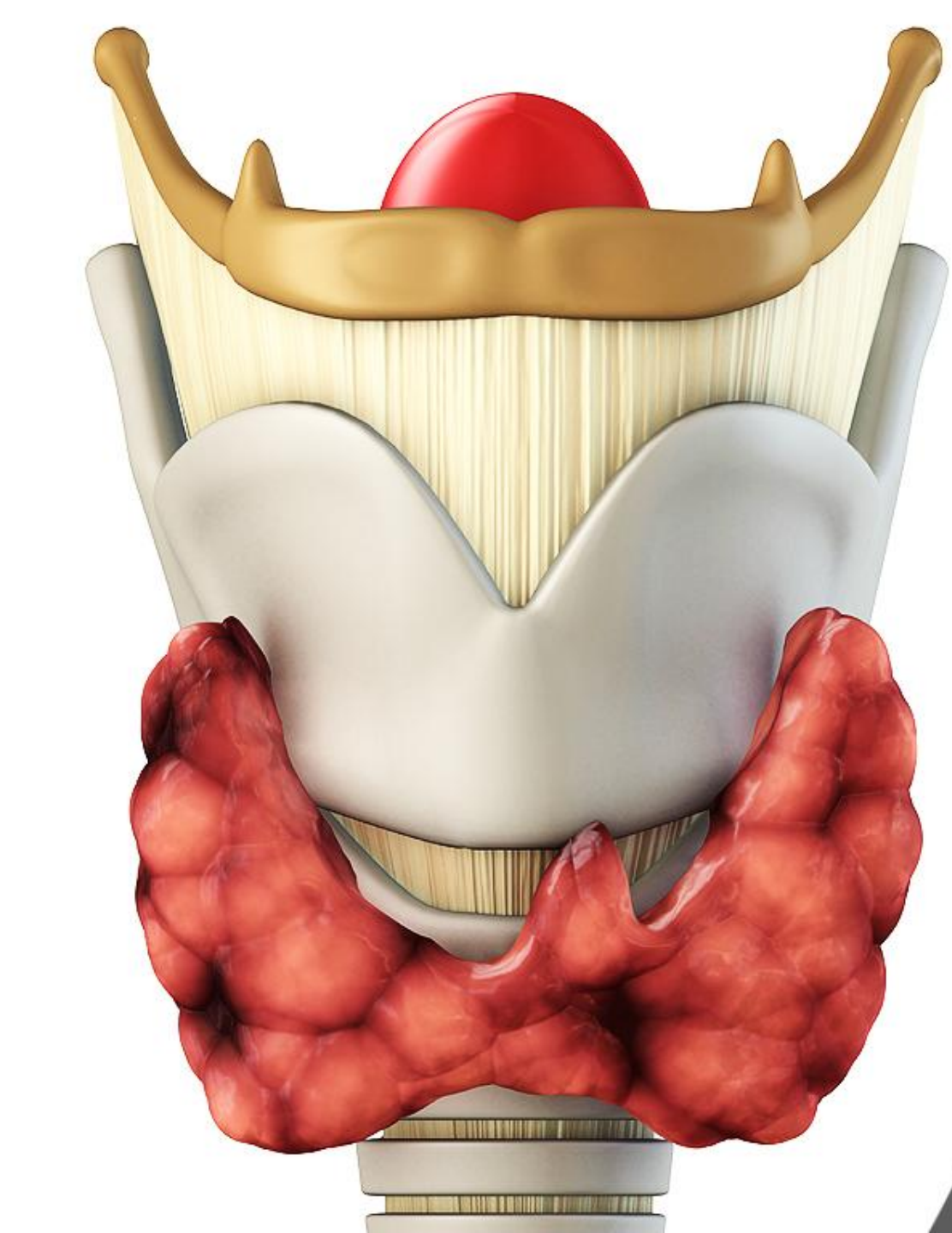


2025 American Thyroid Association Management Guidelines for Adult Patients with Differentiated Thyroid Cancer

Marjan Golshani

General definitions

- **Active surveillance:**

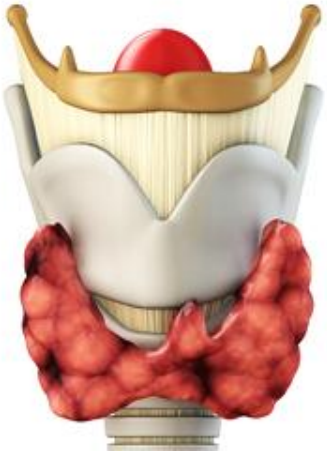
The ongoing observation or active monitoring of a known or suspected primary, intrathyroidal, low-risk DTC with serial imaging as an alternative to upfront surgical intervention.

- **Disease monitoring:**

Monitoring for biochemical (elevated level of serum Tg) and/or structural persistence or recurrence of disease (as confirmed by imaging and/or biopsy) following the diagnosis and initial treatment (surgery – RAI) of thyroid cancer.

- **Response to therapy:**

Excellent response, Indeterminate response, Biochemically incomplete response, Structurally incomplete response



General definitions

- **Clinically Persistent Disease:**

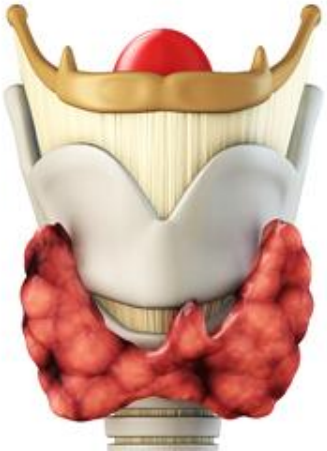
Biochemical or structural evidence of disease within 90 days of initial therapy (or intervention for persistent disease).

- **Clinically Recurrent Disease:**

Biochemical or structural disease subsequently identified in patients previously deemed to have an excellent response following therapy. Clinically recurrent disease likely represents **progression of residual disease** that is below the lower limits of detection.

- **Risk of Recurrence:**

We use the term “recurrence” to mean clinical recurrence, recognizing that most recurrences reflect growth of residual disease to clinically detectable levels. For the purpose of these guidelines, categories are designated as low (<10%), low-intermediate (10–15%), intermediate-high (‡16–30%), and high (>30%) risk of recurrence.



Estimated Risk of Structural Recurrence

	PTC AND SUBTYPES[Φ]	FTC/IEFVPTC[Φ]	OTC[Φ]
RISK OF RECURRENCE	HIGH >30%	HIGH >30%	HIGH >30%
	T3a + microscopic ETE, T3b, or T4; or ANY T with any of the following: Pooly differentiated or high grade Gross incomplete resection (R2) cN1 ≥3 cm Extranodal extension (ENE) Distant metastasis (M1)	T3a + microscopic ETE, T3b, or T4; or ANY T with any of the following: Pooly differentiated or high grade Widely invasive Encapsulated angioinvasive: extensive vascular invasion ≥4 vessels cN1 ≥3 cm** Extranodal extension (ENE) Distant metastasis (M1)	T3a + microscopic ETE, T3b, or T4; or ANY T with any of the following: Pooly differentiated or high grade Widely invasive Encapsulated angioinvasive: extensive vascular invasion ≥4 vessels cN1 ≥3 cm** Extranodal extension (ENE) Distant metastasis (M1)
INTERMEDIATE-HIGH ≥16-30%	T1, T2, or T3a with any of the following: Bilateral multifocality >1 cm Clinically evident lateral LN mets (cN1b) <3 cm 2+ Low-intermediate risk factors Aggressive histology Vascular invasion	T1, T2, or T3a with any of the following: Clinically evident lateral LN mets (cN1b) <3 cm** 2+ Low-intermediate risk factors	T1, T2, or T3a with any of the following: Clinically evident lateral LN mets (cN1b) <3 cm** 2+ Low-intermediate risk factors
LOW-INTERMEDIATE 10-15%	T3a or; T1 or T2 with any of the following: Unilateral multifocality Microscopic ETE cN1a or pN1a >2mm* or >5LNs Negative margins or microscopic + posterior margin (R1)	T3a or; T1 or T2 with any of the following: Microscopic ETE Limited vascular invasion <4 vessels[Φ] cN1a or pN1a >2mm* or >5LNs** Negative margins or microscopic + posterior margin (R1)	T3a or; T1 or T2 with any of the following: Microscopic ETE Limited vascular invasion <4 vessels[Φ] cN1a or pN1a >2mm* or >5LNs** Negative margins or microscopic + posterior margin (R1)
LOW <10%	T1 and T2 (≤4cm): Unifocal pN0a, or cN0 and pN1a (≤5 LNs, all ≤2 mm) Negative margins or only microscopic + anterior margin (R1)	T1 and T2 (≤4cm): Minimally invasive: capsular invasion only[Φ] pN0a, or cN0 and pN1a (≤5 LNs, all ≤2 mm)** Negative margins or only microscopic + anterior margin (R1)	T1 and T2 (≤4cm): Minimally invasive: capsular invasion only[Φ] pN0a, or cN0 and pN1a (≤5 LNs, all ≤2 mm)** Negative margins or only microscopic + anterior margin (R1)

LEGEND: PTC: Papillary Thyroid Carcinoma FTC/IEFVPTC: Follicular Thyroid Carcinoma/Invasive Encapsulated Follicular Variant of Papillary Thyroid Carcinoma OTC: Oncocytic Thyroid Carcinoma [Φ]: WHO 2022 definition

*: No clear cutoffs for LNs between low-intermediate and high-intermediate risk groups. In general, smaller size and fewer lymph node metastases are associated with lower risk of recurrence.

**: LN mets are uncommon in OTC and FTC/IEFVPTC

General definitions

- **Total Thyroidectomy:**

Surgical removal of the entire thyroid gland.

- **Near-Total Thyroidectomy:**

a small remnant may be left for a specific reason (usually confidence in nerve preservation).

- **Lobectomy or Hemithyroidectomy with or without Isthmusectomy:**

- **Subtotal Thyroidectomy:**

leaving 3–5 g of thyroid tissue with the intent of maintaining adequate thyroid hormone production. This operation is not recommended if the diagnosis of thyroid cancer is known preoperatively.

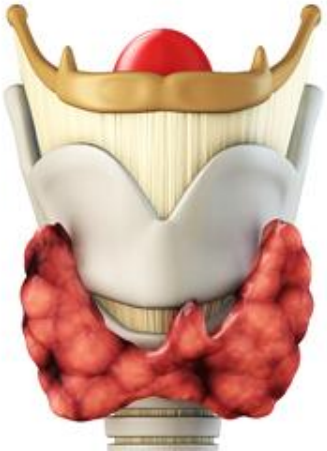
General definitions

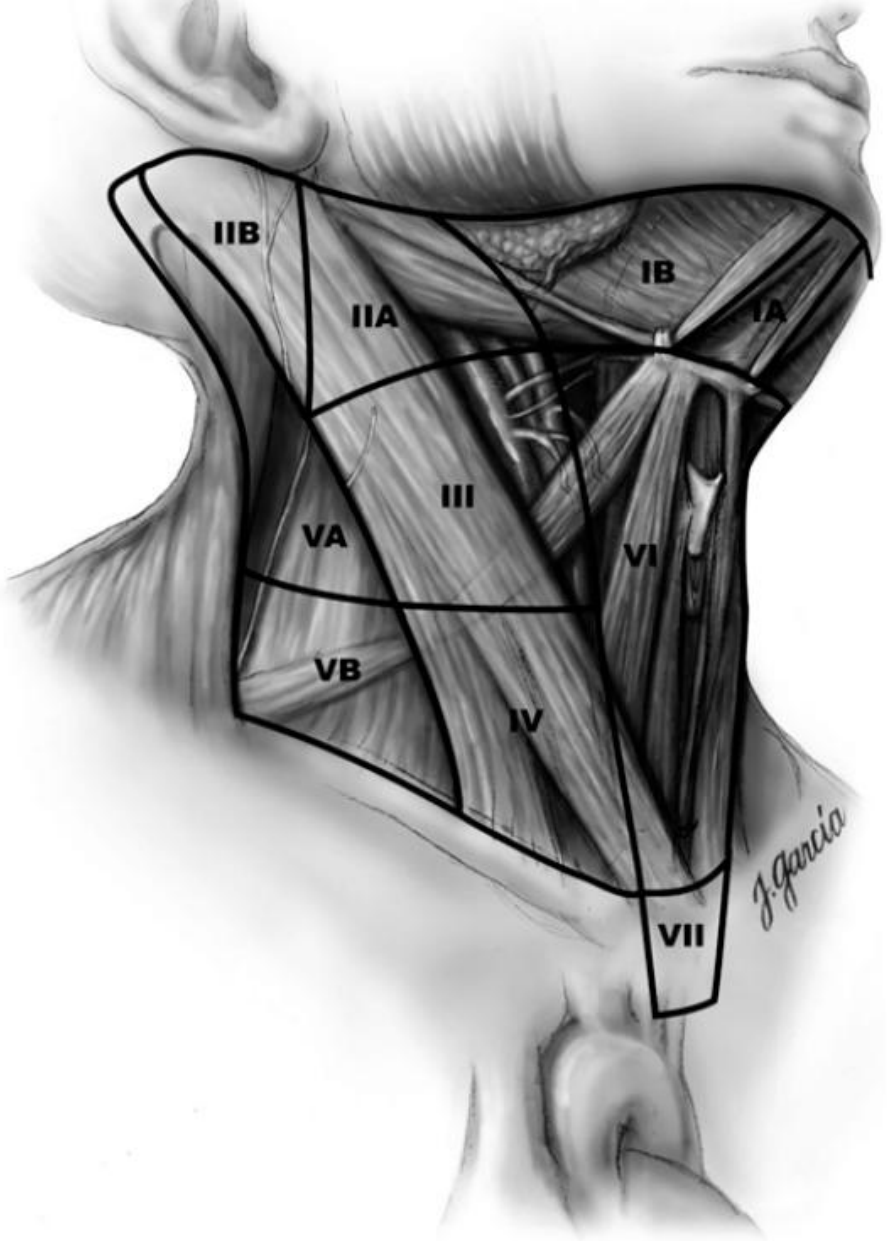
- **Central Neck Dissection:**

Central neck lymph nodes include Levels **VI and VII**. Central neck dissection is a comprehensive removal of **pretracheal** and **prelaryngeal** lymph nodes, along with at least one **paratracheal** nodal basin. It can be unilateral or bilateral; the laterality and extent of dissection should be documented at the time of operation in addition to surgical intent (therapeutic vs. prophylactic).

- **Lateral Neck Dissection:**

Full compartment dissection of the lateral cervical neck lymph nodes in Levels **IIA, III, IV, and VB** ipsilateral to the tumor and performed for clinical evidence of metastatic involvement. Dissection of Levels I, IIB, and VA are not regularly performed but can be considered based on findings suggestive of metastatic disease in these compartments.





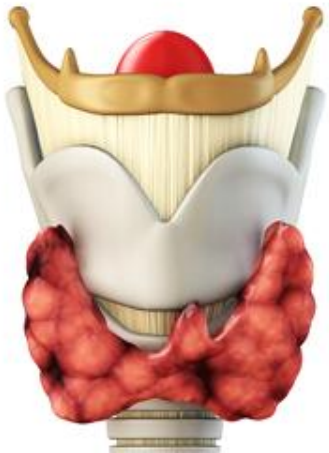


FIG. 3. Nodal levels with corresponding anatomical landmarks (used with permission from R. Udelsman, MD).

General definitions

- **R0 Resection:**

the surgical margin is microscopically negative for residual tumor.

- **R1 Resection:**

there is no residual macroscopic tumor but that microscopically positive margins still demonstrate the presence of tumor.

- **R2 Resection:**

gross (macroscopic) disease remains post-surgery.

General definitions

- **Remnant Ablation:**

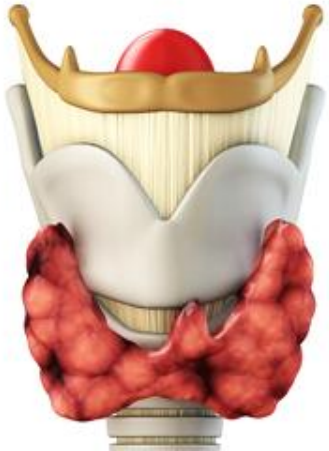
RAI administration to destroy benign remnant thyroid tissue following total or near-total thyroidectomy.

- **Adjuvant therapy:**

RAI administration to destroy suspected (but not identified) remaining thyroid cancer following total or near-total thyroidectomy.

- **Therapeutic treatment:**

RAI administration to treat known residual or recurrent thyroid cancer



Thyroid Cancer Pathology

- Throughout this document, the 5th edition of the WHO Classification of Thyroid Tumors has been utilized for descriptions of the types of non-anaplastic follicular cell derived thyroid carcinomas and NIFTP.

- Approximately **90%** of thyroid cancer cases are **well differentiated** and are classified based on the predominant **histomorphology**; however, they now also **can be categorized based on their molecular profiles**.

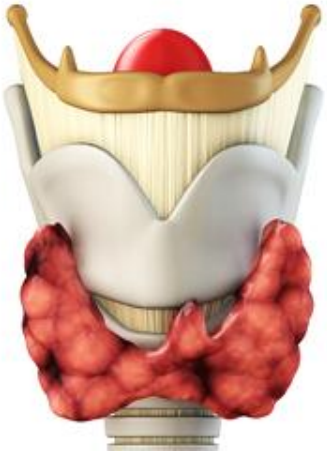
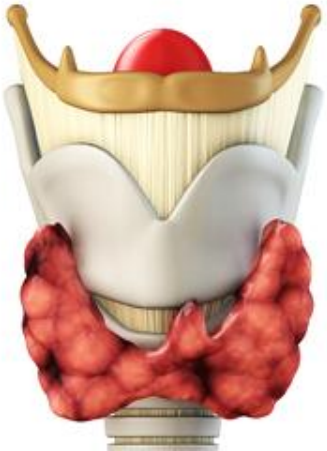


Table 3. WHO Pathological Classification of Differentiated Thyroid Carcinoma (WHO, 5th Edition)[24]

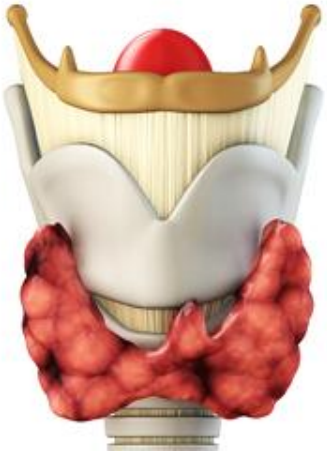
Follicular cell-derived neoplasms	*Subtypes*
Low-risk neoplasms	1. NIFTP[a,b] 2. Follicular tumor of uncertain malignant potential 3. Hyalinizing trabecular tumor
Malignant neoplasms	1. Follicular thyroid carcinoma a. Minimally invasive b. Encapsulated angioinvasive c. Widely invasive 2. Invasive encapsulated follicular variant papillary carcinoma 3. Papillary thyroid carcinoma-subtypes a. Classical b. Encapsulated classical c. Infiltrative follicular d. Tall cell e. Columnar cell f. Hobnail g. Diffuse sclerosing h. Solid / trabecular i. Warthin-like j. Oncocytic k. Others[c] 4. Oncocytic carcinoma a. Minimally invasive b. Encapsulated angioinvasive c. Widely invasive
Malignant neoplasms—high-grade follicular-cell derived non-anaplastic carcinoma	1. Poorly differentiated carcinoma (Turin-criteria): a. Solid/trabecular architecture b. Absence of nuclear features of papillary thyroid carcinoma c. Tumor necrosis d. Mitotic index ≥3/10 high power fields (HPFs) e. And/or convoluted tumor nuclei 2. Differentiated high-grade thyroid carcinoma a. Differentiated cytological and architectural features b. At least one the following two histomorphologic features c. Mitotic count ≥5/2 mm^2 and/or tumor necrosis
Other rare neoplasms	1. Salivary gland-type carcinomas a. Mucoepidermoid carcinoma of the thyroid b. Secretory carcinoma of salivary gland type 2. Thyroid tumors of uncertain histogenesis a. Sclerosing mucoepidermoid carcinoma with eosinophilia b. Cribriform morular thyroid carcinoma 3. Thymic tumors within the thyroid

[a]Formerly classified as noninvasive and encapsulated follicular variant of papillary thyroid carcinoma.
[b]See Table 2.
[c]Includes rare subtypes such as PTC with fibromatosis/fasciitis-like stroma, clear cell subtype, spindle cell subtype, and so forth.
PTC, papillary thyroid carcinoma; WHO, World Health Organization.



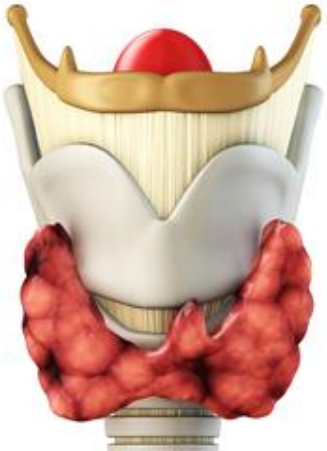
DTC/PTC

- most common type of DTC
- typically indolent
- associated with excellent long-term survival: 96% at 5 years, 93% at 10 years, and >90% at 20 years.
- Overall mortality rates: 1–6.5%
- overall recurrence rate:15–35%
- tumor recurrence: typically in the tumor bed, cervical LNs or (rarely) distant sites
- Characteristic nuclear features and can present as infiltrative and encapsulated tumors.
- Most PTCs (90%) develop by the activation of a **MAPK pathway-event**. This activation occurs via mutually exclusive mutations in **BRAF** or **RAS** oncogenes.
- A subset of PTCs is acquired by gene fusions involving **RET**.
- Oncogenic mutations at **BRAFV600E** are the **most common in PTC**; a minority can show non-V600E mutations, such as BRAFK601E or BRAF fusions.



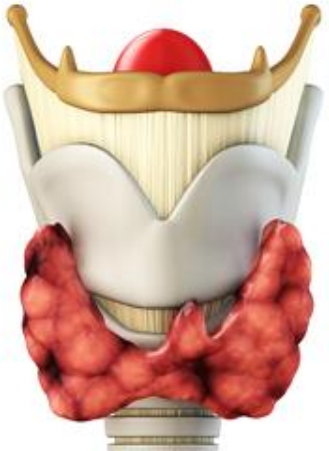
DTC/ IEFVPTC

- The IEFVPTC is an encapsulated and invasive follicular-patterned tumor. Based on its tendency for vascular invasion, distant metastasis, and molecular profile, it can behave similarly to FTC



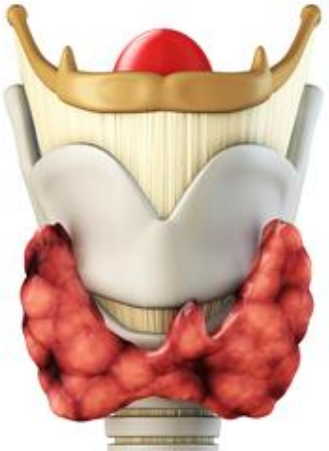
DTC/ FTC

- Encapsulated follicular patterned tumors without the nuclear features of PTC
- characterized by the presence of vascular (limited or extensive) and or capsular invasion.
- are mostly driven by activating mutations in **RAS** oncogenes (NRAS>HRAS>KRAS), PAX8::PPARc fusions, EIF1AX mutations, PIK3CA mutations, or loss of PTEN expression.
- **BRAFV600E and RET fusions typically are not seen in FTC.**
- Mutations in **DICER1**, which encodes a ribonuclease in the processing of microRNA precursors, **occur in RAS-like thyroid neoplasms** and are prevalent in FTC.
- DICER1 mutations can also be seen in subsets of PTC, differentiated high-grade thyroid carcinoma (DHGTC), poorly differentiated thyroid carcinoma (PDTC), and anaplastic thyroid carcinoma (ATC).



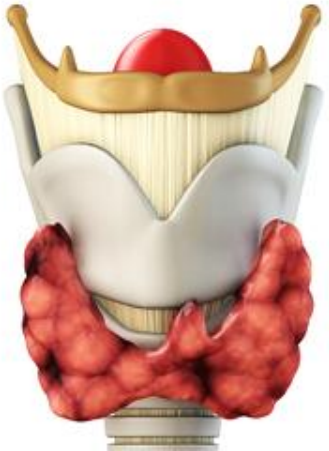
DTC/ OTC

- Previously known as Hurthle cell carcinoma
- Has different clinical behavior from classical forms of FTC
- are now considered a third form of DTC rather than a subtype of FTC
- account for ~3% of all DTC
- are usually encapsulated and composed of ≥75% oncocytic cells.
- Oncocytic features can be identified in some PTC or FTC cells at lower frequencies.
- Most of these tumors are larger in size; however, smaller tumors can be identified.
- Like FTC, the presence of invasive characteristics (i.e., tumor capsule and/or vascular invasion in an encapsulated oncocytic neoplasm) is diagnostic of OTC
- can be classified as minimally invasive, encapsulated angio-invasive, and widely invasive.
- have a greater tendency toward lymph node metastases while retaining a predilection for distant metastases.
- **unlike FTC, OTCs often are not radioiodine avid despite retaining other differentiated features, such as Tg secretion and TSH receptor expression**.



High-grade follicular cell derived, non-anaplastic carcinoma

- includes PDTC (Poorly Differentiated) and DHGTC (Differentiated High Grade)
- By molecular analysis, PDTC and DHGTC harbor driver mutations in **BRAF** (BRAFV600E) and **RAS** genes, and some cases may show gene fusions (often RET and NTRK3).
- Additional mutations in the TERT promoter, PIK3CA, and TP53 are commonly identified.
- **DHGTC**: has certain histological and cytopathologic ,are invasive, they have one of the following two histological features: mitotic count $\geq$5 per 2 mm2 and tumor necrosis.
- **PDTC:** are follicular cell derived tumors that show a minor component of DTC (papillary, follicular, oncocytic), show solid and/or insular growth pattern with presence of either necrosis or $\geq$3 per 2 mm2, and lack the usual histological characteristics and aggressiveness of ATC.
- In both cases, clinical behavior is considered intermediate between DTC and ATC.



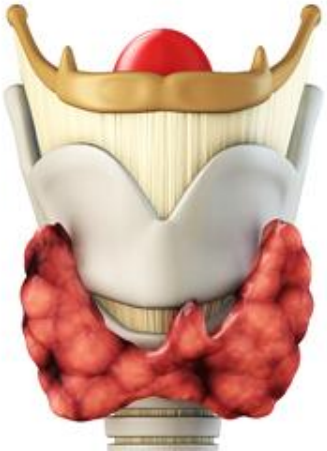
NIFTP

- In 2017, NIFTP were classified as a distinct category in the revised WHO Classification of Tumors of Endocrine Organs, corresponding to a neoplasm with very low malignant potential.
- It comprise approximately 2.1–9.6% of follicular cell derived thyroid neoplasms, with relatively lower incidence in Asia than in North America and Europe.

TABLE 2. PATHOLOGICAL DIAGNOSTIC CRITERIA OF NIFTP

A. Encapsulation or clear demarcation[a]
B. Follicular growth pattern, including:
Absent papillae[b]
Absent psammoma bodies (reminiscent of dead papillae)
<30% solid, trabecular, or insular growth pattern
C. Nuclear features of papillary thyroid carcinoma
D. No invasive characteristics (no capsular or vascular invasion)[b]
E. No tumor necrosis
F. No high mitotic activity, defined as <3 mitoses per 10 high-power field

[a]Tumors are well demarcated from the surrounding thyroid parenchyma and can be thinly or partially encapsulated.
[b]Features requiring histopathologic examination of the entire tumor capsule and tumor.
NIFTP, noninvasive follicular tumors with papillary-like nuclear features.



- NIFTPs often coexist with one or more NIFTPs or other thyroid malignancies in the ipsilateral or contralateral lobes.

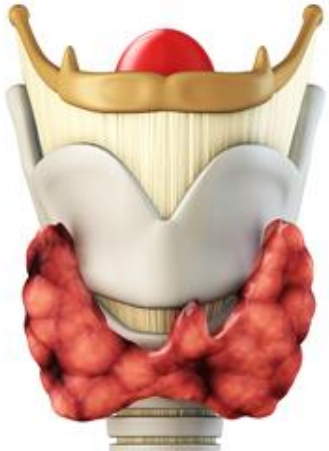
Is NIFTP Considered Thyroid Cancer?

RECOMMENDATION 1

- NIFTP and other tumors of uncertain malignant potential (Follicular Tumor of Uncertain Malignant Potential and Hyalinizing Trabecular Tumor) are diagnosed pathologically and have a very low malignant potential (lower than the lowest-risk DTC). Further treatment with completion thyroidectomy/lymphadenectomy and/or RAI is not advised routinely. The optimal approach to postoperative monitoring of these tumors is uncertain. (Good Practice Statement)

Thyroid cancer epidemiology

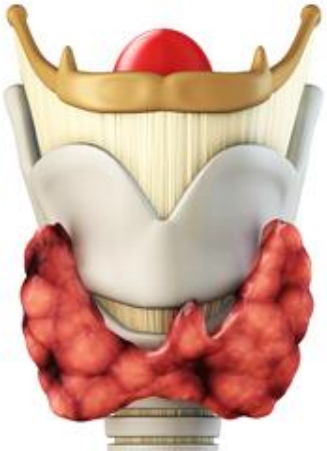
- 1985-2015: rising thyroid cancer incidence peaked in 2015
- 2015-2017: a decline was observed for the first time in 30 years.
- The initial increase in incidence: was related to a true increase in the incidence of PTC as well as widespread use of diagnostic imaging and potential overdiagnosis.
- The decline in incidence: may be due to a heightened awareness of the potential harms of overdiagnosis.
- In 2017, the U.S. Preventative Services Task Force (USPSTF) recommended against thyroid cancer screening in asymptomatic adults. This also might have contributed to decreasing thyroid cancer incidence.
- The 2016 reclassification of NIFTP also is reported to have contributed to the observed decline.



Thyroid cancer epidemiology

Accepted risk factors for thyroid cancer:

- history of childhood head and neck radiation
- total body radiation for bone marrow transplantation
- exposure to ionizing radiation from fallout in childhood or adolescence.
- Adult occupational radiation exposure in the low-to-moderate dose range (<0.5 Gy) has not been associated with a significantly increased risk of thyroid cancer.



Additional potential risk factors:

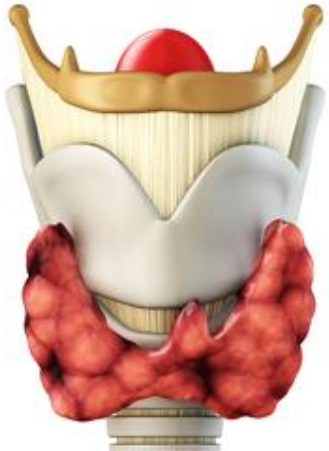
- obesity
- Flame retardants (FR):

Thyroid cancer epidemiology

DTC can occur in families: FNMTC, It can be classified as:

- Syndromic: when it is one of a constellation of tumors (e.g., PTEN, Cowden disease, FAP, Carney complex, Werner syndrome/progeria)
- Non-syndromic: when DTC is the single or prevailing inherited malignancy.

- It has been shown that High Ki-67 proliferation index correlates with poor prognosis in thyroid carcinomas; however, additional studies are needed to make this an essential step in the pathological assessment of well-differentiated thyroid carcinomas.



Which patients with DTC should be offered germline genetic testing?

RECOMMENDATION 2

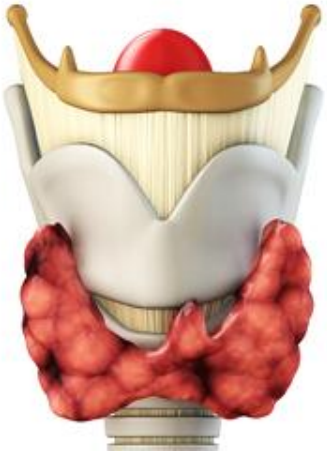
Germline genetic testing may be offered in the following scenarios (Table 4):

- A. Clinical suspicion for Cowden/PTEN hamartoma tumor syndrome (PHTS) due to a combination of DTC and non-thyroid malignancy/tumors/features (Conditional recommendation, Moderate certainty evidence)
- B. In patients who were diagnosed with **FNMTC as children**, clinical and family history should be evaluated for features of DICER1 tumor predisposition. Consideration may be given to germline DICER1 testing in patients from families with pediatric patients with DTC. (Conditional recommendation, Very low certainty evidence)
- C. Pathologic diagnosis of **cribriform morular thyroid carcinoma (APC gene)** (Conditional recommendation, Moderate certainty evidence)
- D. Other combinations of tumors and/or cancers in a patient and/or their family members may raise concern for a hereditary predisposition condition, including rare conditions such as **Carney complex** or **Werner syndrome**. In these patients, genetic counseling and testing may be offered. (Conditional recommendation, Moderate certainty evidence)

Which patients with DTC should be offered germline genetic testing?

The recommendations put forth by the International DICER1 Symposium suggest that germline DICER1 testing be considered based on the presence of **multinodular goiter or thyroid cancer** in **two or more first-degree relatives.**

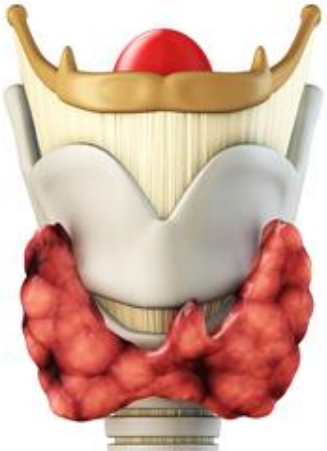
However, given the commonality of this presentation in adults and the relative rarity of germline pathogenic variants in DICER1, the yield in this scenario may be low. Further research is required to determine the best screening strategy.



Should patients with non-syndromic FNMTC receive genetic testing?

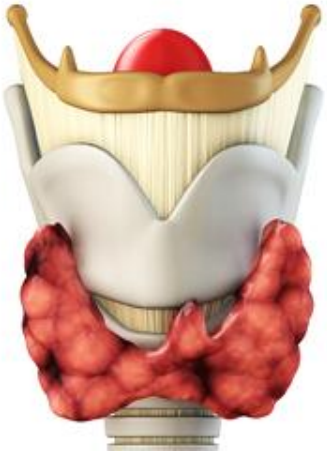
RECOMMENDATION 3

There is a lack of evidence to suggest the utility of clinical germline genetic testing in non-syndromic FNMTC. In non-syndromic FNMTC, the non-thyroid malignancies in the family may drive decision-making regarding genetic testing. (Conditional recommendation, Moderate certainty evidence)



Should patients with non-syndromic FNMTC receive genetic testing?

- Several studies done: in some families candidate genes identified
- To date, these genes **while important for individual families**, are **nonrecurring** and appear to be "**private**" to those families.
- Therefore, data do not support their inclusion in clinical panel testing.
- Because of the **AD** inheritance pattern in most families, there may be a role for **thyroid cancer screening** in selected non-syndromic FNMTC in which there appears to be high penetrance, early age onset thyroid cancer, or aggressive disease.
- Some families with FNMTC may have enrichment of nonthyroid malignancies, which may be an indication for germline genetic testing.



Should family members of patients with FNMTC be screened for thyroid cancer?

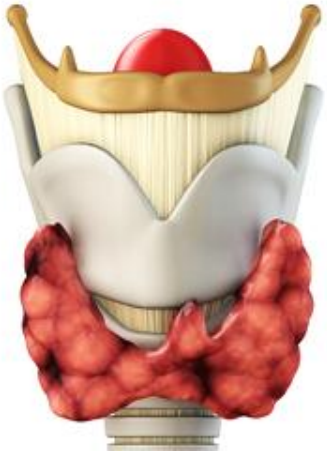
RECOMMENDATION 4

- Individuals with a family history of FNMTC should have a careful history and directed neck examination as a part of regular health maintenance. Ultrasound screening may be considered in first-degree family members of individuals who meet criteria for a clinical diagnosis of FNMTC due to the presence of three or more (first or second degree) related individuals with diagnoses of NMTC. Ultrasound screening may also be considered in families with only two affected individuals showing other concerning features (such as particularly young ages of diagnosis) or with limited family structure. The age for initiation of such screening requires further study and should be carefully weighed against the risk of overtreatment. (Conditional recommendation, Very low certainty evidence)

Should family members of patients with FNMTC be screened for thyroid cancer?

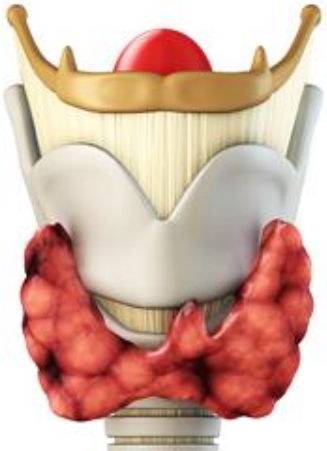
- Family members of patients with FNMTC may be considered at risk:

  5–10% of NMTC have a familial occurrence.
- However, in most of these families, only two members are affected.
- There is controversy about whether two family members are sufficient to define familial disease rather than a coincidental or screening-related association.
- Estimates suggest that when **only two first-degree family members** are affected, the probability that the disease is **sporadic** is **62%**, with the probability decreasing to **<6%** when the number of affected family members is **three or more.**
- However, while controversial, stratification of families with two first-degree family members based on age of diagnosis (both **<45** years vs. one or both >45 years) has been reported to predict subsets of individuals with more frequent **multifocal/bilateral cancers**, more **extrathyroidal** extension, and **compromised outcomes** when compared to matched sporadic NMTC, and no significant differences when comparing families with one or more members with older ages at diagnosis.



Should family members of patients with FNMTC be screened for thyroid cancer?

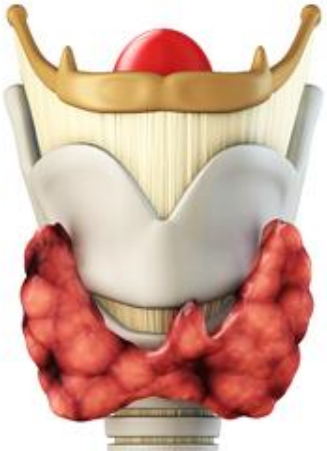
- A prospective interventional screening program investigated the impact of yearly screening in a cohort of 109 individuals from 25 kindreds (12 with two members affected and 13 with ≥3 members affected):
- Screening started as early as 7 years of age and included neck ultrasound and FNA of thyroid nodule(s) >0.5 cm.
- This led to the detection of thyroid cancer in 4.6% (2/43) of at-risk individuals from families with two members affected and in 22.7% (15/66) of at risk members from families with ≥ 3 patients affected (p = 0.01).
- The youngest age of thyroid nodule detection was 7 years, and the youngest age of thyroid cancer diagnosis was 18 years.
- Based on these data, Capezzone et al. suggest consideration of **screening with yearly ultrasound** in kindreds with ≥ 3 affected family members, **starting from the age of 20 years**, or **10 years before the earliest age of diagnosis** in the family.
- Further studies are needed to determine the optimal approach to family screening that address costs and the potential risks of overtreatment.



When should germline genetic testing be offered to patients with DTC with alterations detected on tumor samples (somatic testing)?

RECOMMENDATION 5

- When genomic testing is performed on tumor samples for clinical purposes, both somatic and germline genetic alterations can be detected. If a potentially clinically relevant germline cancer-predisposing variant is detected, evaluate patients and their family histories for clinical correlation, and consider referral for genetic counseling for possible germline testing. (Conditional recommendation, Moderate certainty evidence)

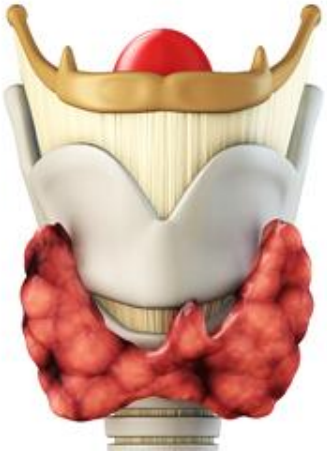


When should germline genetic testing be offered to patients with DTC with alterations detected on tumor samples (somatic testing)?

- **Sequencing** of thyroid cancer specimens: at initial diagnosis as **part of thyroid nodule evaluation**, or later to **assist in determining treatment options**.

- These tests are optimized for somatic variant detection. While paired tumor and analysis of normal tissue can help distinguish variant origin, such analysis is not a reliable method to detect germline variants, and studies have shown that up to 8.1% of pathogenic germline variants are missed on standard tumor sequencing assays.

- Therefore, confirmatory germline testing in the context of genetic counseling should be performed prior to further evaluation of a family.

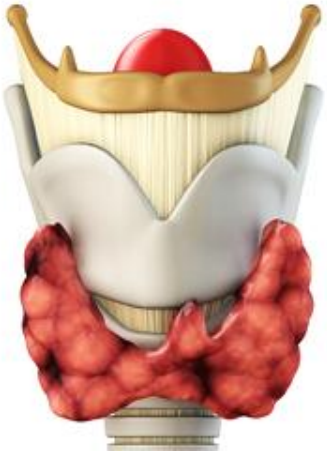


Initial Management of DTC

Shared decision-making between patients and their treating clinicians is essential.

1. In patients selected for thyroid surgery, the initial goal is to resect the primary tumor, any disease that has extended beyond the thyroid, and clinically significant lymph node metastases. **Completeness of surgical resection is an important determinant of outcome**, as lymph nodes represent the most common site (74%) of neck disease persistence/recurrence, followed by the thyroid remnant (20%) and the trachea and adjacent muscle (6%).

2. Consider which of the available multimodal treatment options is appropriate, to (a) decrease the risk of disease persistence/recurrence and metastatic spread and (b) minimize treatment-related morbidity.

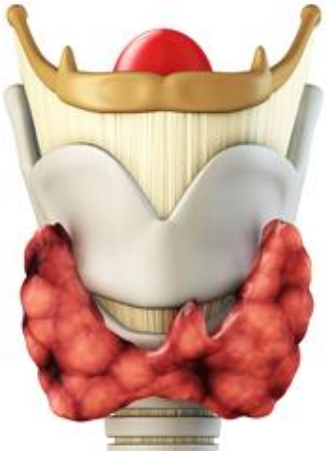


3. Determine staging and risk stratification to estimate prognosis. Cancer **staging** is useful to estimate risks of **disease-specific mortality**, while initial **risk stratification** can be used to estimate **short- and long-term risks of disease persistence/recurrence**.

Does surgical experience influence complication rates for thyroidectomy?

RECOMMENDATION 6

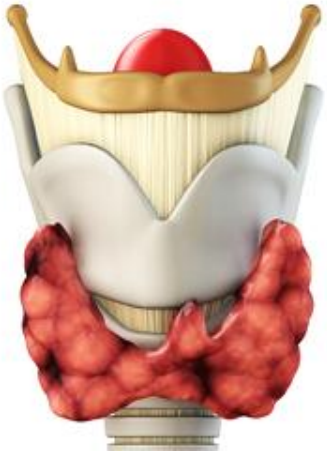
- Due to lower complication rates and improved outcomes on average associated with high volume thyroid surgeons (>25–50 thyroidectomies/year), patients with thyroid cancer should be offered referral to a high-volume surgeon, particularly for tumors requiring more extensive surgery. (Strong recommendation, Moderate certainty evidence)



Does surgical experience influence complication rates for thyroidectomy?

- There are many aspects of care where physician expertise is important in the diagnosis, staging, and management of patients with thyroid cancer, including sonography, pathology, surgery, endocrinology, nuclear medicine, oncology, and radiation therapy.

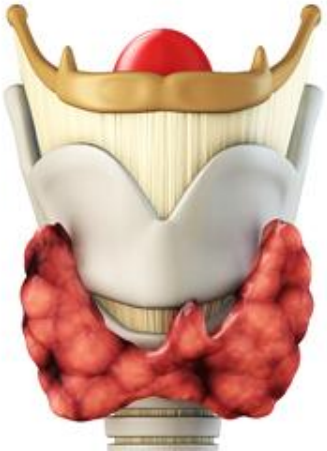
- There is a strong association between higher surgeon volume and favorable patient outcomes:
  - less recurrent laryngeal nerve injury
  - less wound complications
  - less thyroid remnant tissue after resection resulting in a reduced RAI dose
  - less involved tumor margin
  - less complication rates
  - lower hospital mortality



- 25- 50 surgery/year: thyroid surgical volume necessary to achieve lower complication rates
- >50 cases for more advanced thyroid cancer.

Does surgical experience influence complication rates for thyroidectomy?

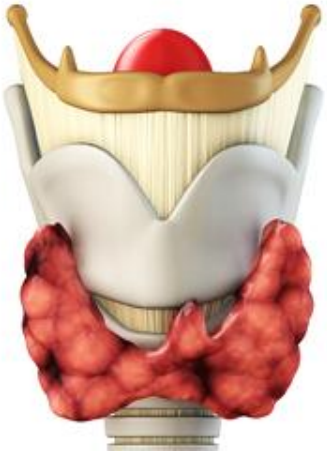
- Even high-volume surgeons have a higher overall postoperative complication rate when performing total thyroidectomy (when compared with lobectomy).
- In the HCUP-NIS study, **high-volume** thyroid surgeons had a complication rate of **7.6**% following thyroid **lobectomy** compared with a rate of **14.5**% following **total thyroidectomy**.
- For **low-volume** surgeons, the complication rates were **11.8**% and **24.1**%, respectively.



What is the role of preoperative staging with diagnostic imaging and laboratory tests?

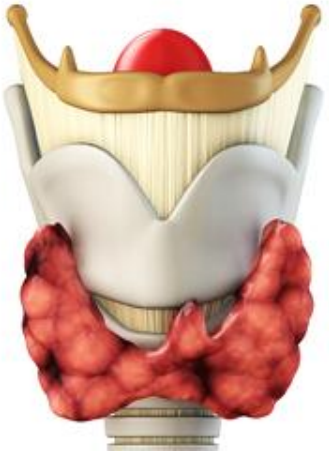
RECOMMENDATION 7

- A. Preoperative neck ultrasound to evaluate cervical lymph nodes in the central and lateral neck compartments as well as for gross extrathyroidal extension is recommended for all patients undergoing surgery for malignant cytologic or molecular findings. (Strong recommendation, Moderate certainty evidence)
- B. Ultrasound-guided FNA of sonographically suspicious lymph nodes greater than 8–10 mm in the smallest diameter should be performed to confirm malignancy if this would change management. (Strong recommendation, Moderate certainty evidence)
- C. The addition of FNA-Tg washout in the evaluation of suspicious cervical lymph nodes may be performed in select preoperative patients, but interpretation may be difficult in patients with an intact thyroid gland. (Conditional recommendation, Low certainty evidence)



Preoperative Sonography

- DTC (and particularly PTC) involves **cervical lymph nodes** in **20–50**% of patients using standard **pathological** techniques, and these metastases may be present even when the primary tumor is small and intrathyroidal.
- The frequency of **micrometastases** (less than 2 mm) may approach **90**%, depending on the sensitivity of the detection method.
- However, the clinical implications of **micrometastases** are likely less significant compared with macrometastases, and they **do not appear to affect survival**; when they are in the central neck, they also **do not appear to increase recurrence**.

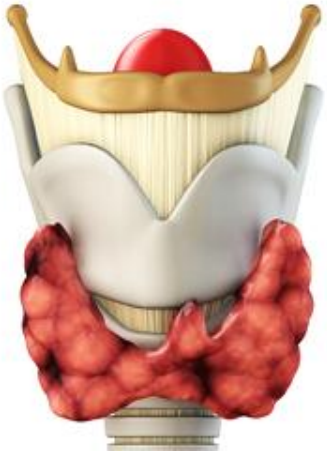


- **Preoperative ultrasound** identifies suspicious cervical adenopathy in **20–31%** of cases, potentially altering the surgical approach in as many as 20% of patients.
- It has **significantly less clinical utility in identifying central neck lymph nodes** due to the presence of the overlying thyroid gland.

Preoperative Sonography

- Sonographic features suggestive of abnormal metastatic lymph nodes:
  - Enlargement
  - loss of the fatty hilum (OR 1.9)
  - rounded rather than oval shape (long axis/short axis ≤2; OR 1.6)
  - hyper-echogenicity (OR 5.4)
  - cystic change (OR 71.8)
  - calcifications (OR 6.2)
  - peripheral vascularity or abnormal blood flow (OR 3.8)

- No single sonographic feature has adequate sensitivity for detecting metastatic lymph nodes



- All features have a high specificity: 87–99.6%

- Absence of a fatty hilum has the highest sensitivity but low specificity at 66.4%.

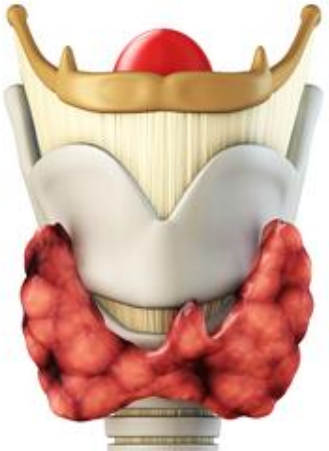
Preoperative Sonography

- Metastatic lymph nodes: more likely to occur in Levels **III**, **IV**, and **VI** than in Level II, although this **may not be true** for PTC tumors arising in the **upper pole** of the thyroid, which have a higher propensity to produce skip metastases to Levels **II** and **III**.

- Confirmation of malignancy in lymph nodes: ultrasound-guided FNA aspiration for cytology and/or measurement of Tg in the needle washout (FNA-Tg).

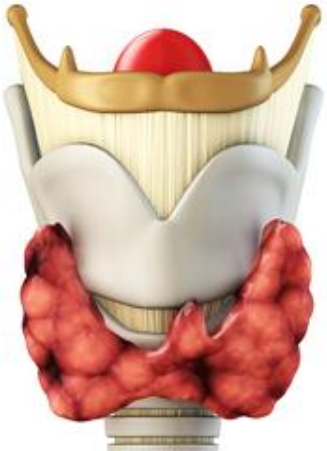
- **Tg washout** is a helpful adjunct to FNA, particularly in cases where the lymph nodes are **cystic**, **cytological evaluation** of the lymph node is **inadequate**, or the **cytological and sonographic evaluations disagree** (e.g., normal cytological biopsy of a large lymph node with microcalcifications).

- **False positive Tg washout** may occur, particularly in lymph nodes in the **central** compartment when the thyroid gland is still present, but it remains valid in the presence of positive serum TgAb.



Preoperative Tg Washout

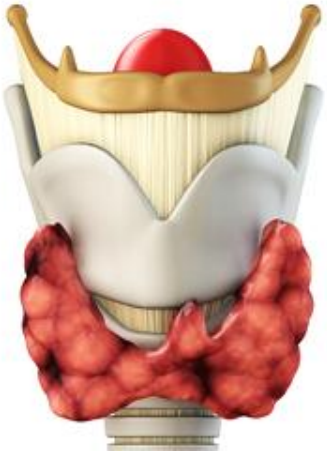
- Data are limited to support a definitive FNA-Tg threshold.
- A systematic review and meta-analysis showed that **FNA cytology with FNA-Tg washout** has a **NPV of 99.4%** and **accuracy of 86.8% .**
- If the FNA-Tg level is ≤1.0 ng/mL , then the NPV approximates 100%.
- However, non-metastatic lymph nodes can have concentrations as high as 32 ng/mL.
- In a systematic review: the **highest sensitivity** was observed with a FNATg cut-off of **1 ng/mL** and the **highest specificity** was observed with a cutoff of **40 ng/mL.**
- Other factors that influenced the accuracy of FNA-Tg included TSH suppression, presence of serum Tg, and methodologic differences in Tg measurement.
- The presence of serum TgAb interferes with circulating serum Tg measurement but does not appear to interfere with FNA-Tg measurements.



When should preoperative cross-sectional or 18F-FDG-PET imaging be performed?

RECOMMENDATION 8

- Preoperative use of cross-sectional imaging studies (CT, magnetic resonance imaging [MRI]) of the neck and mediastinum with intravenous contrast is recommended as an adjunct to physical examination and ultrasound for patients with clinical suspicion for advanced or invasive disease, including primary tumors with gross extrathyroidal extension, extensive (e.g. bulky or invasive) adenopathy, or disease concerning for aerodigestive tract and/or thoracic involvement (Strong recommendation, Moderate certainty evidence)
- Performing preoperative cross-sectional imaging of the chest, abdomen, and pelvis in search for distant metastases is recommended in situations when results will influence extent of surgery. (Good Practice Statement)
- Routine preoperative 18F-fluorodeoxyglucose (FDG)-PET/CT is not recommended prior to surgery. (Strong recommendation, Moderate certainty evidence)

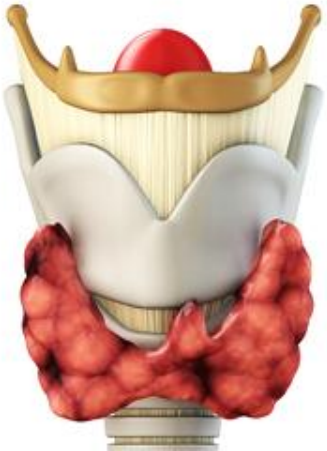


Preoperative CT Scan

- Since ultrasound evaluation is operator-dependent and cannot always adequately image deep anatomical structures or those acoustically shadowed by bone or air, alternative imaging procedures may be preferable or useful adjuncts in some clinical settings.

- While **ultrasound** is more **specific** for nodal disease, **CT** is more **sensitive**, and the **combination of both may increase diagnostic accuracy**.

- In view of the higher cost of CT compared with ultrasound, the associated radiation exposure, and potential risks of intravenous contrast administration in specific populations, it is important to determine the imaging needs on an individual patient basis.

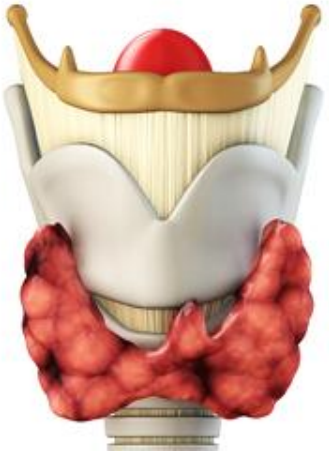


Preoperative CT Scan

- If there is evidence of more advanced locoregional disease in sonography, additional imaging with computed tomography (CT) may be useful.

- Patients displaying **bulky** or **widely distributed nodal disease** on initial ultrasound may have nodal regions involved beyond typical cervical stations (some of which may be difficult to evaluate by ultrasound, including the **mediastinum, infra-clavicular, retropharyngeal, and parapharyngeal** regions).

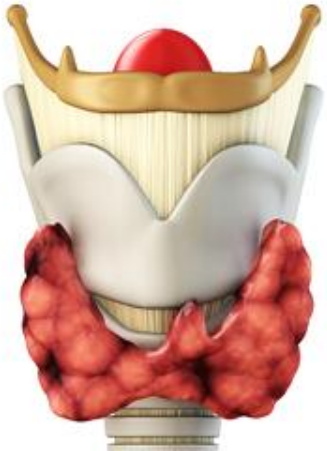
- Neither modality (sonography and CT) performed well in the central compartment (sensitivity of CT 40% vs. 28% for ultrasound). While ultrasound had a higher specificity, the addition of CT reduces the rate of missed disease and improves surgical planning.



- Iodine is cleared within 4–6 weeks in most patients, so concern about iodine burden from IV contrast causing a clinically significant delay in subsequent whole body scans or RAI treatment after preoperative imaging is unfounded for most patients. The benefit gained from improved anatomical imaging almost invariably outweighs any potential risk of deferring RAI imaging or therapy. When there is a clearance concern, a spot urinary iodine level can be measured.

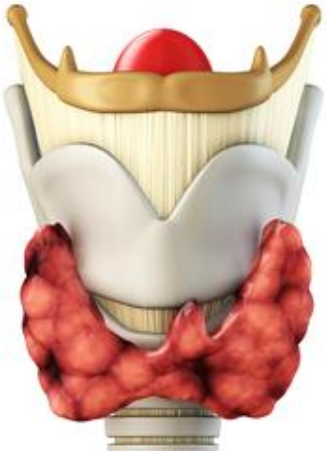
Preoperative MRI

- MRI does not entail exposure to ionizing **radiation**, and its contrast agents are **less nephrotoxic** than those employed in CT scanning.
- However, MRI is more subject to **motion artifacts** during the scan.
- CT and MRI with IV contrast probably perform comparably in the detection of cervical nodal disease.



Preoperative 18FDG-PET

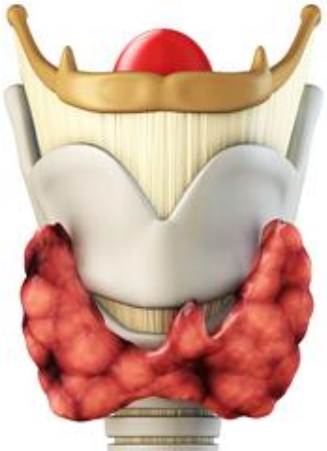
- a meta-analysis of 759 patients with thyroid cancer showed a pooled **sensitivity** of only **30**% despite a high **specificity** of **94**%.
- For all lymph node levels, ultrasound is superior in terms of PPV, NPV, and accuracy.
- Therefore, 18FDG-PET or 18FDG-PET/CT should not regularly be undertaken prior to initial treatment.



- Locally invasive DTC (rapid tumor enlargement, vocal cord paralysis, tumor fixation to the airway or neck structures, progressive dysphagia, respiratory compromise, hemoptysis, and significant voice change): occur in 10–15% of patients at the time of diagnosis.

- For this group of patients, cross-sectional imaging can be useful for surgical planning to delineate the extent of laryngeal, tracheal, esophageal, or vascular involvement.

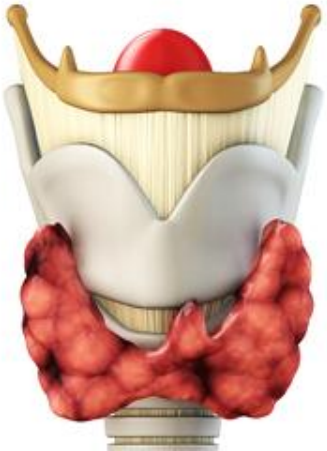
- Prior to resection, tracheoscopy and/or esophagoscopy, with/out sonography, looking for evidence of intraluminal extension also may be helpful in cases of suspected aerodigestive tract invasion.



- Sonographic features of the primary tumor, including **extrathyroidal** extension (especially with **posterior capsular penetration** and disease reaching the **mediastinum**), also may prompt axial imaging.

- Chest CT can be useful in defining the inferior border of disease (and determining the extent to which mediastinal structures are involved) in cases with significant caudal spread.

- CT findings may influence management by suggesting the uncommon need for sternotomy and/or tracheal or laryngeal resection/reconstruction, which often would require assembling additional resources and personnel in preparation for the operation.



Should a serum Tg level be measured prior to surgery?

RECOMMENDATION 9

- Routine preoperative measurement of serum Tg or TgAb levels is not recommended. (Conditional recommendation, Low certainty evidence)

Preoperative Serum Tg level

- high preoperative Tg may predict a higher sensitivity for postoperative surveillance with serum Tg.
- **preoperative Tg is not a significant predictor of malignancy**.
- The addition of preoperative serum Tg to the McGill Thyroid Nodule Score for DTC improved its sensitivity in predicting malignancy in thyroid nodules.
- In a study, There is a linear association between preoperative Tg level and size of primary tumor and number of lymph node metastasis.
- However, in a retrospective review of 422 patients with thyroid cancer who had preoperative Tg levels, they found that while preoperative Tg was significantly correlated with size of the gland and T category, it did not correlate with presence of metastasis and was of low utility in the preoperative evaluation of thyroid cancer.

Preoperative Serum Anti-Tg level

- While the presence of TgAbs preoperatively **do not appear** to be an independent preoperative predictor of stage in patients with DTC, evidence is limited.

- In a cross-sectional analysis of 1770 patients with perioperative TgAb level data in the NTCTC, serum TgAb status was not significantly associated with the stage of disease on multivariable analysis, nor was it associated with disease-free or overall survival on univariate or multivariable analyses.

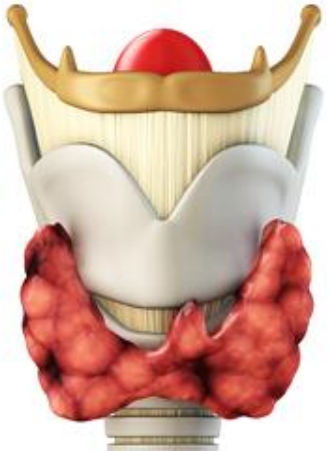
Should preoperative somatic genomic testing be performed to inform the extent of surgery?

RECOMMENDATION 10

- Genomic evaluation of confirmed DTC prior to surgery is not recommended routinely. However, if the genomic profile is known or performed, the presence or absence of specific combinations of abnormalities may be considered in the context of clinical, radiographical, and cytopathologic data to inform extent of surgery. (Conditional recommendation, Low certainty evidence)

Should preoperative somatic genomic testing be performed to inform the extent of surgery?

- combination of **TERT promoter and BRAFV600E** mutations correlates with **worse prognosis**. somatic TERT promoter mutation?!!
- **BRAFV600E** mutations are commonly found in both small and large DTCs, and their presence in isolation is **not clearly associated with more aggressive disease** or worse outcomes.
- mutations that include TP53, PIK3CA, and AKT1: more aggressive disease
- **RAS genes** (most commonly NRAS), PIK3CA, PTEN, and PAX8/PPARc fusions are more common in FVPTC or FTC but can be found in benign follicular adenomas and NIFTP; therefore, they are **not specific for thyroid cancer.**
- **FTCs with RAS mutations** have been reported to have a **higher incidence of metastases**.
- Expression of specific miRNAs also may be associated with increased risk of locoregional disease; however, robust data are lacking.



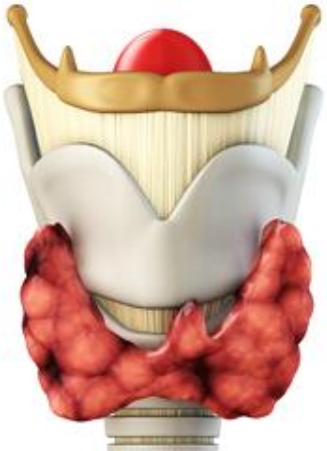
Should preoperative somatic genomic testing be performed to inform the extent of surgery?

Based on molecular profile in cytology for predicting tumor behavior and surgical planning:

- Low risk: RAS and RAS-like mutations (i.e., BRAFK601E, PAX8/PPARc fusions)
- Intermediate risk: BRAF-like alterations (i.e., BRAFV600E, NTRK3 fusions, and RET)
- high-risk: TERT promoter, TP53, AKT1, and PIK3CA mutations

patients with **high-risk molecular profiles** had **more extensive initial surgery**, **larger cancers**, a **higher frequency of nodal metastasis**, and **vascular invasion** as well as **shorter recurrence-free survival** than those with low risk molecular profiles.

Patients **high-risk** molecular testing might benefit from **total thyroidectomy** and patients with **low-risk** molecular results might be selected for **lobectomy**.



intermediate molecular risk category: more likely to recur than those in the low-risk category (7.2% vs. 0.7%). **Recurrence rates** for the intermediate-risk group were influenced by **tumor size**: Patients with tumors **2-4 cm recurred more** frequently than those with tumors between 1 and 2 cm.

Should preoperative somatic genomic testing be performed to inform the extent of surgery?

- Several retrospective studies assessing a possible role for molecular testing among patients being considered for **active surveillance** (T1a PTC) have **conflicting** results. Thus, there are **insufficient data** to support use of molecular testing to stratify the approach for patients with T1a PTC.

- The potential application of molecular testing for preoperatively defined DTC to individualize initial therapy may be particularly relevant for select patients with **cT2N0 DTC for whom extent of surgery is not clear** after consideration of clinical and radiographical features, and patient preferences (see Recommendation 15).

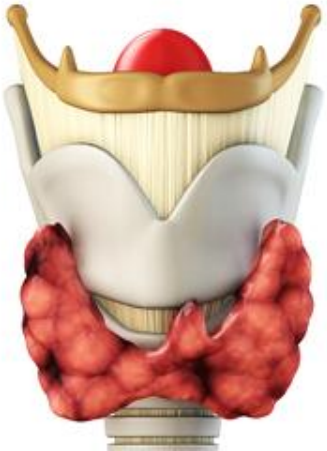
- cost–benefit analyses are necessary, particularly given the **relatively low frequency of higher risk molecular profiles in cT2N0 DTCs** that would lead to total thyroidectomy (e.g., combinations of BRAFV600E and TERT promoter or TP53 mutations).

- **Clinical trials of neoadjuvant therapy for very large invasive DTCs are ongoing; therefore, molecular tests in such patients are best utilized in the context of a clinical trial.**

Are there patients in whom active surveillance and percutaneous ablation are appropriate management options?

RECOMMENDATION 11

- A. Active surveillance may be offered as an appropriate management option for some patients with cT1aN0M0 PTCs. Shared clinical decision-making between the patient and clinical team regarding risks and benefits of this approach is essential. (Conditional recommendation, Low certainty evidence)
- B. Ultrasound-guided percutaneous ablation may be considered as an alternative to active surveillance or resection for cT1aN0M0 PTC in selected patients. Shared clinical decision-making between the patient and clinical team regarding risks and benefits of this approach is essential. (Conditional recommendation, Low certainty evidence)



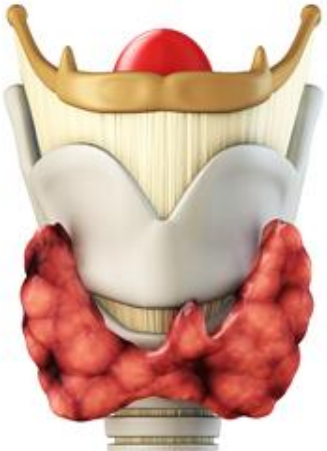
Active Surveillance

- FNA is not routinely recommended for thyroid nodules ≤1 cm with low-risk features. However, if thyroid cancer is diagnosed in a tumor ≤ 1 cm by FNA, active surveillance is an acceptable management option in selected patients.

- In patients managed with active surveillance, **rates of tumor growth were low**.

- **Rates of later surgery** varied and were driven **more by patient choice** than signs of progression.

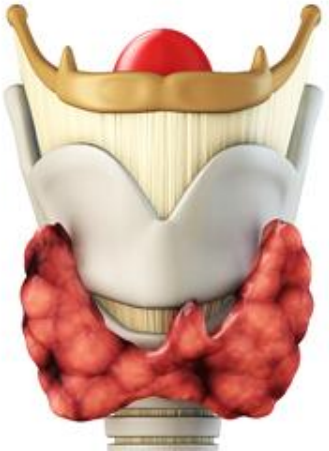
- small or no differences in QoL.



Active Surveillance

- There are limited data on the role of active surveillance in cancers >1 cm.
- One study evaluated 77 patients with tumor size ≤ 1.2 cm who underwent active surveillance: only one had progression of disease requiring surgery after 30 months of follow up; in that case, tumor growth was associated with suspicion of extrathyroidal invasion.

- One study on 392 patients with tumors ≤ 2 cm (T1bN0M0): only 61 (16%) of the patients selected active surveillance as management over immediate surgery (vs. 89% of those with tumor size ≤ 1 cm). During a mean follow-up of 7.4 years (range 0.5–25 years), no significant difference was seen in the tumor progression of patients with tumor sizes ≤ 1 cm versus ≤ 2 cm; however, the cohort was small, and there was a risk of selection bias.



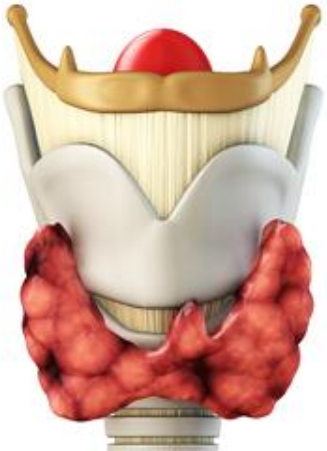
- A prospective, nonrandomized controlled trial of **222 patients with Bethesda V and VI** nodules that were **≤ 2 cm** over a mean follow-up **of 37.1** months found **equivalent disease-specific and overall survival**. Of the 112 patients who underwent active surveillance, **90% continued**, **41%** experienced **tumor shrinkage**, and **none developed regional/distant metastases**. Size **growth of >5 mm** was observed in **4%** of those undergoing active surveillance, and **volumetric growth of >100%** was seen in **7%**.

Active Surveillance

- Determining which patients are candidates for active surveillance involves shared decision-making among the patient, endocrinologist, surgeon, and other clinicians involved in the patient's care.

- In addition to patient preferences regarding surgery versus active surveillance, consideration should be given to the tumor and patient characteristics and the medical team's ability to provide long-term observation.

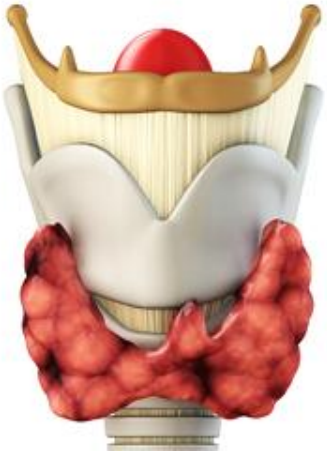
- For patients considering an active surveillance approach, it is important that clinicians provide a description of the "unknown." For example, the risk of tumors growing or dedifferentiating over time could narrow the window of earlier effective treatment if they are not properly monitored. Practitioners should stress the critical need for long-term follow-up and how non-compliance with such follow-up invalidates claims for safety of this approach. In this context, some patients may choose earlier treatment rather than active surveillance.



Active Surveillance

- Patients who have evidence of **aggressive histology** on review of cytopathology; patients with cancers that on imaging studies appear to **invade** the recurrent laryngeal nerve, trachea, or esophagus, or exhibit **visible extrathyroidal extension**; or **regional or distant metastases** are not candidates for active surveillance.

- Due to concern for tumor growth near critical local structures, active surveillance for cancers that abut the posterior capsule/trachea have been excluded from studies. Although this exclusion limits our ability to draw conclusions from existing data, it is reasonable to infer that **active surveillance of posteriorly located tumors may be inappropriate** due to the risk of invasion into vital structures.



- A cohort study from Japan (N = 1235, mean follow-up 75 months) suggested that older patients (i.e., **patient age >60** years) with **T1a** PTCs may be better candidates for active surveillance because they are significantly less likely to experience tumor size increase of ≥3 mm, new lymph node metastases, or new clinical disease compared to young adults (age <40 years).

Percutaneous Ablation

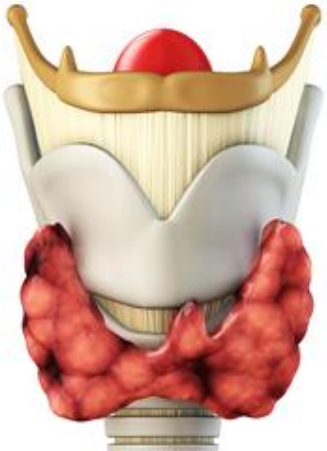
- RFA, MWA, laser (LA) and ethanol ablation have been studied as primary treatment of low risk PTC in carefully selected patients.

- Selection criteria: similar to those employed for active surveillance. Patients who are uncomfortable with active surveillance or with surgery may prefer a percutaneous ultrasound-guided ablative treatment for their cancer.

- Compared with lobectomy: lower likelihood of hypothyroidism, less certainty of complete tumor eradication, does not permit histopathologic evaluation.

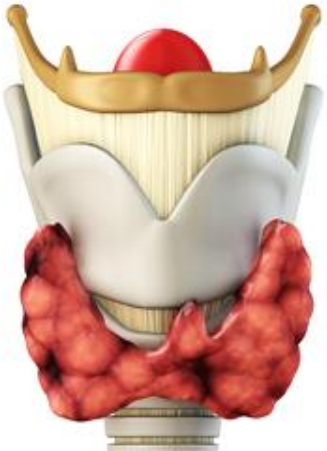
- A meta-analysis involving 715 patients from Asia: significant heterogeneity between the studies, The **pooled rate of complete tumor disappearance** was **57.6%** [confidence interval (CI) 35–80%] with **a pooled recurrence rate** of **0.4%** [CI 0.0–1.1%]. **Complication rates** were **3.2%** overall and 0.7% for major events, the latter of which consisted mostly of temporary voice changes.

- Subset analysis comparing modalities: no significant difference in rates of complete tumor disappearance ($p = 0.35$) or complications; however, there was a **significant difference in volume reduction rates** (**RFA 99%**, MWA95%, and LA 89%, $p < 0.001$).



Percutaneous Ablation

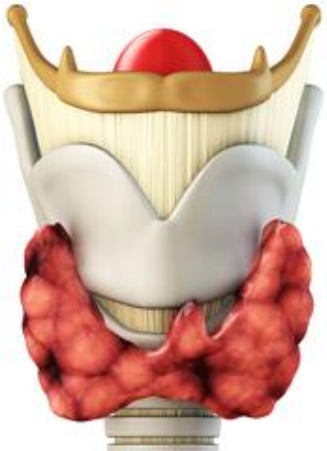
- An more recent meta-analysis of thermal ablation for cT1N0M0 included 36 studies:
- **pooled complete tumor disappearance rate** of **91%** [CI 83–97%] for **cT1a** and **60%** [CI 50–70%] for **cT1b** carcinomas using RFA.
- The **local recurrence rates** were **2–3%** with **nodal metastasis rates** of **1–2%**, across three thermal ablation techniques (RFA, LA, and MWA).
- **Minor complication rates** varied from **3% to 13%,** and **major complications** were **not reported**.
- Comparisons of effectiveness between techniques were difficult to perform due to potential different tumor sizes.



Percutaneous Ablation

- A single-institution, prospective study of RFA for low-risk cT1a PTC included 98 tumors in 92 patients:
  - complete tumor disappearance 42% at 6 months
  - complete tumor disappearance 96% at 1 year
  - At 18 months, no recurrences or nodal metastases were identified.

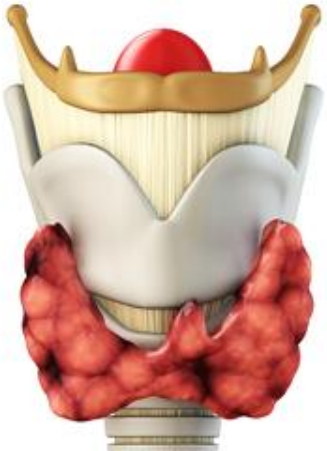
- Another single-institution, retrospective study with at least 5 years of follow-up from RFA for cT1a PTC, including 84 nodules in 74 patients:
  - complete tumor disappearance rates 99% at 2 years
  - complete tumor disappearance rates 100% at 5 years
  - 15% of nodules required repeat RFA
  - 4 additional cancers developed in 3 patients, they were successfully ablated, and no patients developed metastases.
  - The major complication rate was 1.4%.



Percutaneous Ablation

- A larger retrospective study of 414 patients with low-risk, unifocal cT1a PTC treated with RFA with an average **follow-up of 3.5 years** (range 2–5 years). :
  - complete tumor disappearance rate of 88%
  - 3% of patients requiring additional ablation
  - overall rate of local tumor progression: 4%
  - Local recurrence: 2.4% of patients
  - nodal metastasis: 1%
  - No life-threatening complications were observed.

- A single-institution, retrospective cohort study of 1613 individuals with PTC ≤2 cm treated with RFA with a median follow-up of 58.5 months:
  - local tumor progression: 4.3%
  - tumor recurrence: 2.6% patients
  - persistence: 1.7%
  - Mean time after RFA to development of local tumor progression: 21.5m
  - The disease-free survival rate differed based on tumor size (T1a vs. T1b), number of tumors (unifocal vs. multifocal), and subcapsular tumor location distance from the capsule or trachea (≤2 mm or >2 mm).



Percutaneous Ablation

- Another retrospective study evaluated RFA for patients with unifocal (n = 432) versus multifocal (n = 55) cT1a PTC:

  no significant differences in outcomes between the two groups with a mean follow-up of 4 years.

  Complete disappearance rates: 89% versus 96% (p = 0.2)

  There were no significant differences between the two groups in rates of local progression, nodal metastasis rates, local recurrence, disease persistence, and recurrence-free survival.

- However another study demonstrated better outcomes for **unifocal** versus multifocal PTC with RFA (hazard ratio [HR] 0.5, $p < 0.001$), as well as for **T1a** versus T1b PTC (HR 0.4, $p < 0.001$).

Percutaneous Ablation

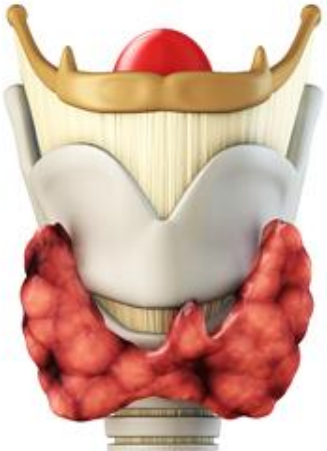
- retrospective results evaluating RFA for cT1a PTC in 91 patients with tumors adjacent to the tracheoesophageal groove and anticipated location of recurrent laryngeal nerve (“danger triangle”):
  - no significant difference in complete tumor disappearance rates (74% vs. 78%, p= 0.5)
  - no difference in disease progression (2% vs. 2%, p = 0.99)
  - no significant difference in complications (3.3% vs. 1.7%, p = 0.65) but may have been underpowered to show a difference.

- A retrospective study of MWA for multifocal, cT1a PTC in 66 patients with 158 tumors and 5 years of follow-up:
  - complete tumor resolution in all lesions
  - tumor progression in 3%,
  - nodal metastases in one patient
  - development of a new cancer in another, Repeat MWA was successful,
  - complication rate: 3%.

Percutaneous Ablation

- Retrospective results using ultrasound-guided percutaneous ethanol ablation for cT1aN0M0 PTC involving 15 patients with 17 tumors utilizing injections on two successive days and a median 5-year follow-up:
  - 47% of cancers completely resolved
  - median tumor volume reduction: 80–90%
  - No new cancers developed
  - no nodal metastasis occurred

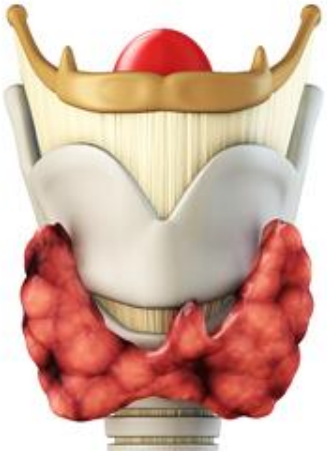
- A retrospective study comparing RFA versus surgery for unilateral multifocal papillary microcarcinoma with over a 5-year follow up period:
  - no statistically significant differences in disease progression (4.5% vs. 3.8%; $p > 0.99$), lymph node metastasis (2.3% vs. 3.8%; $p > 0.99$), persistent lesions (2.3% vs. 0%; $p = 0.27$) and RFS rates (97.7% vs. 96.2%; $p = 0.67$).



Percutaneous Ablation

- The data suggest that percutaneous ablation may represent an alternative to active surveillance or resection in selected patients.

- Additional studies are needed to assess widespread applicability, particularly given that many of the referenced studies are subgroup analyses from a single group.



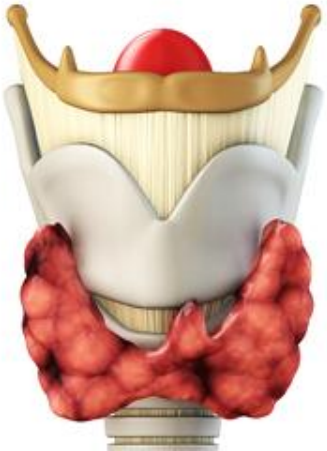
What is the optimal approach for patients undergoing active surveillance?

RECOMMENDATION 12

- For patients undergoing active surveillance, neck ultrasound should be used to monitor disease progression. (Good Practice Statement)

What is the optimal approach for patients undergoing active surveillance?

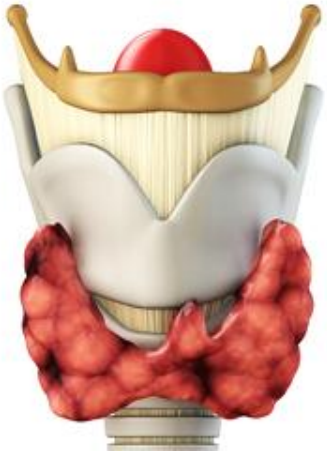
- It is important that members of the medical team offering active surveillance have experience and confidence in their use of neck ultrasound.
- Neck ultrasound, assessing the thyroid gland and all cervical lymph node compartments, is key to monitoring for cancer progression.
- Based on prior studies addressing active surveillance, **neck ultrasound** should be performed **every 6 months for 1–2 years** and **then annually**.
- The length of necessary follow-up remains unknown.
- None of the prior studies on active surveillance used neck CT for routine follow-up.



Should serum Tg and TgAb levels be measured during active surveillance?

RECOMMENDATION 13

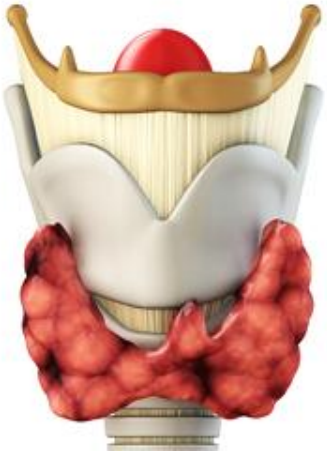
- For patients undergoing active surveillance, routine measurement of serum Tg and/or TgAb levels is not recommended. (Good Practice Statement)



Should serum Tg and TgAb levels be measured during active surveillance?

- **Data are lacking** on the role of serum Tg levels when the entire thyroid is intact, as is the case during active surveillance.

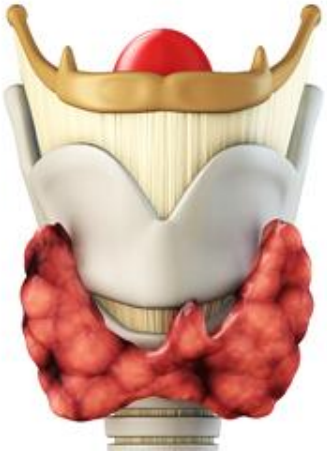
- Since there is no clear role for measuring serum Tg levels preoperatively or postoperatively after lobectomy for thyroid cancer monitoring (Recommendation 9), serial serum Tg levels are unlikely to prove meaningful during active surveillance.



Are there clear indications for when patients undergoing active surveillance should pursue resection?

RECOMMENDATION 14

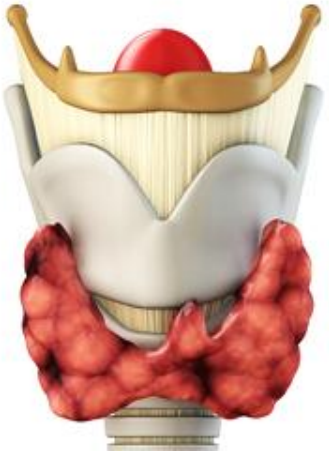
- In patients undergoing active surveillance, surgical resection is indicated if there is evidence of new biopsy-proven lymph node metastases, growth of the primary tumor by ≥3 mm, distant metastases, evidence of extrathyroidal extension, posterior growth, when there is patient anxiety, inability to follow-up, and/or expressed preference for surgery. (Good Practice Statement)



What is the optimal operative approach for DTC?

RECOMMENDATION 15

- A. When resection is performed for patients with thyroid cancer ≤2 cm without gross extra-thyroidal extension (cT1) and without metastases (cN0M0), the initial surgical procedure should be a thyroid lobectomy unless there are bilateral cancers or other indications to remove the contralateral lobe. (Strong recommendation, Moderate certainty evidence)
- B. For patients with low risk, unilateral thyroid cancer >2 and ≤4 cm (cT2N0M0), thyroid lobectomy may be the preferred initial surgical treatment due to significantly lower risk and side effects. However, the patient and treatment team may adopt total thyroidectomy to enable RAI administration and/or enhance follow-up based on disease features, suspicious contralateral nodularity, and/or patient preferences. When thyroid lobectomy is offered as initial treatment, counsel the patient about the possibility of conversion to total thyroidectomy or need for subsequent completion thyroidectomy if higher-risk factors emerge intraoperatively or postoperatively. (Conditional recommendation, Low-moderate certainty evidence)
- C. For patients with thyroid cancer >4 cm (cT3a), cancer of any size with gross extra-thyroidal extension (cT3b or cT4), or clinically apparent metastatic disease to lymph nodes (cN1) or distant sites (cM1), the initial surgical procedure should include a total thyroidectomy with gross removal of all primary tumor and node dissection unless there are contraindications to this procedure. (Strong recommendation, Moderate certainty evidence)



What is the optimal operative approach for DTC?

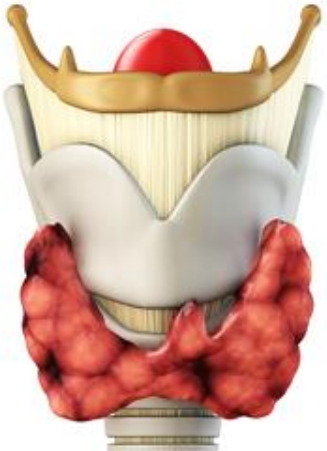
- A preoperative FNA biopsy diagnostic for DTC is almost always interpreted as conventional PTC based upon cytology (Bethesda VI), whereas IEFVPTC, FTC, and OTC more often fall into one of the indeterminate categories (Bethesda III, IV, or V).
- The identification of a BRAFV600E mutation or RET fusion on molecular testing of a thyroid nodule FNA sample, if performed, is diagnostic of PTC.
- Thus, in the absence of clinical features confirming malignancy with indeterminate cytology, the preoperative diagnosis of DTC typically involves classical PTC.
- Surgery for thyroid cancer is an important element of an often straightforward but potentially complex treatment approach, best coordinated preoperatively with a multidisciplinary team and reflecting patient desires.

What is the optimal operative approach for DTC?

- Earlier ATA guidelines endorsed total thyroidectomy as the primary initial surgical treatment option for nearly all DTCs >1 cm with or without evidence of loco-regional or distant metastases, with lobectomy sufficient for unilateral T1a carcinomas (T1a PTC) without metastasis.

- However, the 2015 ATA guidelines suggested lobectomy as an alternative to total thyroidectomy for cT1b-T2N0M0, low risk, unilateral PTCs (particularly follicular variant) and FTCs.

- This change was based on data demonstrating that for properly selected patients, clinical outcomes are very similar following unilateral or bilateral thyroid surgery.



What is the optimal operative approach for DTC?

- Since publication of the 2015 guidelines suggesting that thyroid lobectomy/hemi-thyroidectomy may be sufficient for low risk (cT1-2N0M0) DTC, numerous studies have been published evaluating this recommendation:

- Several systematic reviews and meta-analyses have been performed, with approximately **half** showing **no difference** in **recurrence** or survival but with **higher complication rates for total thyroidectomy**.
- The **other approximate half** demonstrate statistically significant, **lower recurrence rates with total thyroidectomy** compared with lobectomy alone.
- Only one meta-analysis found improved overall survival with total thyroidectomy over lobectomy, but the benefit was confined to T2 primary tumors.
- This result is influenced by a National Cancer Database (NCDB) study analyzing PTC (1–4 cm, T1b-2) demonstrating significantly better survival with total thyroidectomy for classical PTC but not FVPTC; however, in subset analysis, this seemed to be true only for T2 (not T1b) classical variant PTC. A recent narrative review of these studies and published guidelines concluded that lobectomy was sufficient for low-risk T1 tumors and that either lobectomy or total thyroidectomy would be reasonable treatment alternatives for low-risk T2 tumors.

What is the optimal operative approach for DTC?

- They recommended that patients with cT2N0M0 tumors should be informed that lobectomy has a significantly lower risk of complications and side effects but carries a slightly higher risk of locoregional recurrence and possibly reduced overall survival.
- This conclusion was supported by another recent systematic, qualitative narrative review. Most recurrences following lobectomy alone appear to occur in the contralateral lobe and are successfully salvaged with completion thyroidectomy.
- A Surveillance, Epidemiology and End Results (SEER) database study involving only FTC without extrathyroidal extension or metastasis (cT1a-T3aN0M0) found no difference in 15-year disease-specific survival between lobectomy and total thyroidectomy (98% vs. 97%, respectively), but it did not evaluate recurrence. A large, single-institution study of minimally invasive FTC found patient age >55 years and tumor size >4 cm were both independently associated with higher 10-year risk of recurrence on multivariable analysis.345 Results of single-institution studies of primarily PTC are mixed.

What is the optimal operative approach for DTC?

- A few studies have addressed the issue of multifocality with lobectomy versus total thyroidectomy for PTC <1cm (T1a). One found a significantly higher recurrence rate with lobectomy versus total thyroidectomy (26% vs. 5%, respectively), with lower disease-free survival at 5 and 10 years, particularly in male patients with a sum of all tumors >1 cm.
- Another study found a higher recurrence rate for lobectomy in patients with PTC T1a tumors, with a higher rate of recurrence beyond the contralateral lobe in the presence of multifocality.
- additional studies looked specifically at pathologically node positive disease discovered in the central compartment at the time of lobectomy (cN0 but pN1a); one demonstrated no significant difference in recurrence-free survival at 15 years between total thyroidectomy and less than total thyroidectomy, but the other showed a significantly lower recurrence rate but higher complication rate with total thyroidectomy compared with lobectomy, with no difference in recurrence if pN0.

What is the optimal operative approach for DTC?

- A study examining the impact of minimal extrathyroidal extension in T1N0 PTC tumors found no difference in recurrence rates between lobectomy and total thyroidectomy (3% vs. 2%, respectively).

- A recent SEER database study of patients with unilateral T1a PTCs found no difference in overall or disease-specific survival between lobectomy and total thyroidectomy after propensity matching;
- a subset analysis revealed lower disease-specific survival for younger patients (<55 years) and those with multifocality and/or extrathyroidal extension treated with lobectomy alone.
- Another database study involving a Chinese cohort suggested younger patients (<35 years) benefit from total thyroidectomy over lobectomy, and particularly for T3 (>4 cm) cancers.

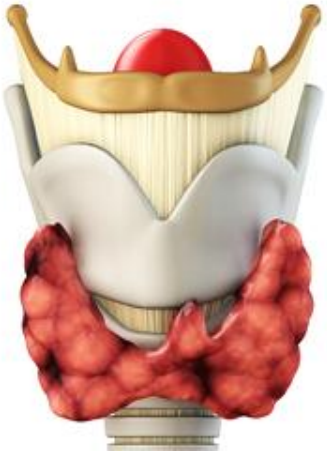
What is the optimal operative approach for DTC?

- Recent studies of intermediate-risk (see Recommendation 28) PTC have demonstrated conflicting results, with two finding no significant difference in recurrence- or disease-specific survival but another demonstrating significantly reduced recurrence with total thyroidectomy versus lobectomy (0% vs. 8%, respectively) but no significant difference in overall survival.
- A NCDB study demonstrated reduced survival among patients undergoing lobectomy alone versus total thyroidectomy with RAI for T1b-T2 DTCs with intermediate-or high-risk features.
- A recent report of high-risk patients confirmed a survival advantage associated with total thyroidectomy and adjuvant RAI therapy.

What is the optimal operative approach for DTC?

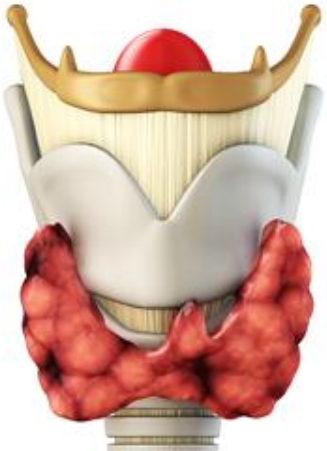
- Several retrospective studies have examined the estimated proportion of patients who **might require completion thyroidectomy** after initial lobectomy for clinically low-risk, unilateral, intrathyroidal, node-negative DTCs; estimates ranged greatly, from **5% to 43%** of patients, which is similar to a meta-analysis estimate of 11–34%.

- Two additional studies found a **21%** rate of **conversion to total thyroidectomy** from lobectomy based on high risk findings identified intraoperatively and a 27–30% rate of completion thyroidectomy based on pathologically higher-risk findings.



What is the optimal operative approach for DTC?

- More important, one study that compared actual rates of initial total thyroidectomy versus lobectomy and rates of completion thyroidectomy after initial lobectomy (before and after publication and implementation of the 2015 ATA guidelines) found a reduction in the utilization of total thyroidectomy (from 61% to 31% of all initial operations) and also completion thyroidectomy (from 74% to 20%), suggesting that doing more lobectomies for lower-risk cancers does not result in a higher rate of completion thyroidectomy.
- Several additional studies document increased use of lobectomy for cancer after publication of the 2015 ATA guidelines, as well as lower rates of completion thyroidectomy (from 50% to 25%).
- However, total thyroidectomy remains the more commonly performed initial operation (70–88%), even for cT1-2N0M0 cancers, despite significantly higher postoperative morbidity.
- Increasing primary tumor size from T1a-T1b to T2 was associated with increased utilization of initial total thyroidectomy and completion thyroidectomy.



What is the optimal operative approach for DTC?

- The one prospective study of lobectomy for T1a PTC found only a 3% conversion rate to total thyroidectomy due to higher risk intraoperative findings and a 20% salvage surgery rate, with resultant 99% disease-free survival (similar to a retrospective cohort treated with initial total thyroidectomy and central neck dissection).

- Accurate preoperative ultrasound and targeted use of frozen section can help identify patients best treated with total thyroidectomy, reducing the need for subsequent completion thyroidectomy.

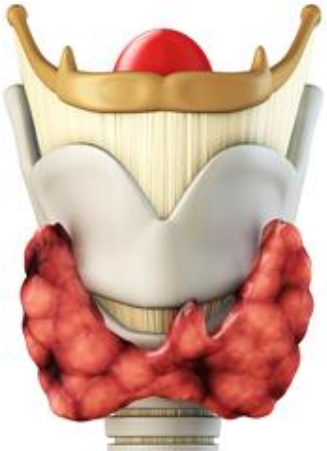
- Cost-effectiveness assessment found greater utility with lobectomy over total thyroidectomy for PTCs that are 1–4 cm (T1b-2N0M0).

What is the optimal operative approach for DTC?

- The risks of total thyroidectomy are significantly greater than those for thyroid lobectomy, with a meta-analysis suggesting a relative risk (RR) significantly greater for all complications, including recurrent laryngeal nerve injury (transient RR = 1.7, permanent RR = 1.9), hypocalcemia (transient RR = 10.7, permanent RR = 3.2), and hemorrhage/hematoma (RR = 2.6).
- Total thyroidectomy is associated with the rare risk of bilateral recurrent laryngeal nerve injury necessitating tracheostomy.
- Surgeon experience likely influences the risks of thyroidectomy, with higher-volume surgeons having lower complication rates.
- However, as noted above, even high-volume surgeons still have a higher complication rate when performing total thyroidectomy versus lobectomy (14.5% vs. 7.6%, respectively), which is higher on average than the complication rate for lobectomy undertaken by low-volume surgeons (11.8%). Highest risk is associated with total thyroidectomy at the hands of a low-volume surgeon (24.1%).
- Therefore, patients should carefully weigh the relative benefits and risks of total thyroidectomy versus thyroid lobectomy, even when the operation is performed by high-volume surgeons.

What is the optimal operative approach for DTC?

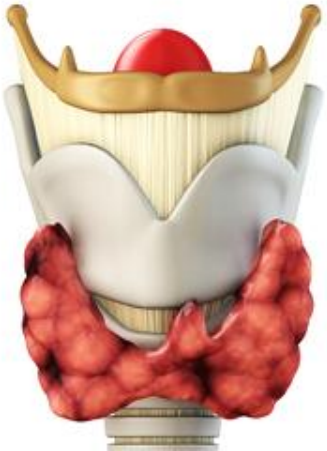
- Total thyroidectomy necessitates thyroid hormone replacement, while lobectomy is associated with postoperative biochemical hypothyroidism estimated on average to be 22%, with clinical or overt hypothyroidism estimated at 4%.



What is the optimal operative approach for DTC?

- Total thyroidectomy necessitates thyroid hormone replacement, while lobectomy is associated with postoperative biochemical hypothyroidism estimated on average to be 22%, with clinical or overt hypothyroidism estimated at 4%.

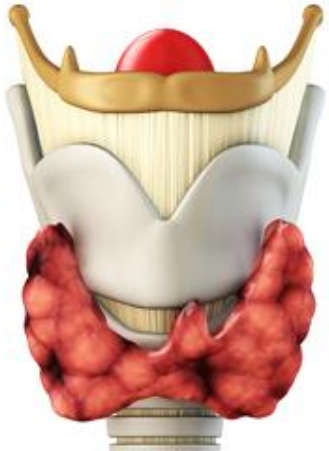
- A significantly increased risk of hypothyroidism following lobectomy has been reported in the presence of autoimmune thyroid disease (e.g., as reflected by the presence of thyroid antibodies) or high normal/elevated preoperative TSH. Hypothyroidism is not an indication for thyroidectomy, and its use as justification for total thyroidectomy over lobectomy should be weighed against the other higher risks associated with total thyroidectomy. In contrast, coexistent hyperthyroidism may be an indication for total thyroidectomy, depending upon the etiology.
- Patients with high-normal TSH levels following lobectomy for cancer may still need thyroid hormone supplementation to reduce TSH levels into their target range (see TSH target section).



What is the optimal operative approach for DTC?

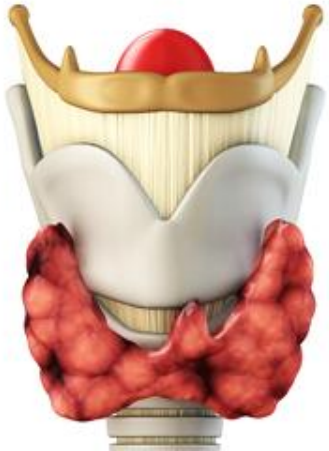
- Regardless, two recent studies confirm significantly better quality-of-life measures in patients undergoing lobectomy compared with total thyroidectomy for cancer.

- A third found this was only true for the first few months postoperatively, with no significant differences at 6–12 months.398 A separate report found a decreased rate of chronic asthenia (generalized weakness) with lobectomy.



Preoperative somatic molecular testing and neoadjuvant therapy:

- Preoperative molecular testing obtained from FNA has been proposed to help determine extent of initial thyroid surgery in selected patients with cT1-cT2 cN0 DTC (see Recommendation 10).
- Retrospective studies have demonstrated that high-risk molecular test results (BRAFV600E or RAS mutations with a TERT promoter and/or TP53 mutations) correlate with postoperative ATA Risk of Recurrence assessment.
- These studies included patients with cytologically indeterminate nodules (66% Bethesda III–IV) not addressed in these thyroid cancer guidelines.
- In addition, patients with ATC and/or advanced DTC that was evident preoperatively were included without adjusting for clinical TNM staging.

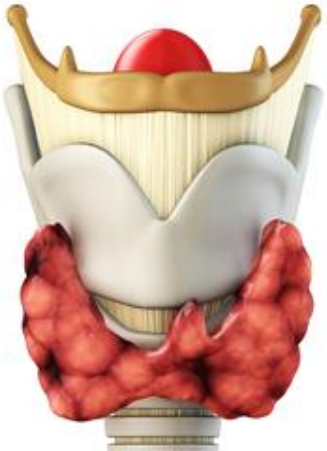


What is the optimal operative approach for DTC?

- Finally, many of the patients only had postoperative molecular testing (i.e., not on preoperative FNA).
- Another study from the same team reported on a cohort that included many of the same patients with tumors 1–4 cm.
- This series excluded patients with cT3, cN1, and/or cM1 disease but did not appear to have excluded patients with locally advanced (cT3b-4) disease.
- There were no recurrences in the lobectomy group during follow-up, suggesting that preoperative clinical risk assessment was sufficient.
- Molecular high-risk assessment could not be evaluated due to differences in the clinically available molecular tests over time.
- Intermediate molecular risk (BRAFV600E-like) and the presence of pN1a disease both predicted recurrence with estimates of 11% for 2–4 cm and 6% for 1–2 cm tumors, respectively, in patients treated with total thyroidectomy.

What is the optimal operative approach for DTC?

- In contrast, another study of 1–4 cm DTCs in which cT4, cN1, or cM1 disease were excluded (but included cT3b tumors) found no difference between lobectomy and total thyroidectomy in 10-year cause-specific survival for BRAF and/or TERT promoter-mutated tumors.
- No patients died of their disease. Disease-free survival was not significantly better in patients with TERT promoter-mutated tumors (predominately also BRAFmutated) treated with total thyroidectomy versus lobectomy (100% vs. 65%, p = 0.09). There was no difference in disease free survival for patients whose tumors were TERT promoter negative and predominantly BRAF mutation-positive treated with total thyroidectomy versus lobectomy (97% vs. 97%, p = NS).

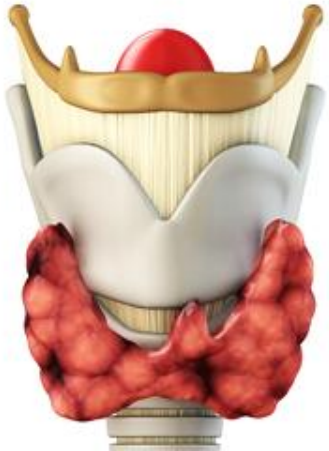


What is the optimal operative approach for DTC?

- Another retrospective study of 105 patients with PTC and Bethesda V or VI cytologies (85% Bethesda VI) found high risk mutations in 6%, all of whom underwent total thyroidectomy and had T3b-4 and/or N1 and/or M1 disease.
- An increased recurrence rate was observed for patients with high risk molecular tumors versus low- and intermediate-genomic risk groups, although the number of patients in the high risk group was small (n = 6).
- Of the 19% of patients who underwent initial lobectomy, 21% underwent completion thyroidectomy based upon postoperative risk of recurrence assessment.
- None had a high-risk mutation, and no comparison between low- or intermediate-risk mutations was performed.

What is the optimal operative approach for DTC?

- In summary, high-risk mutations appear to be uncommon in patients with cT1b-2N0M0 DTC.
- BRAFV600E and BRAFV600E-like mutations are common in these tumors, as most patients with Bethesda VI cytology have classical PTC.
- Because low-risk mutations (RAS-like) occur primarily in cytologically indeterminant (Bethesda III–V) nodules, data for these nodules may not be as applicable for patients with Bethesda VI cytology on preoperative FNA.
- Thus, routine use of molecular testing is not recommended for patients with these smaller intrathyroidal DTCs as prospective studies that included cost analyses have not yet been performed (see Recommendation 10).

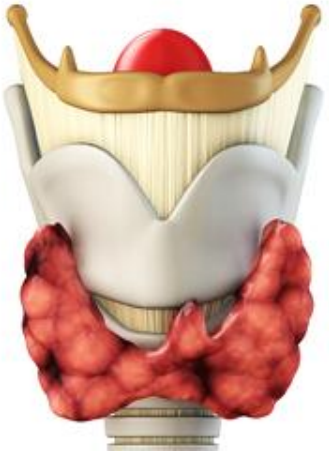


What is the optimal operative approach for DTC?

- For patients with large, locally invasive DTC in whom high-risk mutations are more common and a R0 or R1 resection is unlikely without high morbidity, use of systemic multi-kinase or targeted therapy with or without immunotherapy in the neoadjuvant setting has been reported.
- These reports thus far show variable results depending on the type and side effects of therapy. Results from larger prospective clinical trials are needed to determine for whom such a strategy may be appropriate to consider.

What is the optimal operative approach for DTC?

- In view of the significantly lower risk of complications and better QoL with lobectomy in comparison to total thyroidectomy, and limited oncologic benefit of total thyroidectomy, it appears that lobectomy for low-risk DTC is the preferred initial operation when the primary tumor is clinically small, unilateral, intrathyroidal, and without evidence of regional or distant metastasis.
- However, patients must be aware of a ≥20% possibility of conversion to total thyroidectomy intraoperatively, or subsequent completion thyroidectomy.
- Multifocality with clinically significant contralateral nodularity may make total thyroidectomy the preferred initial operation for some patients to reduce the risk of recurrence and need for additional surgery.
- Most recurrences in the setting of multifocality/contralateral nodularity can be successfully salvaged with completion thyroidectomy if the patient is compliant with sonographic surveillance.



What is the optimal operative approach for DTC?

- With appropriate follow-up, deferral of completion thyroidectomy has little to no impact on survival.
- Patients with larger cT2N0M0 classical PTC are also good candidates for lobectomy but may prefer to undergo total thyroidectomy and RAI postoperatively to possibly reduce their risk of recurrence and improve survival.
- Patients with clinically more advanced primary tumors (cT3-4), nodal involvement (cN1), and/or distant metastasis (cM1) are generally best treated with total thyroidectomy to facilitate RAI and biomarker surveillance (Table 5).
- Decisions regarding the extent of initial thyroidectomy should be part of a patient centered, multidisciplinary treatment plan; patient preference serves as a very important component.
- Clinical risk factors such as age, male sex, family history of thyroid cancer, and/or history of radiation exposure may further influence decision-making regarding total thyroidectomy.