

# Consensus Guidelines for the Diagnosis and Treatment of Thyroid Cancer

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## THYROID NODULE EVALUATION

The following organizations have released guidelines for the diagnosis and/or management of thyroid cancer:

- American Thyroid Association (**ATA**) [1-4]
- National Comprehensive Cancer Network (**NCCN**) [5]
- American Association of Clinical Endocrinologists/Associazione Medici Endocrinologi/ European Thyroid Association (**AACE/AME/ETA**) [6] (diagnosis only)

All the guidelines advocate ultrasound evaluation of thyroid nodules along with measurement of serum Thyroid-Stimulating Hormone (**TSH**) levels to determine whether a Fine Needle Aspiration Biopsy (**FNAB**) is indicated. A routine measurement of serum Thyroglobulin (**Tg**) for the initial evaluation of thyroid nodules is not recommended because Tg levels are elevated in most benign thyroid conditions [1,5,6].

Although all the guidelines recommend FNAB as the procedure of choice in the evaluation of solid thyroid nodules, there is variance in the size of the nodule as an indication for FNAB, as follows [1,5,6]:

- >0.5 cm in diameter **(ATA)** [1]
- >1 cm, in the absence of suspicious sonographic features **(AACE/AME/ETA)** [6]
- >1 cm if suspicious sonographic features are present; >1.5 cm if no suspicious sonographic features are present **(NCCN)** [5]

AACE/AME/ETA and NCCN suggest a serum calcitonin assay as an optional test, [5,6] but the ATA guidelines make no recommendation on the routine measurement of serum calcitonin because of insufficient evidence [1]. All three guidelines recommend radionuclide imaging in patients with a low TSH level [1,5,6].

## DIAGNOSIS

### Differentiated Thyroid Cancers

Differentiated thyroid cancers arise from thyroid follicular epithelial cells and constitute 90% of all thyroid cancers. The subtypes and approximate frequencies of differentiated thyroid cancers are as follows:

- Papillary – 85%
- Follicular – 10%
- Hürthleoroxiphil – 5%

ATA guidelines state that FNAB provides the most economical and accurate methodology for diagnosing differentiated thyroid cancers. Due to potential false negatives or sampling error, it is recommended that FNAB procedures be performed Under Ultrasound **(US)** guidance. US guidance is particularly important for nodules located posteriorly and for those that are difficult to palpate. Additionally, certain features found on US examination are predictive for malignancy and may guide FNAB decision-making [1].

Papillary Thyroid Cancer Is Characterized By The Following US Features:

- Solid or predominantly solid
- Hypo-echoic
- Micro calcifications (highly specific)
- Infiltrative irregular margins (common)
- Increased nodular vascularity

Follicular Thyroid Cancer Is Characterized By The Following US Features:

- Iso- to hyper-echoic
- Thick irregular halo

Benign US features are as follows:

- Purely cystic nodule
- Spongiform appearance (aggregation of multiple micro-cystic components >50% volume)

Malignancy Risk

Cytological analysis of FNAB specimens is used to estimate malignancy risk. The most appropriate cytological classification of malignancy risk is the Bethesda system for thyroid cytopathology, which comprises the following categories [7]:

- Malignant (risk 97-99%)
- Suspicious for malignancy (risk 60-75%)
- Follicular neoplasm or suspicious for follicular neoplasm (risk 15-30%)
- Atypia of undetermined significance or follicular lesion of undetermined significance (risk 5-15% based on repeated atypicals)
- Non-diagnostic or unsatisfactory (risk 1-4%)
- Benign (risk 0-3%)

For cytology “diagnostic of” or “suspicious for” papillary thyroid cancer, surgery is recommended [1].

If FNAB cytology is indeterminate, the use of molecular markers such as BRAF, RAS, RET/PTC, Pax8-PPAR $\gamma$ , or galectin-3 may be considered to guide management [1].

An iodine-123 (<sup>123</sup>I) thyroid scan may be considered if the cytology report documents a follicular neoplasm, especially if serum Thyroid-Stimulating Hormone (**TSH**) is in the low-normal range [1]. No radionuclide scan is needed for a reading of “suspicious for papillary carcinoma” or “Hürthle cell neoplasm”, as either lobectomy or total thyroidectomy is recommended depending on the nodule size and risk factors [1].

The NCCN recommends that FNAB should be the primary test for differentiated thyroid cancer. If FNAB reveals papillary carcinoma, follicular neoplasm, follicular lesion of undetermined significance, or Hürthle cell neoplasm, the following diagnostic recommendations should be undertaken (these are uniform for all differentiated thyroid carcinomas):

- Thyroid and neck ultrasound (including central and lateral compartments) if not previously done
- Computed Tomography (**CT**)/Magnetic Resonance Imaging (**MRI**) for fixed, bulky, or

substernal lesions (iodinated contrast optimal for cervical imaging)

- Consider evaluation of vocal cord mobility

## Medullary Thyroid Carcinoma

Patients with Medullary Thyroid Carcinoma (**MTC**) can be identified by pathologic diagnosis or by prospective genetic screening. According to the revised ATA guidelines, an FNAB result suspicious for MTC should prompt the following:

- Ultrasound of the neck
- Serum calcitonin assay
- Serum Carcino Embryonic Antigen (**CEA**) measurement
- DNA analysis for RET germline mutation

According to 2009 ATA guidelines, a calcitonin level >100 pg/mL should be considered suspicious of MTC [2]. Although calcitonin is a valuable tumor marker in patients with MTC, the 2015 Revised ATA guidelines note that clinical judgment should be exercised in the interpretation of calcitonin test results. Serum levels can be falsely high or low in a variety of clinical diseases, can be elevated in children under 3 years of age, and can be higher in males than females [4].

The NCCN recommends the following diagnostic procedures when FNAB results indicate MTC [5]:

- Basal serum calcitonin level
- CEA level
- Pheochromocytoma screening
- Serum calcium assay
- Consider genetic counseling
- Screen for RET proto-oncogene mutations (exons 10, 11, 13-16)
- Thyroid and neck ultrasound (including central and lateral compartments), if not previously done
- Consider evaluation of vocal cord mobility
- Consider contrast-enhanced CT of chest and mediastinum or MRI if N1 disease or calcitonin >400 pg/mL

## Prevention of Medullary Thyroid Cancer

The familial Medullary Thyroid Carcinoma (**MTC**) syndromes consist of Multiple Endocrine Neoplasia (**MEN**) types 2A and 2B and familial MTC. They are inherited in an autosomal dominant fashion. Children inheriting any of these syndromes have a 100% risk of developing MTC.

MEN 2A (Sipple syndrome) consists of MTC, pheochromocytoma (in 50% of patients), and hyperparathyroidism (10-20% of patients). MEN 2B consists of MTC, pheochromocytoma (in 50% of patients), marfanoid habitus, and ganglioneuromatosis. FMTC consists of MTC alone.

MTC in MEN 2B has the most aggressive biologic features. In this situation, MTC usually develops around 10 years of age, and it has a high propensity for rapid growth and metastasis. MTC in MEN 2A can appear in the first decade of life, and it almost always develops by the second decade. MTC in FMTC usually develops during adulthood.

Genetic testing is now the mainstay in the diagnosis of the familial MTC syndromes. Germline RET proto-oncogene mutations (on chromosome arm 10q) discovered in these syndromes include the following [2]:

- MEN 2A – Majority of cases show substitutions of conserved cysteine residues in exons 10 and 11
- MEN 2B – 95% of cases show threonine-for-methionine substitution in codon 918 of exon 16.
- Familial MTC - Most commonly seen with mutations in exons 10, 13 & 14

Guidelines from the American Thyroid Association (**ATA**) recommend prophylactic thyroidectomy for individuals that have a documented RET mutation and are at risk for aggressive medullary thyroid carcinoma [2].

The original ATA guidelines [2] stratified risk level of RET carriers into four categories, A through D, based upon the increasing aggressiveness of the particular mutation. Due to some confusion and lack of uniformity with other staging guidelines, the revised ATA guidelines [4] transition category D to “Highest Risk” (**HST**), transition category C to “High Risk” (**H**), and combine categories B and A into “moderate risk”. The risk stratification, screening schedules, and prophylactic thyroidectomy schedules are described in the table below.

**Table 1:** Revised ATA MTC Risk Levels and Pediatric Recommendations.

| Risk Level          | RET Codon Mutation  | Possible Diagnoses | Prophylactic Thyroidectomy Recommendations  | Follow-up   |
|---------------------|---------------------|--------------------|---|---|
| Highest Risk (HST)  | M918T+All MEN2B     | MEN2B              | Within the first year of life or the first months of life based upon specialist and parental discussions. The ability to identify and preserve or transplant parathyroid glands determines level VI dissection. | Physical exam, neck US, serum Ctn, and serum CEA every 6 months first year, then annually; begin screening for pheochromocytoma at age 11 years   |
| High Risk (H)       | C634, A883F         | MEN2A              | At or before age 5 yr, to be determined on the basis of serum Ctn   | Physical exam, neck US, serum Ctn, and serum CEA every 6 months first year, then annually. Begin screening for pheochromocytoma at age 11. Evaluate every 6 months for 1 year. Annual follow-ups thereafter if serum Ctn is normal or undetectable. Begin screening for pheochromocytoma at age 16 yr |
| Moderate Risk (MOD) | All other mutations | MEN2A              | When serum Ctn becomes elevated or in childhood to avoid lengthy evaluation period.   |   |

CEA = Carcino Embryonic Antigen; Ctn = Calcitonin; MEN = Multiple Endocrine Neoplasia; US = Ultrasound

## Staging

The staging for thyroid cancer follows the TNM system, developed by the American Joint Committee on Cancer (AJCC) [8]. See Thyroid Cancer Staging.

## Primary Treatment Of Differentiated Thyroid Cancers

The treatment of choice for differentiated thyroid cancers is surgery, whenever possible, followed by radioiodine (131I) in selected patients and thyrotropin suppression in most patients, according to the National Comprehensive Cancer Network (NCCN) guidelines [5].

## PAPILLARY THYROID CARCINOMA (PTC)

NCCN guidelines recommend total thyroidectomy for patients who meet any of the following criteria [5]:

- Radiation history
- Known distant metastases
- Bilateral nodularity
- Extra thyroidal extension
- Tumor >4 cm in diameter
- Cervical lymphnode metastases
- Poorly differentiated tumor

The NCCN considers either total thyroidectomy or lobectomy to be acceptable for patients who meet all of the following criteria, [5]:

- No prior radiation
- No distant metastases
- No cervical lymphnode metastases
- No extrathyroidal extension
- Tumor <4 cm in diameter

If a lobectomy is performed, completion of the thyroidectomy is recommended for any of the following [5]:

- Tumor>4 cm in diameter
- Positive margins
- Extrathyroidal extension
- Macroscopic multifocal disease
- Macroscopic nodal metastases
- Confirmed contralateral disease
- Vascular invasion

ATA guidelines recommend near-total or total thyroidectomy for all patients with thyroid cancer >1 cm, unless there are contraindications to this surgery. Lobectomy may be considered for small (<1 cm), low-risk, thyroidal papillary carcinomas in the absence of prior radiation or clinically involved cervical nodal metastases [1].

Both the NCCN and ATA recommend that therapeutic neck dissection for patients with clinically involved central or lateral neck lymph nodes should accompany total thyroidectomy to provide clearance of disease from the central neck. Prophylactic central-compartment neck dissection (level VI) may be considered in patients with clinically uninvolved central neck lymph nodes, especially for advanced primary tumors (T3 or T4) [1,5].

## **FOLLICULAR THYROID CANCER AND HÜRTHLE CELL CARCINOMA**

The ATA does not have comprehensive guidelines for the treatment of Follicular Thyroid Cancer (**FTC**) and Hürthle cell carcinoma as separate entities from papillary thyroid cancer; however, there are several individual recommendations that apply decision-making principles to these conditions [1].

The ATA recommends that if cytology readings report a follicular neoplasm, an 123I thyroid scan may be considered, especially if serum Thyroid-Stimulating Hormone (**TSH**) is in a low-normal range. If a concordant autonomously functioning nodule is not seen, lobectomy or total thyroidectomy should be considered.

If the cytology report indicates “Hürthle cell neoplasm” or “suspicious for papillary carcinoma”, the ATA recommends a lobectomy or thyroidectomy, depending on nodule size and other risk factors.

For patients with an isolated indeterminate (“follicular neoplasm” or “Hürthle cell neoplasm”) solitary nodule who prefer a more limited approach, the ATA recommends an initial lobectomy.

The ATA recommends a total thyroidectomy for patients with indeterminate nodules in any of the following situations:

- The tumor exceeds 4 cm
- Marked atypia is observed
- Biopsy result is reported as “suspicious for papillary carcinoma”
- The patient has a family history of thyroid carcinoma
- The patient has a history of radiation exposure

The ATA recommends that patients with indeterminate nodules who have bilateral nodular disease or who wish to avoid future surgery should undergo total or near-total thyroidectomy [1].

The NCCN guidelines recommend lobectomy plus isthmusectomy as the initial surgery for patients with follicular neoplasms and Hürthle cell carcinomas, with prompt completion of thyroidectomy if invasive cancer is found on the final histologic section. Therapeutic neck dissection of involved compartments is recommended for clinically apparent/biopsy-proven disease.

The NCCN recommends total thyroidectomy as the initial procedure only if invasive cancer or metastatic disease is apparent at the time of surgery, or if the patient wishes to avoid a second, completion thyroidectomy should the pathologic review reveal cancer [5].

## RADIOIODINE THERAPY

NCCN guidelines recommend radioiodine (<sup>131</sup>I) therapy if any of the following are present [5]:

- Extrathyroidal extension
- Tumor >4 cm in diameter
- Postoperative unstimulated Thyroglobulin (**Tg**) level >5-10 ng/mL

Radioiodine therapy is not recommended if all of the following are present [5]:

- Classic Papillary Thyroid Carcinoma (**PTC**)
- Primary tumor <1 cm
- Intrathyroidal tumor



- Unifocal or multifocal tumor
- No detectable anti-Tg antibodies
- Postoperative unstimulated Tg < 1 ng/mL

Radioiodine therapy is selectively recommended if any of the following are present when the combination of clinical factors predicts a significant risk of recurrence [5]:

- Primary tumor 1-4 cm
- High-risk histology
- Lymphovascular invasion
- Cervical lymphnode metastases
- Macroscopic multifocality (one focus >1 cm)
- Presence of anti-Tg antibodies
- Postoperative unstimulated Tg < 5-10 ng/mL

The ATA recommends radioiodine therapy for all patients if any of the following are present [1]:

- Distant metastases
- Extrathyroidal extension of the tumor regardless of tumor size
- Primary tumor size >4 cm even in the absence of other higher-risk features.

Radioiodine therapy is not recommended for patients with unifocal cancer <1 cm without other higher- risk features; or for patients with multifocal cancer when all foci are <1 cm in the absence of other higher-risk features [1].

Radioiodine therapy is also recommended for selected patients with 1-4 cm thyroid cancers confined to the thyroid who have documented lymph node metastases or other higher risk features, when the combination of age, tumor size, lymph node status, and individual histology predicts an intermediate to high risk of recurrence or death from thyroid cancer [1].

The ATA and NCCN guidelines recommend treatment with levothyroxine to suppress Thyroid-Stimulating Hormone (**TSH**) levels. Degree of suppression is based on risk, as follows [1,5]:

- Low-risk patients - Maintenance of the TSH at or slightly below the lower limit of normal (0.1 to 0.5 mU/L)
- Intermediate-risk patients - Initial TSH suppression to below 0.1 mU/L
- High-risk patients - Initial TSH suppression to below 0.1 mU/L

## Primary Treatment of Medullary Thyroid Cancer

The National Comprehensive Cancer Network (**NCCN**) guidelines recommend total thyroidectomy and bilateral central neck dissection (level VI) for all patients with Medullary Thyroid Carcinoma (**MTC**) whose tumor is  $\geq 1$  cm or who have bilateral thyroid disease, as well as the following [5]:

- Therapeutic ipsilateral or bilateral modified neck dissection for clinically or radiologically identifiable disease (levels II–V)
- Prophylactic ipsilateral modified neck dissection for high volume or gross disease in the adjacent central neck may be considered

External Beam Radiation Therapy (**EBRT**) is an option for treatment of incomplete tumor resection when further surgical resection is no longer possible. EBRT can also be considered for adjuvant treatment for extrathyroidal extension (T4a or T4b) with positive margins

Other therapy considerations are as follows:

- Total thyroidectomy is recommended and neck dissection can be considered for those whose tumor is  $< 1$  cm and for unilateral thyroid disease
- Radioiodine ( $^{131}\text{I}$ ) therapy is not effective

Suppression of Thyroid-Stimulating Hormone (**TSH**) is not appropriate; TSH is kept in the normal range by adjusting levothyroxine dose.

- Pheochromocytoma removal prior to thyroid surgery by laparoscopic adrenalectomy, and treatment preoperatively with alpha-adrenergic blockade (phenoxybenzamine) or with alpha-methyltyrosine to avoid a hypertensive crisis during surgery

## Treatment of Anaplastic Thyroid Cancer

No curative treatment currently exists for Anaplastic Thyroid Cancer (**ATC**). The majority of patients present with unresectable or metastatic disease. National Comprehensive Cancer Network (**NCCN**) guidelines recommend attempting total thyroidectomy in patients with resectable disease [5].

The 2012 American Thyroid Association (**ATA**) guidelines recommend total lobectomy or total or near-total thyroidectomy with a therapeutic lymph node dissection for patients with intrathyroidal ATC. In patients with extrathyroidal invasion, an en bloc resection should be considered if grossly negative margins (R1 resection) can be achieved [3]. Both the NCCN and ATA guidelines recommend adjuvant radiation therapy, chemotherapy, or both [3,5].

## Treatment of Metastatic Disease

National Comprehensive Cancer Network (**NCCN**) recommendations for treatment of recurrent or metastatic thyroid disease include External Beam Radiation Therapy (**EBRT**) [5].

Systemic therapy can be considered for tumors with all the following characteristics:

- Not resectable
- Not responsive to radioiodine (<sup>131</sup>I) therapy
- Not amenable to EBRT
- Showing significant disease progression

Oral kinase inhibitors (eg, vandetanib) are associated with longer progression-free survival but are not curative; side effects that may have a significant effect on quality of life should be considered. Kinase inhibitor therapy may not be appropriate for a symptomatic patients with indolent disease progression.

## PEDIATRIC THYROID CANCERS

Thyroid cancer in the pediatric population is relatively rare, accounting for 1.5-3% of all carcinomas in the United States and Europe. Features of pediatric thyroid cancers areas follows:

- Papillary differentiated thyroid cancer is the most common variant found in children.
- Age, family history, and previous radiation exposure are all indicators for increased risk of disease
- Tumor volume tends to be larger in patients under 20 years of age than in the adult cohort
- Early involvement of the capsular and surrounding tissue along with multi-centricity are more common
- Regional and distant metastases are more common in children, with the lung being the site of highest prevalence
- A greater expression of the sodium-iodide transporter (**NIS**) makes the pediatric population more responsive to radioiodine treatment

Children tend to have a recurrence rate of around 40%, which is higher than the adult population; however, long-term survival rate is higher. Pediatric patients tend to have a 5-year survival rate of 99.3% and a 10-year survival rate of 98.5% [11].

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