Thyroid Nodular Disease andThyroid Cancer

Chapter 397 | Part 12: Endocrinology and Metabolism

KEY CLINICAL POINTS

1. Amiodarone-induced thyrotoxicosis (AIT) occurs in 10% of patients in low iodine areas and 2% in high iodine areas; Type 1 is iodine-induced (Jod-Basedow) in pre-existing disease, while Type 2 is drug-induced destructive thyroiditis.
2. ACR TI-RADS classifies nodules into TR1–5 based on composition, echogenicity, shape, margin, and echogenic foci; FNA cutoffs range from 0.5 cm (TR5) to no FNA (TR1).
3. Toxic adenoma (hyperfunctioning solitary nodule) is caused by activating TSH-R or Gαs mutations (>90% of cases); treatment includes radioiodine ablation or surgery.
4. Papillary thyroid carcinoma (PTC) is the most common malignancy; BRAF V600E mutations occur in up to 60%, and RET/PTC rearrangements occur in 15%.
5. Follicular thyroid cancer (FTC) is distinguished from adenoma by capsular or vascular invasion; PAX8-PPARγ rearrangements are specific to FTC.
6. Medullary thyroid carcinoma (MTC) is derived from C-cells, uses calcitonin as a serum marker, and is associated with MEN 2 syndromes.
7. Overdiagnosis of low-risk thyroid cancer is a major concern; disease-specific mortality for these cases is only 1% over 20 years.
8. Radioiodine (131I) is the treatment of choice for toxic MNG and differentiated thyroid cancer; dosage typically ranges from 370–1070 MBq based on goiter size and uptake.
9. Substernal goiters require CT or MRI evaluation; Pemberton's sign (facial congestion with arms raised) suggests thoracic inlet obstruction.
10. TSH suppression with LT4 is used for high-risk differentiated thyroid cancers to reduce recurrence risk.

DEFINITION & OVERVIEW

- **Goiter:** Defined as an enlarged thyroid gland.
- **Pathophysiology of Goiter:**
  - Biosynthetic defects or iodine deficiency → increased TSH → compensatory thyroid growth.
  - Graves' disease: Growth via TSH-R mediated by thyroid-stimulating immunoglobulins.
  - Hashimoto's thyroiditis: Growth due to acquired defects in hormone synthesis (leading to high TSH) and immune-mediated factors.
- **Thyroid Nodular Disease:** Characterized by disordered growth of thyroid cells, which can be hyperplastic or neoplastic.
- **Multinodular Goiter (MNG):**
  - Presence of nodules in a thyroid of normal size occurs in up to 12% of adults.

  - More common in women and increases with age.
- **Toxic MNG:** Similar pathogenesis to nontoxic MNG, but characterized by functional autonomy.
- **Thyroid Cancer:** Most common malignancy of the endocrine system.
  - **Differentiated Tumors:** Papillary (PTC) or Follicular (FTC); often curable with good prognosis in early stages.
  - **Anaplastic Thyroid Cancer (ATC):** Aggressive, poor response to treatment, and associated with a bleak prognosis.

Goiter Classification

- **Diffuse Nontoxic (Simple) Goiter:**
  - No nodules or hyperthyroidism; characterized by uniform follicles filled with colloid.
  - Endemic goiter: Occurs in >5% of a population, typically due to iodine deficiency.
- **Nontoxic Multinodular Goiter (MNG):**
  - Common in both iodine-sufficient and deficient regions.
- **Toxic Multinodular Goiter:**
  - Characterized by functional autonomy; mutations (TSH-R or Gαs) are not usually found in these areas.

Thyroid Cancer Classification

- **AJCC Staging:** Uses TNM system based on tumor size, extrathyroidal invasion, regional lymph node metastases, and distant metastases.
  - **Risk Factors for Malignancy:**
  - History of head/neck radiation before age 18 (e.g., mantle radiation for Hodgkin's, brain radiation for leukemia).
  - Exposure to ionizing radiation from fallout in childhood/adolescence.
  - Age ≥ 65 years.
  - Male gender (associated with worse prognosis).
  - Rapidly enlarging neck mass.
  - 18FDG or Ga-68 Dotatate PET avidity.
  - Family history of PTC in ≥ 2 first-degree relatives.
  - Genetic syndromes: MEN 2, Cowden's syndrome, familial adenomatous polyposis, Carney complex, PTEN hamartoma tumor.
  - Clinical signs: Vocal cord paralysis, hoarse voice, nodule fixed to adjacent structures, or ipsilateral lateral cervical lymphadenopathy.

EPIDEMIOLOGY

- **Prevalence:**
  - Palpable nodules: 3–7% of adults.
  - Ultrasound detection: Up to 50% of adults.
- **Overdiagnosis:**
  - High incidence is primarily due to small T1 papillary cancer tumors (<2 cm).
  - Mortality for low-risk thyroid cancer is only 1% over 20 years.
- **Trends:** Decreasing diagnosis rates in the US correlate with evidence-based guidelines recommending higher size thresholds for FNA.

ETIOLOGY & PATHOPHYSIOLOGY

- **Goiter Mechanisms:**
  - Iodine deficiency → increased TSH → thyroid growth.
  - Endemic goiter may be caused by environmental goitrogens (e.g., thiocyanate in cassava, cruciferous vegetables).
  - Iodide effects: Direct action on vasculature; indirect effect via endothelin and nitric oxide.
- **Molecular Basis of Autonomy:**
  - TSH-R mutations: Found in >90% of solitary hyperfunctioning nodules; located in transmembrane 5 and intracellular loop 3. These induce conformational changes mimicking TSH binding → increased cAMP → growth/differentiation.
  - Gαs mutations: Impair GTP hydrolysis → constitutive activation of the cAMP pathway.
  - EZH1 mutations: Found in ~25% of autonomous nodules; usually lead to benign tumors.
- **Malignancy Genetics:**
  - PTC: BRAF V600E (up to 60%), RET rearrangements (15%).
  - FTC: PAX8-PPARγ rearrangements (specific to FTC); also contains BRAF and RAS mutations.
  - Shared Pathways: Activation of MAPK cascade (via BRAF/RAS) or PI3K pathway (via PTEN deletion).

Amiodarone-Induced Thyroid Dysfunction (AIT)

- **Prevalence:**
  - Type 1: 10% in low iodine areas; Type 2: 2% in high iodine areas.
- **Type 1 AIT:**
  - Associated with underlying thyroid abnormality (preclinical Graves' or nodular goiter).
  - Mechanism: Jod-Basedow phenomenon (increased iodine → excessive hormone synthesis).
- **Type 2 AIT:**
  - No intrinsic thyroid abnormalities; result of drug-induced lysosomal activation → destructive thyroiditis with histiocyte accumulation.
  - Note: TSH levels must be monitored as T4 is often elevated.

CLINICAL FEATURES

- **General:** Most goiters are asymptomatic unless large enough to cause compression.
- **Compression Symptoms:**
  - Difficulty swallowing, respiratory distress (tracheal compression).
  - Pemberton's sign: Facial/neck congestion when arms raised → indicates thoracic inlet obstruction.
- **Substernal Goiter:** Requires CT or MRI for evaluation of airway/esophageal involvement.
- **Toxic MNG Presentation:**
  - Symptoms: Atrial fibrillation, palpitations, tachycardia, nervousness, tremor, weight loss.
  - Scintigraphy: Heterogeneous uptake with focal areas of increased uptake (hyperfunctioning).

DIFFERENTIAL DIAGNOSIS

- **AIT Differentiation:**
  - Type 1 → Increased vascularity on ultrasound; normal/increased scintigraphy.

– Type 2 → Decreased vascularity on ultrasound; scintigraphy difficult to interpret due to high iodine levels.

- **Nodule Functionality:**
  – Nontoxic MNG vs. Toxic MNG (based on TSH and clinical symptoms).
  – Hyperfunctioning Solitary Nodule vs. Multinodular Goiter.
- **Malignancy Differentiation:**
  – Benign vs. Malignant: Based on ACR TI-RADS and FNA cytology.
  – PTC vs. FTC: Based on histology (capsular/vascular invasion for FTC).
  – MTC: Identified by calcitonin levels and C-cell origin.

DIAGNOSTIC APPROACH

1. **Initial Screening:** Perform TSH, Free T4, and T3 in all patients with goiter.
2. **Ultrasound Assessment:**
   – Identify nodules and assess sonographic features (ACR TI-RADS).
   – TR1–5 classification based on: Composition, Echogenicity, Shape, Margin, and Echogenic Foci.
3. **Scintigraphy:**

→ Perform if TSH is low → differentiate hyperfunctioning from non-functioning nodules.

4. **Fine-Needle Aspiration (FNA):**

→ Performed based on ACR TI-RADS score and size cutoffs.

→ TR1: No FNA; TR2: No FNA; TR3: FNA if ≥ 2.5 cm; TR4: FNA if ≥ 1.5 cm; TR5: FNA if ≥ 1.0 cm (Note: Overall range is 0.5 cm for TR5 to no FNA for TR1).

5. **Cytology Interpretation:**

→ Use Bethesda System to determine risk of malignancy.

→ If cytology is indeterminate/suspidence, proceed to surgery.

Flowchart: Approach to the Patient with a Thyroid Nodule

1. **Initial Assessment:** Identify nodule via palpation or imaging.
2. **TSH Level Check:**

→ **If TSH is Normal or High:**

→ Perform Diagnostic US with LN assessment → Identify Nodule(s) on US → Perform FNA based on US features and size → Evaluate FNA Cytology (Bethesda System).

→ **FNA Outcomes:**

→ Malignant: Surgery.

→ Suspicious for PTC: Surgery.

→ Follicular neoplasm: Consider molecular testing → Surgery if indicated.

→ AUS/FUL: Repeat US-guided FNA or consider molecular testing → Surgery if indicated.

→ Benign: Follow.

→ **If TSH is Low (Hyperthyroid state):**

→ History, physical exam, TSH → Radionuclide scanning.

→ **Branch based on Scintigraphy:**

→ **Nodule not functioning:** → Diagnostic US with LN assessment → Identify Nodule(s) on US → Perform FNA based on US features and size → Evaluate FNA Cytology (Bethesda System) [Follow same outcomes as above].

→ **Hyperfunctioning nodule:** → Evaluate and Rx for hyperthyroidism.

3. **Nondiagnostic FNA Pathway:**

→ If FNA is Nondiagnostic → Repeat US-guided FNA.

→ If still Nondiagnostic → Close follow-up or surgery.

MANAGEMENT & TREATMENT

1. **Hyperfunctioning Solitary Nodule:**

→ Treatment: Radioiodine ablation or surgery.

2. **Toxic MNG:**

→ Treatment of choice: Radioiodine (131I).

→ Dosage: 370–1070 MBq based on goiter size and uptake.

3. **Amiodarone-Induced Thyroid Dysfunction (AIT):**

→ Type 1: Address underlying condition; TSH monitoring required.

→ Type 2: LT4 can be used to normalize thyroid function if needed.

4. **Differentiated Thyroid Cancer:**

→ Surgery for malignant/suspicious cytology.

→ TSH suppression with LT4 for high-risk disease to reduce recurrence risk.

PROGNOSIS & COMPLICATIONS

- **Radioiodine Therapy:**

→ Potential for thyroid ablation; monitor TSH levels in LT4-replaced patients.

- **Survival (PTC):**

→ Stage I and II: Excellent survival (>90%).

→ Stage IV: Significantly lower survival due to lymph node involvement or metastasis.

SPECIAL CONSIDERATIONS

- **Pediatric/Adolescent:**

→ Thyroid enlargement in teenagers is termed juvenile goiter.

- **High-Risk Patients:**

→ Older patients (≥ 65) or males have worse prognosis for thyroid cancer.

→ History of head/neck radiation before age 18 increases risk.

KEY PEARLS & CLINICAL TRAPS

- **Diagnostic Clues:**

→ Low TSH + Normal/High T4 → Hyperfunctioning nodule.

→ "Cold" nodules on scintigraphy have higher risk of malignancy.

- **Clinical Pearls:**

→ Differentiation between PTC and FTC is critical for management (histology-based).

→ TSH suppression with LT4 is used specifically to reduce recurrence in high-risk differentiated cancer.

REFERENCE TABLES

TABLE 397-1

WHO Classification of Thyroid Neoplasms Developmental abnormalities 1. Thyroglossal duct cyst 2. Other congenital…

- Developmental abnormalities 1. Thyroglossal duct cyst 2. Other congenital thyroid abnormalities Follicular cell–derived neoplasms 1. Benign tumors a. Thyroid follicular nodular disease b. Follicular adenoma c. Follicular adenoma with papillary architecture d. Oncocytic adenoma of the thyroid 2. Low-risk neoplasms a. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features b. Thyroid tumors of uncertain malignant potential c. Hyalinizing trabecular tumor 3. Malignant neoplasms a. Follicular thyroid carcinoma b. Invasive encapsulated follicular variant papillary carcinoma c. Papillary thyroid carcinoma d. Oncocytic carcinoma of the thyroid e. Follicular-derived carcinomas, high-grade i. Differentiated high-grade thyroid carcinoma ii. Poorly differentiated thyroid carcinoma f. Anaplastic follicular cell–derived thyroid carcinoma Thyroid C-cell–derived carcinoma 1. Medullary thyroid carcinoma Mixed medullary and follicular cell–derived carcinomas Salivary gland–type carcinomas of the thyroid 1. Mucoepidermoid carcinoma of the thyroid 2. Secretory carcinoma of salivary gland type Thyroid tumors of uncertain histogenesis 1. Sclerosing mucoepidermoid carcinoma with eosinophilia 2. Cribriform morular thyroid carcinoma Thymic tumors within the thyroid 1. Thymoma family 2. Spindle epithelial tumor with thymus-like elements 3. Thymic carcinoma family Embryonal thyroid neoplasms 1. Thyroblastoma

TABLE 397-2

Risk Factors for Thyroid Carcinoma in Patients with Thyroid Nodule from History and Physical Examination History of…

History of head and neck irradiation before the age of 18, including mantle radiation for Hodgkin's disease and brain radiation for childhood leukemia or other cranial malignancies	Family history of papillary thyroid cancer in two or more first-degree relatives, MEN 2, or other genetic syndromes associated with thyroid malignancy (e.g., Cowden's syndrome, familial adenomatous polyposis, Carney complex, PTEN [phosphatase and tensin homolog] hamartoma tumor)
Exposure to ionizing radiation from fallout in childhood or adolescence	Vocal cord paralysis, hoarse voice
Age <20 or >65 years	Nodule fixed to adjacent structures
Rapidly enlarging neck mass	Lateral cervical lymphadenopathy (ipsilateral to the nodule)
Male gender	
18FDG or Ga-68 Dotatate PET avidity	

TABLE 397-3

Bethesda Classification for Thyroid Cytology Version 3

DIAGNOSTIC CATEGORY	RISK OF MALIGNANCY (INCLUDING NIFTP) MEAN % (RANGE)
I. Nondiagnostic or unsatisfactory	13 (5–20)
III. Atypia of unknown significance (AUS)	22 (13–30)
V. Suspicious for malignancy (SFM)	74 (67–83)