

2020 ATA[®] Guidelines for Management of Patients with Anaplastic Thyroid Cancer

**Diagnosis: Cytology, Histopathology,
Differential Diagnosis**

Cytology

FNA cytology can play an important diagnostic role in the initial evaluation of ATC, but parallel core biopsy may be necessary for definitive diagnosis and to obtain sufficient material for molecular interrogation (R1)

- Cytological diagnosis of aggressive types of thyroid cancer, especially ATC, can be challenging and diagnostic yield of FNA is highly variable.
- If cellular yield is insufficient, core biopsy may be diagnostic and permits a broader range of genomic testing.

Diagnosis

Every effort should be made to establish a diagnosis via biopsy before proceeding with surgical resection, as surgery may be inappropriate (R2)

Histopathology

- **Routine surgical pathology evaluation of resection specimens should focus on confirming a definitive diagnosis of ATC, documenting extent of disease, and defining the presence of any co-existing differentiated thyroid carcinoma and/or other pathologies. The proportion of tumor that represents ATC should also be documented (R3)**
- Histopathological spectrum highly variable.
- Morphological subtypes include sarcomatoid or spindle cell, giant cell, and squamoid or epithelial, or mixed morphologies.
- Highly invasive tumors with a high potential for distant metastases.
- Characterized by a high degree of cellular proliferation as well as atypical mitoses.
- Diagnosis of ATC is more straightforward when a coexistent differentiated carcinoma is identified and admixed with an undifferentiated component.

Role of Immunohistochemistry (IHC)

Once ATC diagnosis is considered, assessment of *BRAFV600E* mutation should be expeditiously performed by IHC and confirmed/expeditiously assessed by molecular testing (R4).

Molecular studies should be performed at the time of ATC diagnosis to inform decisions related to the use of targeted therapies, especially as there are now FDA-approved mutation-specific therapies in this context (R5)

- Thyroid-specific proteins such as thyroglobulin and thyroid-transcription factor absent.
- PAX8 expression may be retained, at least focally.
- IHC for cytokeratins can be useful however, absence of cytokeratin expression does not rule out a diagnosis of ATC.
- Cellular proliferation can be assessed by mitotic activity and/or Ki-67 proliferation index (ATC should have Ki-67 of at least 30%).
- Loss of p53 tumor suppressor function via somatic mutation of TP53 is a molecular hallmark of ATC but are not specific to ATC.
- Somatic alterations of *BRAF* common and *BRAFV600E* is reasonably sensitive and specific.

Cytologic and Pathologic Differential Diagnosis of a Rapidly Enlarging Thyroid Mass

- Anaplastic Thyroid Carcinoma
 - Suspect ATC in any patient with a rapidly growing thyroid mass although primary thyroid lymphoma can present similarly.
- Poorly differentiated thyroid carcinoma (insular carcinoma)
- Primary squamous cell carcinoma of the thyroid.
- Medullary thyroid carcinoma.
- Thyroid lymphoma - large B cell lymphoma and anaplastic large cell lymphoma
- Miscellaneous: Non thyroid tumors
- Squamous metaplasia: can be present in differentiated thyroid tumors and chronic thyroiditis and can be confused with ATC.

ATC Risk Factors

POSSIBLE risk factors include

- Low education level
- Type B blood group
- Goiter
- Iodine deficiency
- Adiposity
- Differentiated thyroid cancer (small subset of DTC transform to ATC)
- ***TERT* promoter mutation (C228T) only factor independently implicated as potentially associated with anaplastic transformation of PTC.**

ATC Prognostic Factors

- Factors associated with improved survival
 - Younger age (≤ 65 years)
 - Lower comorbidity score
 - No known nodal disease
 - No known metastasis
 - Smaller tumor size (≤ 6 cm)
 - Intrathyroidal ATC with no evidence of extrathyroidal extension or distant metastasis

ATC Health Care Disparities

- **Private insurance status** was significantly associated with **improved** chance of undergoing surgery or of receiving external beam RT.
- Residing in **high poverty federal designated county** impacted **negatively** on outcome.
- Odds ratio of **non-white patients** with ATC receiving any treatment compared to non-Hispanic whites was **significantly reduced**.
- Providers must be cognizant of the **financial impact of ATC** care on individual patients to fully support them.
- **Health disparities** may also be a factor in higher incidence of ATC in vulnerable populations that have **no access to primary care, screening for thyroid nodules, or treatment of DTC**.

ATC Centers of Excellence and Clinical Trials

- Historical nihilism in the approach to ATC by many non-subspecialist providers can impede active management or onward referral.
- **ATC clinical trials with the aim of improving patient outcomes are critical in order to make progress in treating this rare disease.**
- **Rapidity of decision-making and quality of care in ATC from presentation to diagnosis, to treatment initiation is critical to optimize ATC patient outcomes.**
- Direct contact with an ATC referral center will assure access to the most recent clinical trial information.