

Multinodular Goiter

Pathogenesis • morphology • clinicopathologic interpretation

Follicular nodular disease

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Learning objectives

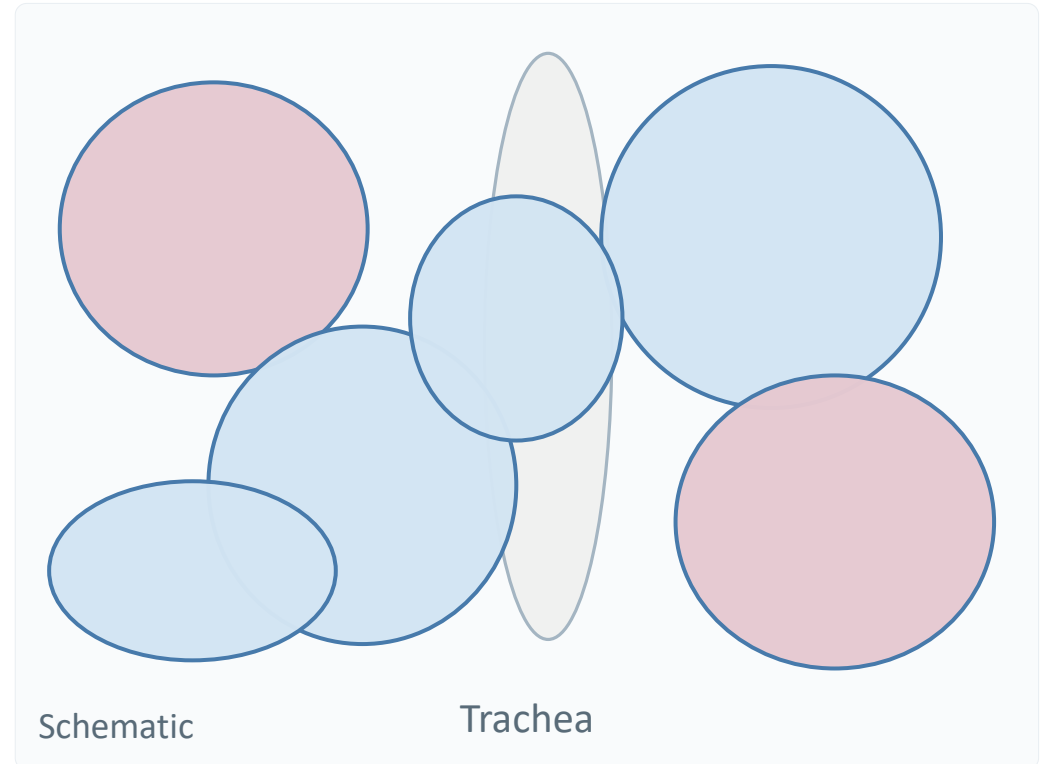
By the end of the lecture, interpret the disease from mechanism through morphology to clinical assessment.

- Distinguish diffuse goiter, multinodular goiter and follicular adenoma.
- Explain repeated hyperplasia–involution and nodular autonomy.
- Recognize gross and microscopic patterns and degenerative change.
- Relate size, location, function and suspicious nodules to clinical consequences.

Core definition: Irregular nodular enlargement

Multinodular goiter arises after repeated episodes of follicular hyperplasia and involution.

- Growth becomes regionally uneven rather than diffusely symmetric.
- The gland contains multiple variably sized and active follicular regions.
- The morphologic term is follicular nodular disease.



Thyroid size does not define function

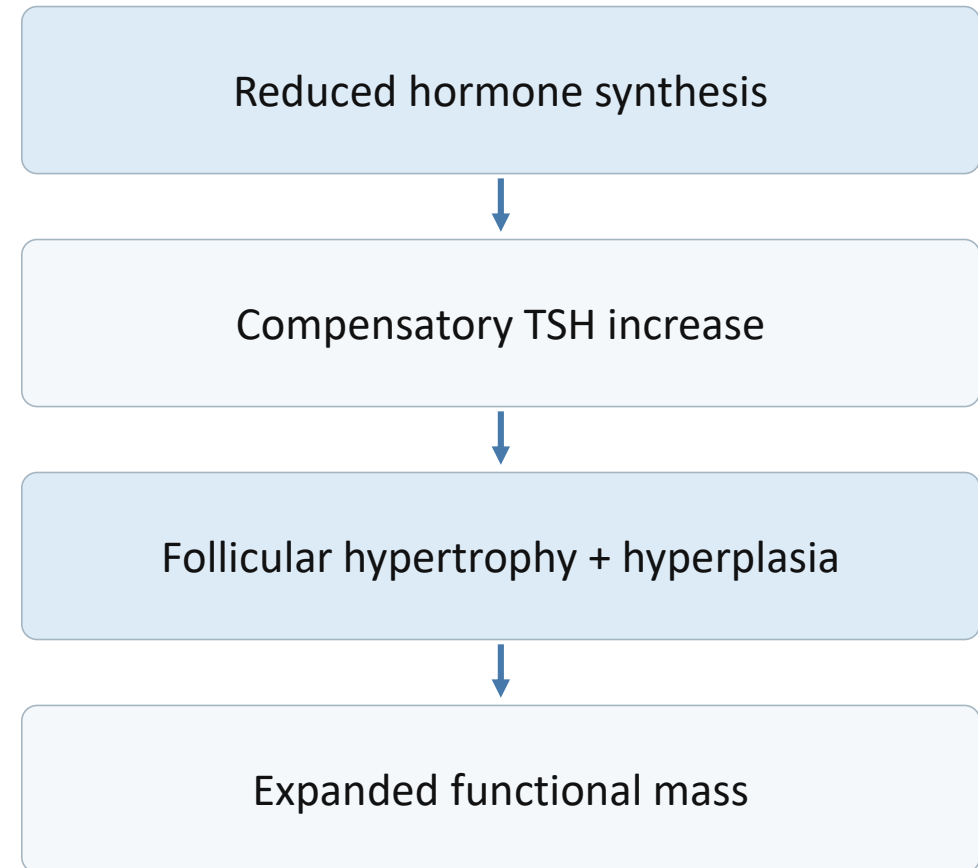
Goiter may occur in euthyroid, hypothyroid or hyperthyroid states.

Enlargement	Functional state
Diffuse or multinodular	Euthyroid is common
Variable gland volume	Hypothyroidism may occur
Mass effect depends on location	Hyperthyroidism in toxic disease

TSH drives compensatory thyroid enlargement

Reduced thyroid-hormone production can increase pituitary TSH stimulation.

- Falling hormone output increases trophic drive to follicular epithelium.
- Follicular hypertrophy and hyperplasia expand functional gland mass.
- This response can restore hormone output despite persistent stimulation.



Why many enlarged glands remain euthyroid

Functional compensation and morphologic enlargement are not contradictory.

- The growing gland may overcome an earlier hormone deficit.
- Thyroid function can be preserved after enlargement becomes established.
- The biochemical state must be assessed independently from gland size.

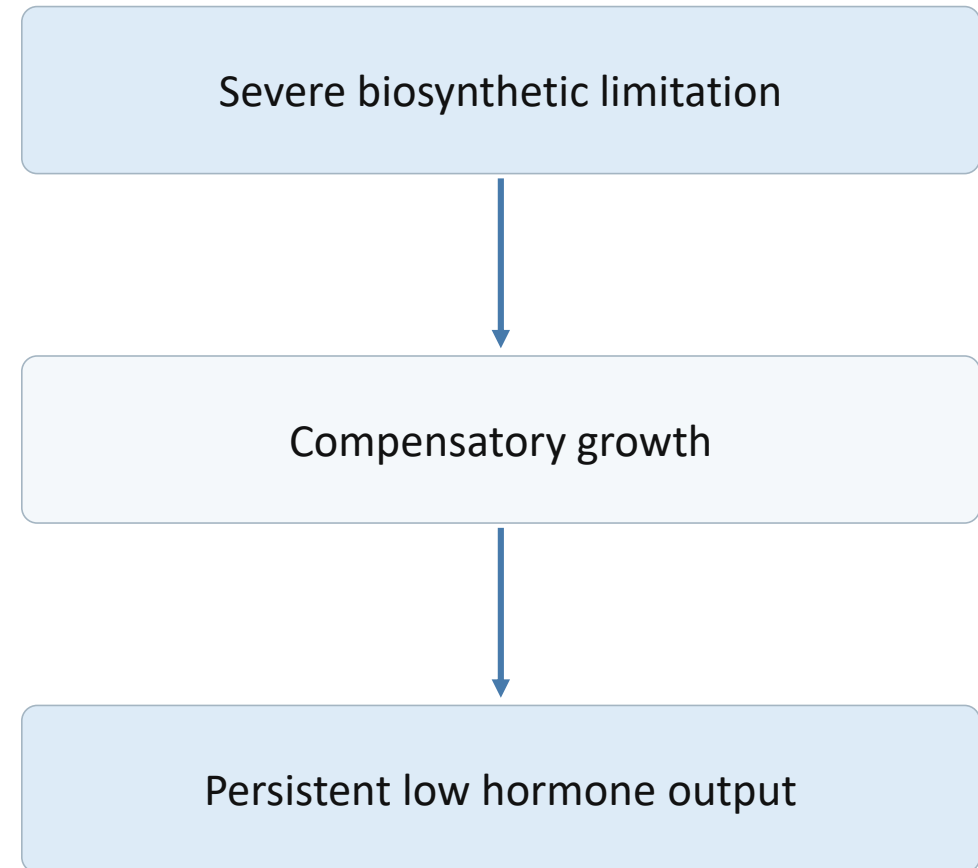
Large gland ≠ hyperthyroidism

Structural enlargement can coexist with preserved thyroid hormone production.

When compensation does not suffice

Severe iodine deficiency or congenital biosynthetic defects may produce goitrous hypothyroidism.

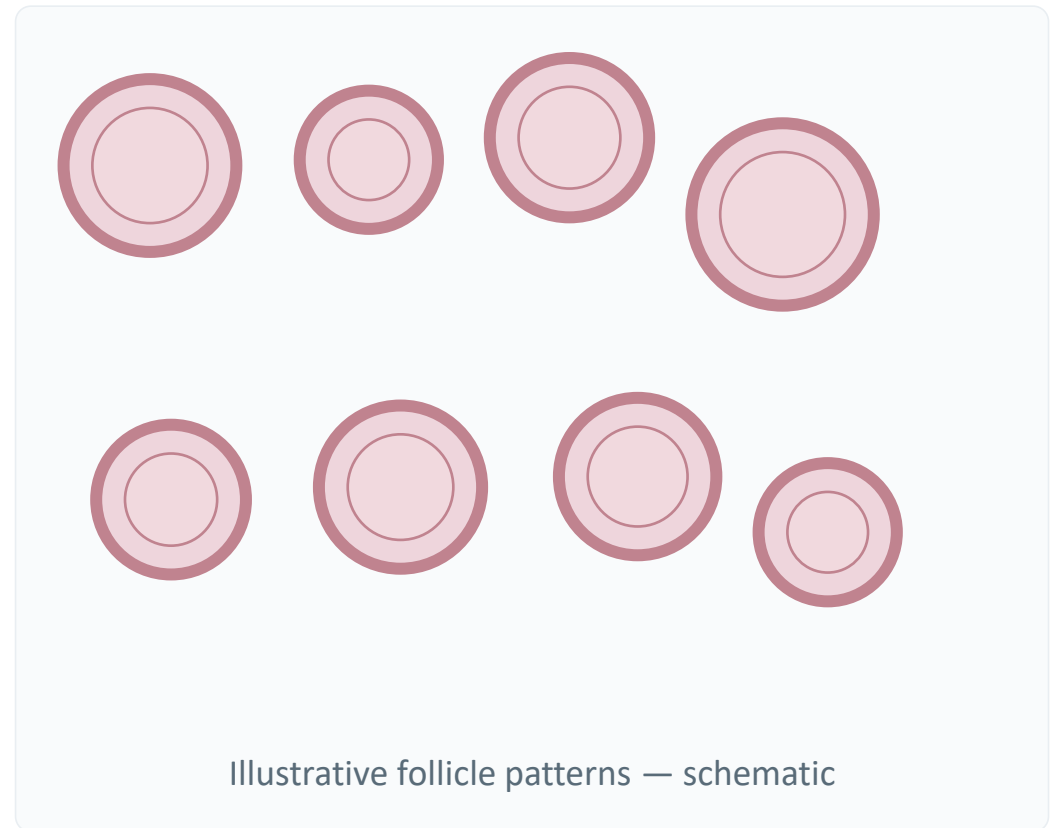
- Impaired synthesis persists despite increased follicular mass.
- The stimulus can drive growth without restoring adequate output.
- This is a parent-context mechanism—not the required state of every multinodular goiter.



Simple diffuse goiter: Hyperplastic phase

The earliest compensatory response is commonly diffuse and relatively symmetric.

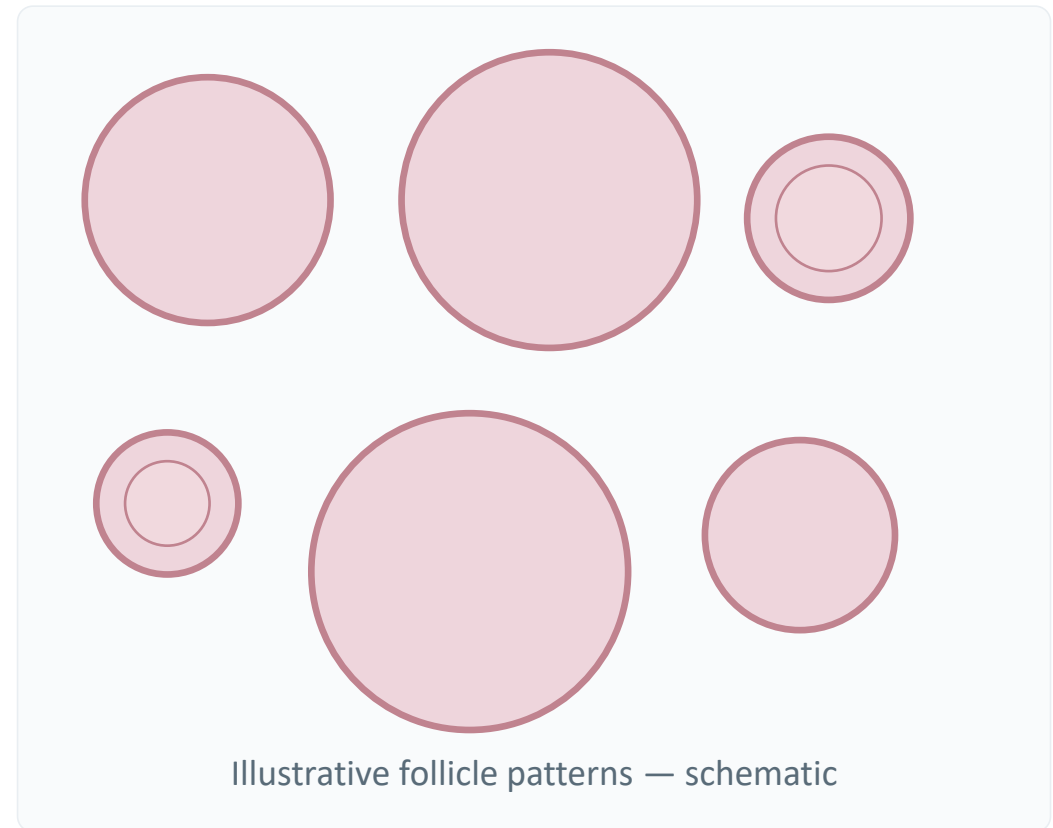
- The gland enlarges, usually far less markedly than advanced multinodular goiter.
- Epithelial cells become crowded and columnar.
- Some follicular linings project into the lumen during active stimulation.



Uneven follicular response begins early

Even diffuse hyperplasia is not morphologically uniform.

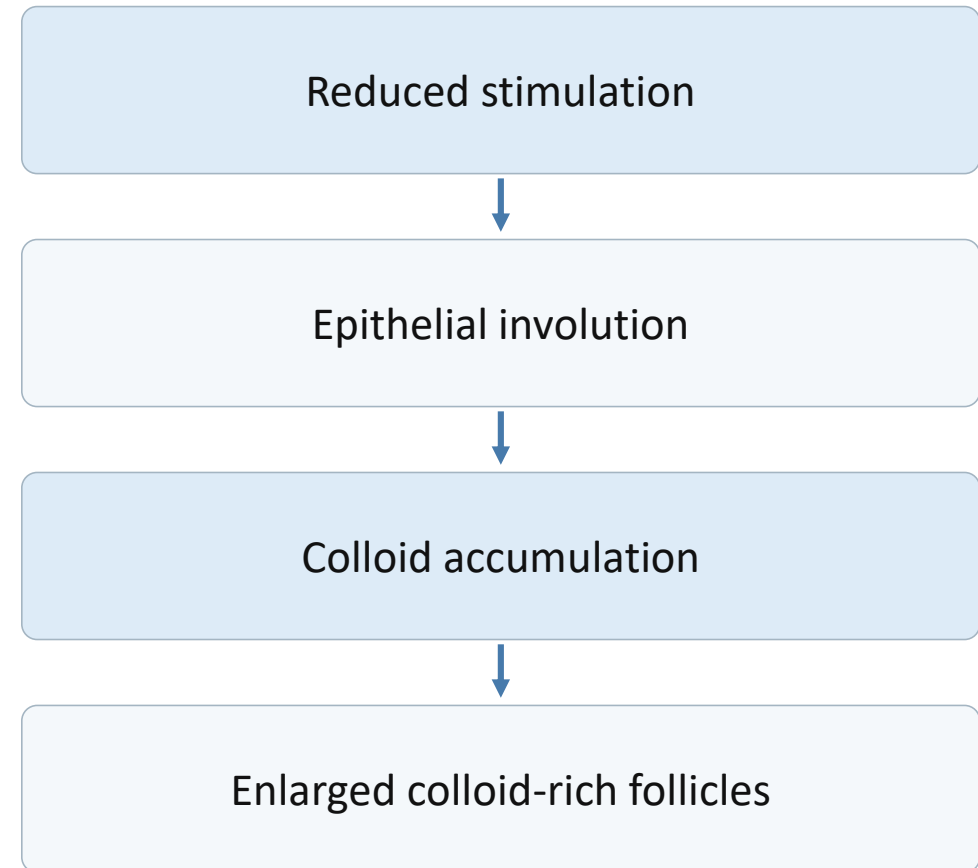
- Some follicles become distended while neighboring follicles remain small.
- Regional differences create an early substrate for later irregular growth.
- This heterogeneity helps explain why repeated cycles do not produce identical nodules.



Involution follows reduced trophic demand

Increased iodine availability or reduced hormonal demand may reverse follicular activation.

- Follicular epithelium becomes low cuboidal or flattened.
- Colloid accumulates within enlarged follicles.
- The gland becomes relatively inactive and colloid rich.



Hyperplasia and involution leave different signatures

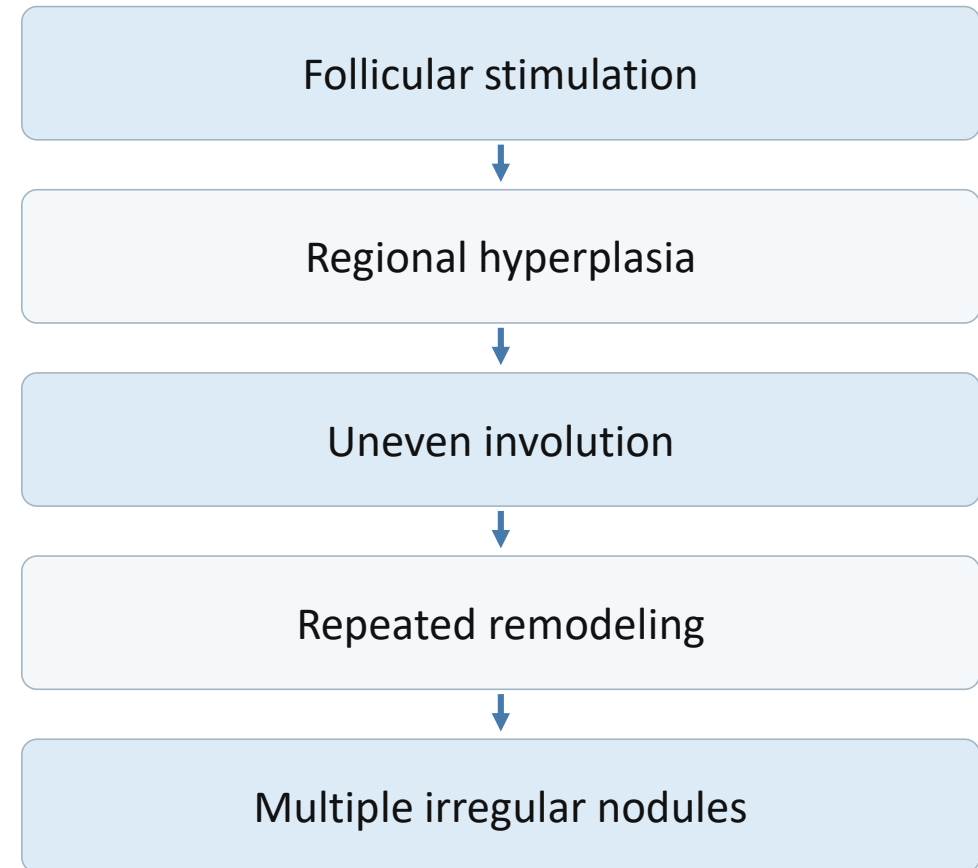
Epithelial height and colloid content reflect different functional phases.

Hyperplastic phase	Colloid involution
Active follicular proliferation	Flattened / low cells
Crowded / taller cells	Enlarged colloid stores
Variable luminal projections	Increased follicle size

Repeated cycles yield the nodular gland

Temporal repetition converts diffuse enlargement into a nonuniform organ.

- Follicular regions do not grow or regress identically.
- Repeated activation and involution establish nodules of differing size.
- Structural changes accumulate across cycles rather than fully resetting.



Multinodular goiter is usually a late lesion

The condition may follow a preexisting simple goiter over time.

- Recurrent growth and involution require time to produce conspicuous heterogeneity.
- Therefore multinodular goiters commonly affect older individuals.
- Age association reflects disease evolution, not a distinct single cause.

Longitudinal process

Simple goiter → repeated remodeling → established multinodular goiter

Sporadic and endemic forms share the phenotype

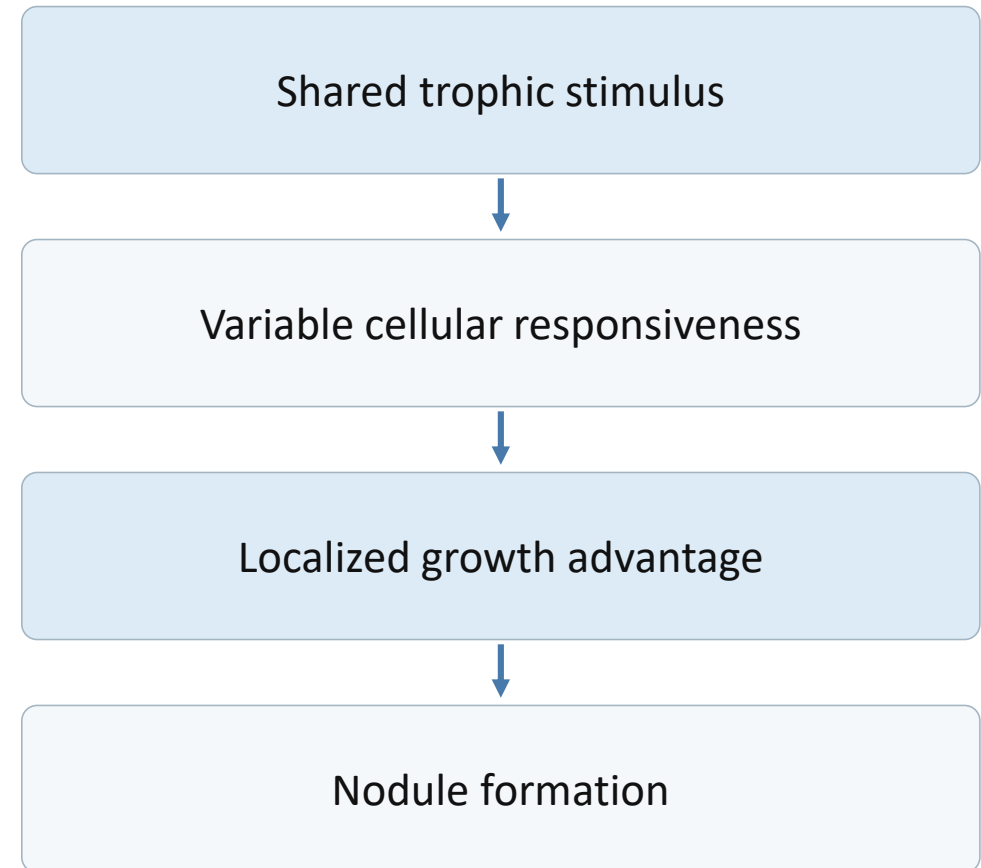
Multinodular goiters may arise from sporadic or endemic simple goiters.

Sporadic origin	Endemic origin
Occurs outside endemic deficiency settings	Related to population iodine deficiency
Can progress from simple goiter	Can progress from simple goiter
Develops over time	Develops over time

Follicular cells differ in growth responsiveness

Regional growth differences may arise from unequal responses to trophic stimuli.

- Follicular cells need not respond identically to the same systemic signal.
- A relatively growth-advantaged population can expand locally.
- This mechanism is presented by Robbins as a proposed model.



The gland contains distinct cellular populations

Polyclonal and monoclonal nodules can coexist within one multinodular goiter.

Polyclonal nodule	Monoclonal nodule
Multiple contributing cell lineages	Growth-advantaged lineage
Heterogeneous response to stimuli	May carry acquired alterations
Part of multinodular remodeling	Can coexist with polyclonal nodules

Acquired growth advantage is a hypothesis

Some nodules may expand because of somatic genetic abnormalities.

- The model is analogous to growth selection in thyroid adenomas.
- A clone may become more responsive or partly independent of trophic control.
- Not every nodule is proven to follow the same molecular route.

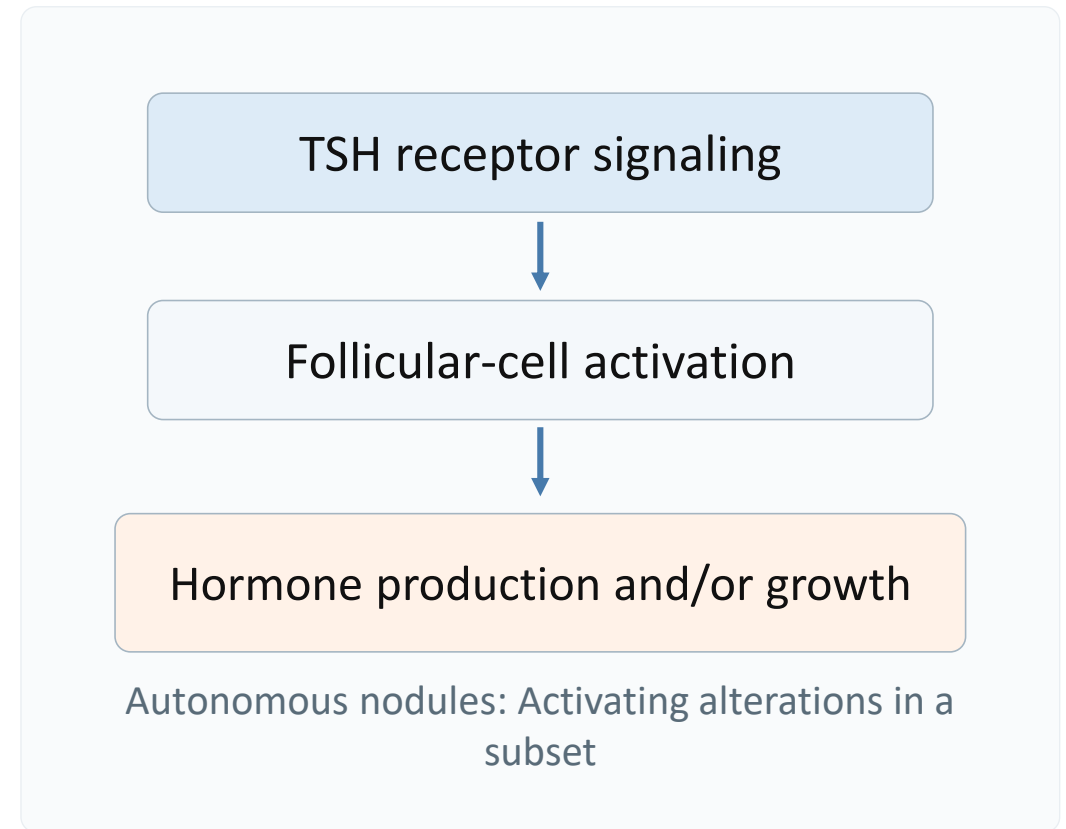
Mechanistic uncertainty

Clonal selection is plausible for some nodules; It is not a universal demonstrated cause.

TSH-signaling alterations occur in some nodules

Activating molecular changes can underlie follicular autonomy.

- TSH-receptor pathway mutations in a subset of autonomous nodules.
- The adjacent adenoma section names TSHR and GNAS as components of this pathway.
- Pathway activation can uncouple hormone production from normal TSH dependence.



Growth autonomy and hormone autonomy differ

A large nodule is not automatically hormone producing.

Growth advantage	Hormone autonomy
Local expansion dominates	TSH-independent hormone output
May contribute to nodularity	May yield a hot nodule
No automatic thyrotoxicosis	Can cause toxic disease

Integrating the pathogenesis

The established phenotype combines repeated remodeling with biological heterogeneity.

- Systemic stimulus may initiate or sustain follicular proliferation.
- Local differences in responsiveness shape nonuniform nodularity.
- Selected autonomous nodules may alter thyroid function in some patients.

Compensatory growth background



Uneven follicular response



Repeated hyperplasia / involution



Clonal selection in some nodules

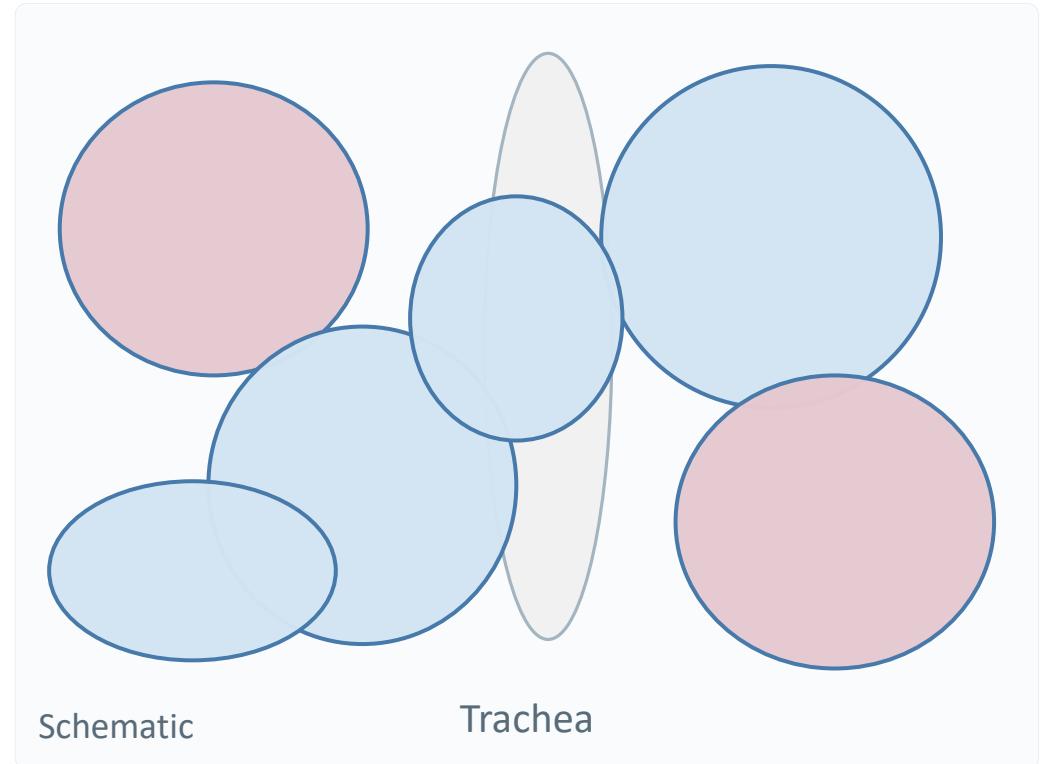


Morphologic and functional heterogeneity

Gross phenotype: Multilobulated enlargement

Multinodular goiter is a markedly irregular, asymmetric gland.

- Multiple lobules replace a smooth symmetric contour.
- Expansion need not be equivalent in the two lobes.
- A cross-sectional view may reveal nodules of very different dimensions.



Extreme enlargement is possible

Among thyroid disorders, multinodular goiter can produce very large glands.

- Glands exceeding 2000 g in extreme examples.
- Size contributes to distortion and compression of adjacent structures.
- Weight is a description of potential magnitude—not a diagnostic cutoff.

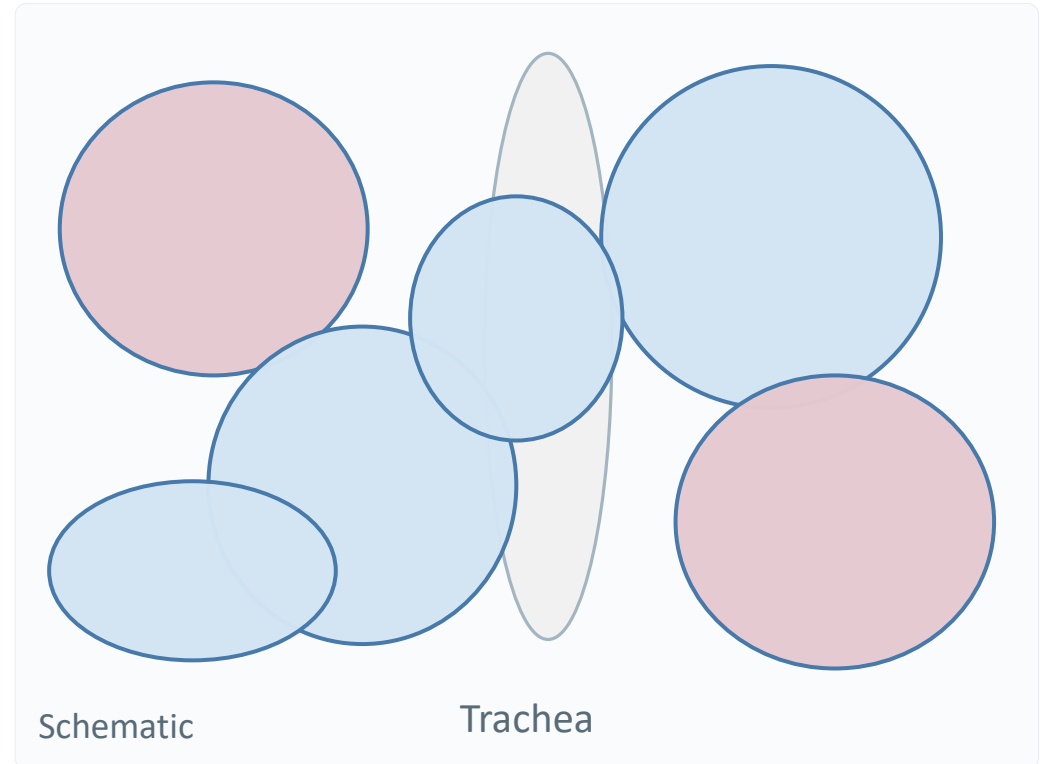
> 2000 g

Reported possible extreme gland weight in the source; Not a routine threshold or expectation.

Asymmetry explains the distorted neck contour

One lobe can expand substantially more than the opposite lobe.

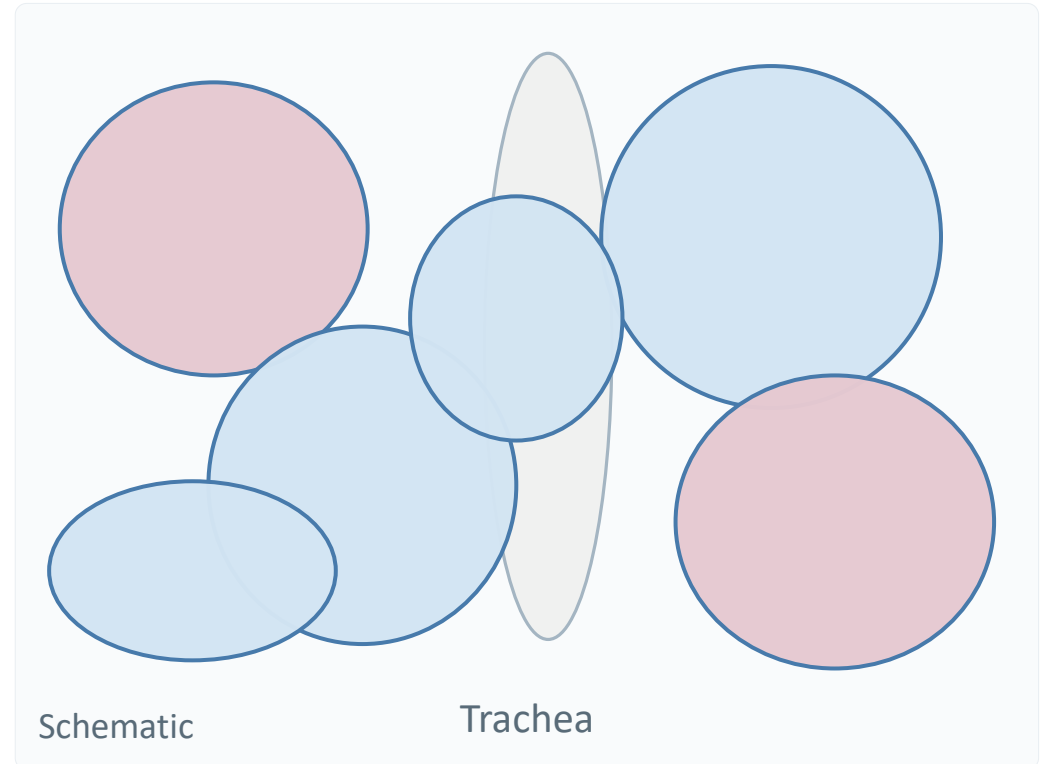
- Gland growth is unpredictable in extent and direction.
- An asymmetric thyroid can displace midline structures.
- Symmetry should not be assumed from a single palpable dominant swelling.



Multiple nodules produce heterogeneous texture

Irregular nodules can differ in size, colloid content and degenerative change.

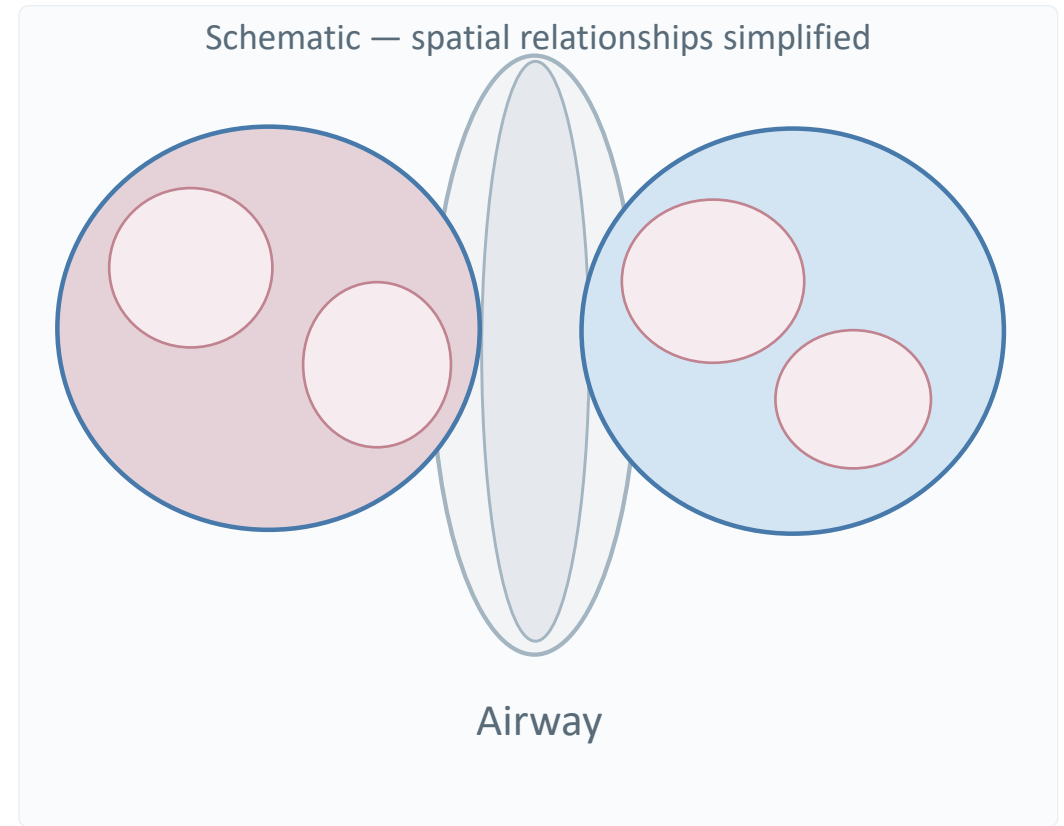
- A nodule-rich gland is not a collection of identical lesions.
- Adjacent lesions may show different phases of the growth–involution cycle.
- The overall architecture is more informative than a single nodule.



Tracheal compression is an anatomic consequence

Large asymmetric goiters may exert pressure on the airway.

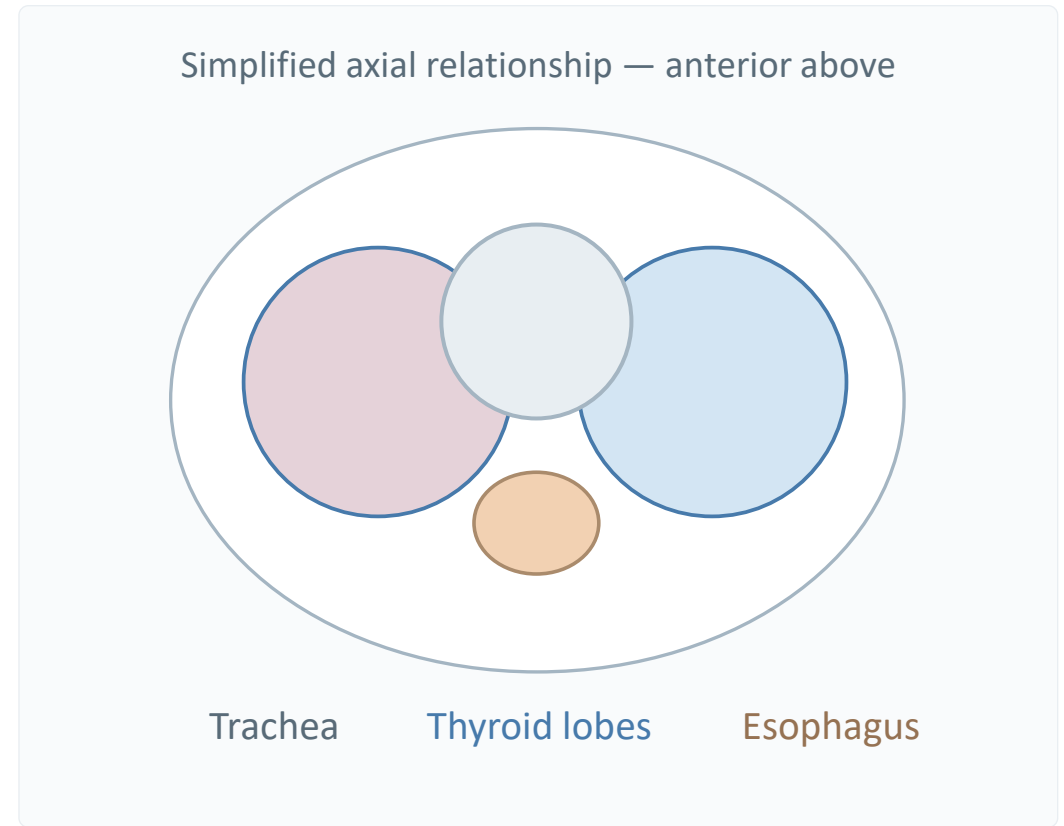
- Growth occurs near central cervical structures.
- Compression may produce respiratory obstruction.
- The site and direction of growth are clinically important, not size alone.



Esophageal compression accounts for dysphagia

Posterior or deep expansion can impinge on the swallowing pathway.

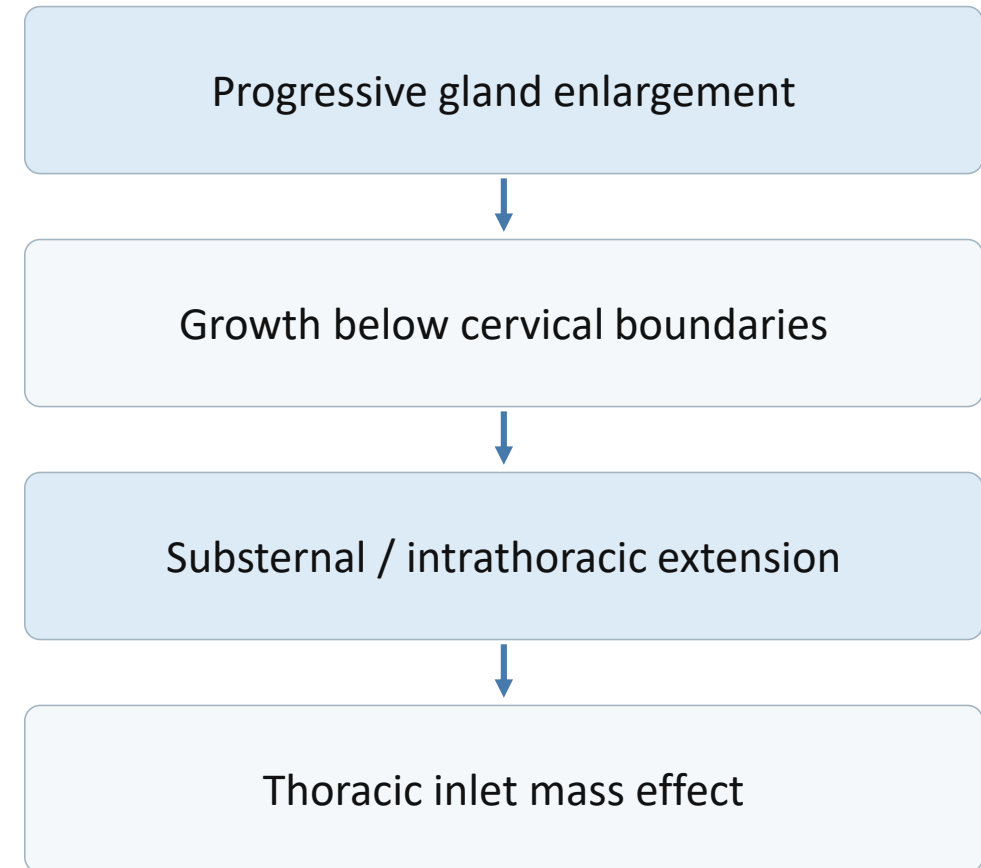
- Enlarged thyroid lobes may extend toward the esophagus.
- Dysphagia is a structural mass-effect symptom.
- Symptom assessment complements morphologic evaluation.



Intrathoracic extension creates a substernal goiter

Some multinodular glands extend behind the sternum and clavicles.

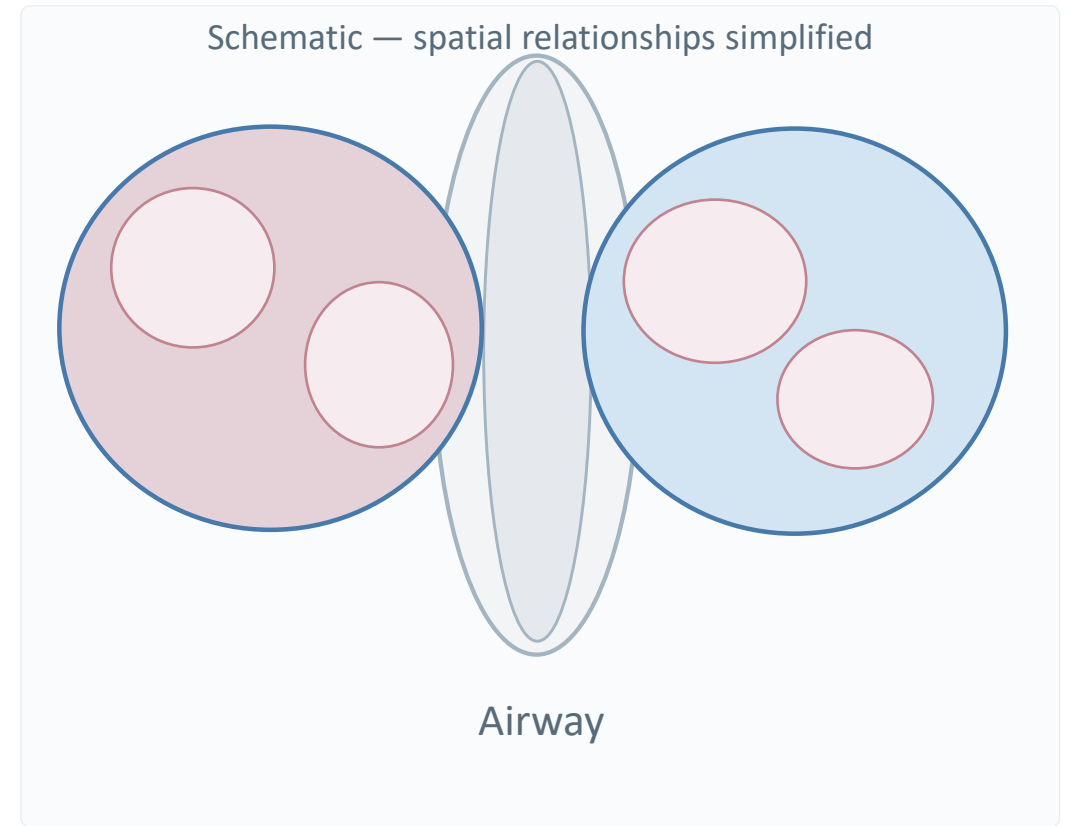
- A substantial component may not be apparent on superficial inspection.
- The enlarged gland can occupy the upper thoracic inlet.
- The distribution helps explain deeper compressive manifestations.



Retrodeep growth can obscure the full extent

The gland may enlarge behind the trachea or esophagus.

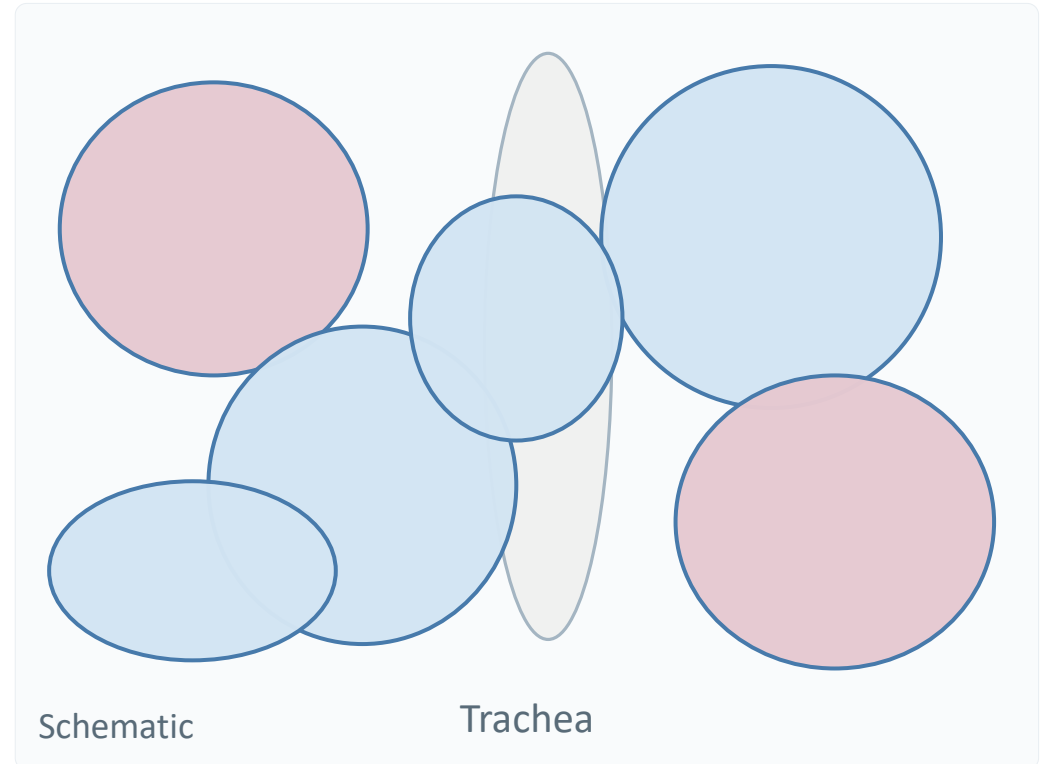
- A relatively modest anterior prominence need not reflect the entire lesion.
- Deep extensions may alter airway or swallowing relationships.
- Anatomic assessment is important when symptoms exceed visible neck findings.



A dominant nodule can simulate a tumor

One prominent nodule may be clinically perceived as a solitary thyroid lesion.

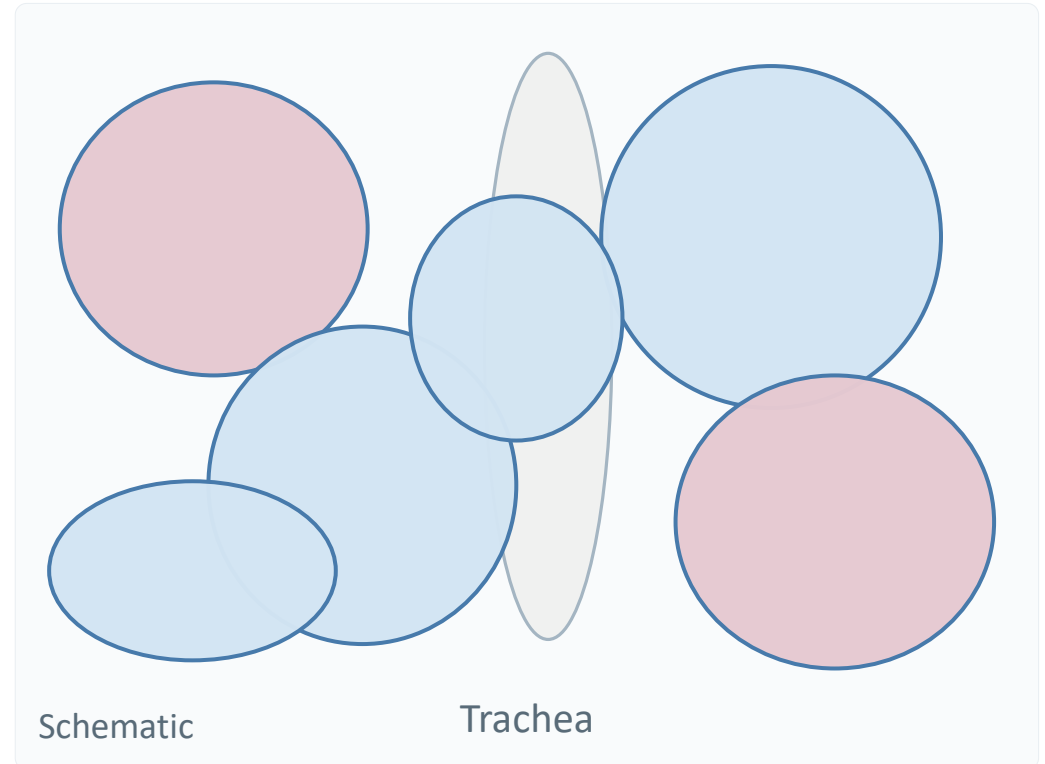
- The remaining gland can still contain multiple nodules.
- A dominant nodule is not synonymous with follicular adenoma.
- This distinction matters for histologic and imaging interpretation.



Cut surface: Colloid-rich, gelatinous nodules

Irregular nodules contain variable amounts of brown gelatinous colloid.

- Colloid imparts a translucent or glistening quality to some nodules.
- The macroscopic appearance varies from region to region.
- These are source-described gross features, illustrated schematically here.



Hemorrhage is a common regressive change

Older multinodular lesions may contain focal bleeding.

- Recurrent growth imposes physical stress on the expanded gland.
- Hemorrhagic areas can coexist with colloid-rich nodules.
- The finding contributes to gross heterogeneity rather than defining a separate tumor.

Hemorrhage

A regressive feature in an established multinodular gland;
Interpret in the overall architecture.

Fibrosis records long-standing remodeling

Fibrotic change is among the degenerative alterations of older nodules.

- The gland is altered by cumulative tissue stresses.
- Fibrosis can partition areas without forming a continuous adenoma-type capsule.
- This distinction prevents overcalling a discrete tumor from scar tissue alone.

Fibrosis ≠ tumor capsule

Nodular goiter lacks a prominent uniform capsule separating all nodules from residual thyroid.

Calcification and cystic change add complexity

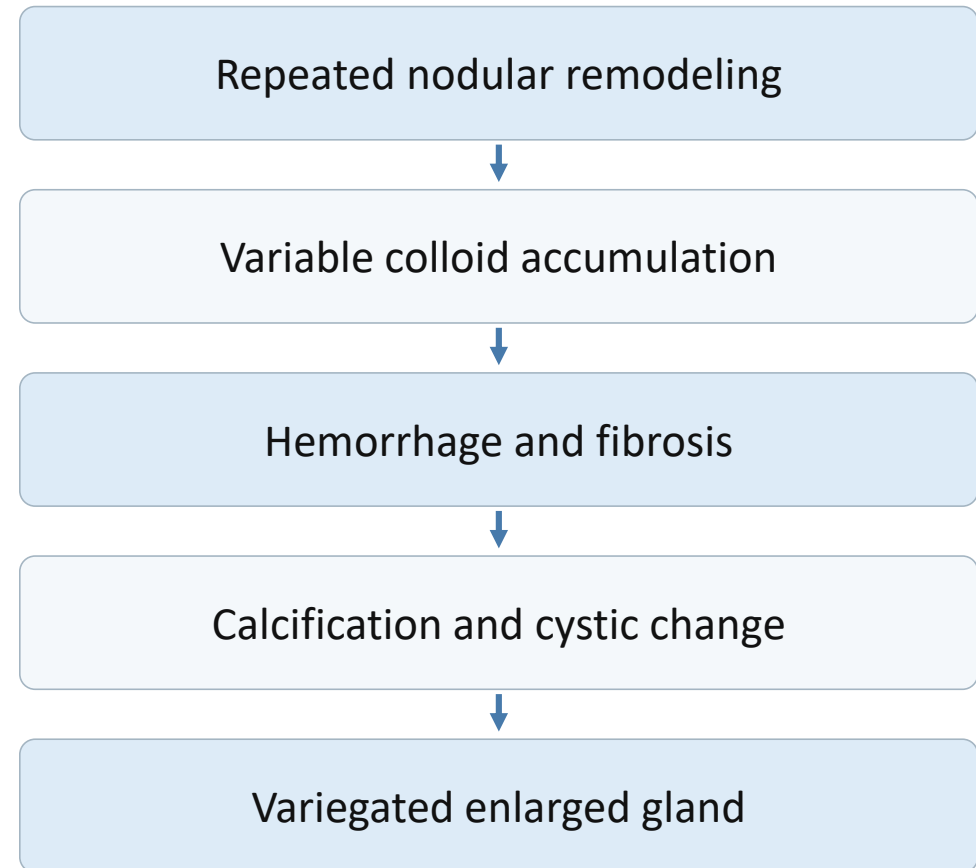
Degeneration can produce calcified and cystically altered regions.

Calcific change	Cystic change
Degenerative mineral deposition	Focal fluid-filled degeneration
May accompany older lesions	May accompany older lesions
Part of the mixed gross appearance	Part of the mixed gross appearance

The whole gross pattern reflects repeated injury

Colloid accumulation and secondary changes build a patchwork appearance.

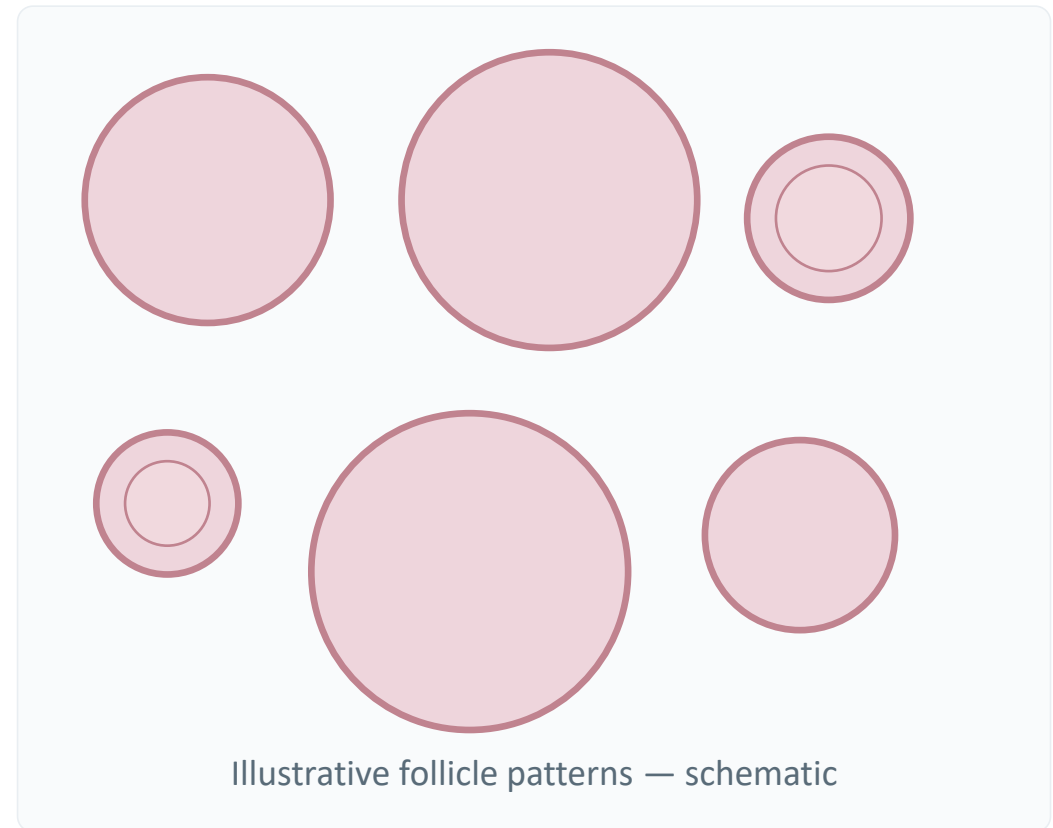
- Nodular hyperplasia and involution create the baseline architecture.
- Hemorrhage, fibrosis, calcification and cysts superimpose additional variation.
- No single cut-surface texture characterizes every region.



Microscopy shows a follicular mosaic

Large colloid-filled follicles and hyperplastic foci often occur in the same gland.

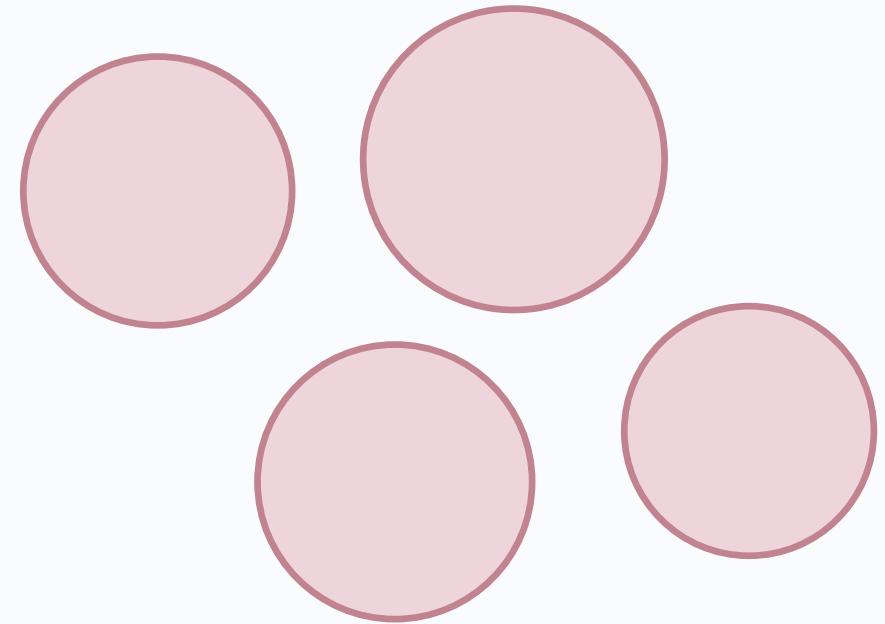
- The microscopic field changes according to the region sampled.
- Follicular caliber varies conspicuously.
- The collective pattern is more diagnostic than one isolated follicle.



Colloid-rich follicles dominate involuted areas

Enlarged lumens contain abundant stored eosinophilic colloid.

- The abundant colloid reflects storage rather than a requirement for active secretion.
- Large follicles often display relatively inactive lining cells.
- Interpret the schematic as an architectural explanation, not a micrograph.

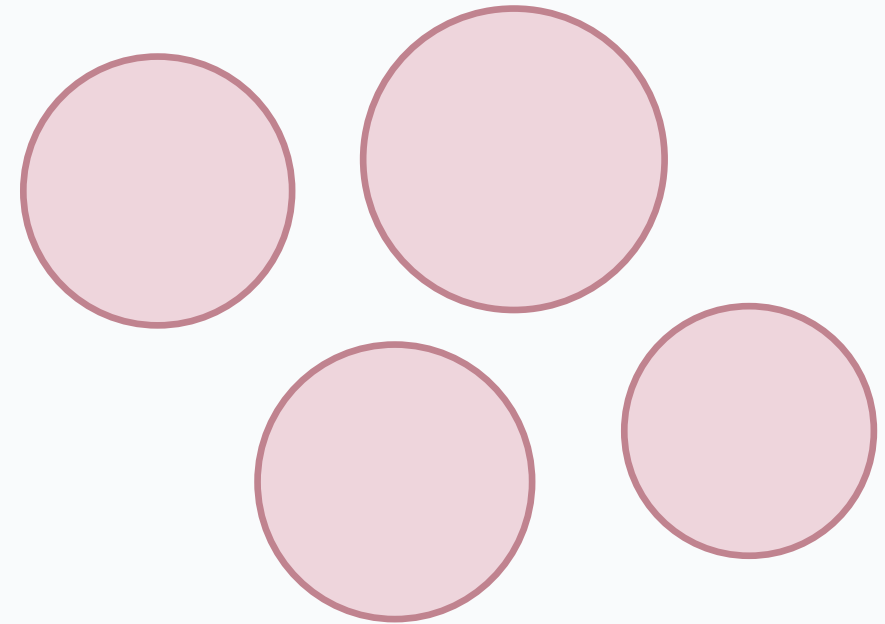


Illustrative follicle patterns — schematic

Flattened follicular epithelium indicates involution

Epithelium can become attenuated when trophic activity declines.

- Flattened cells line distended colloid-rich follicles.
- Cell height is a useful morphologic clue to local activation.
- A single gland may show different levels of epithelial activity.

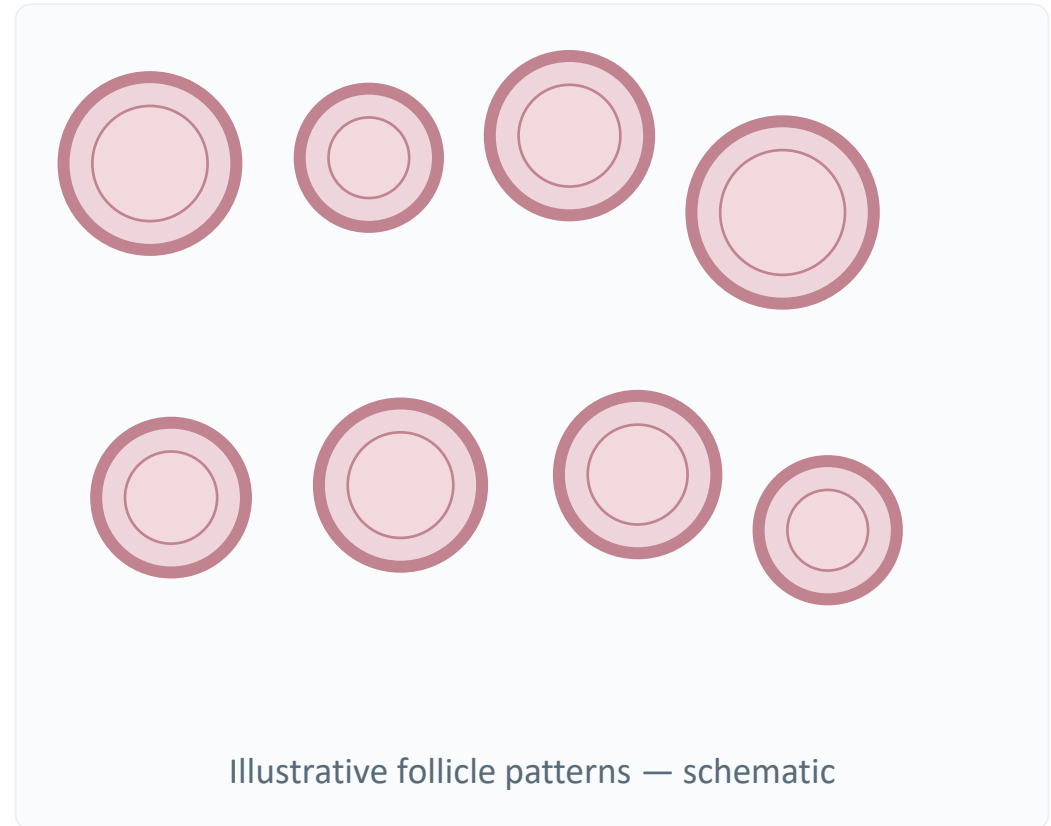


Illustrative follicle patterns — schematic

Hyperplastic follicular foci remain interspersed

Not all follicles undergo identical involution.

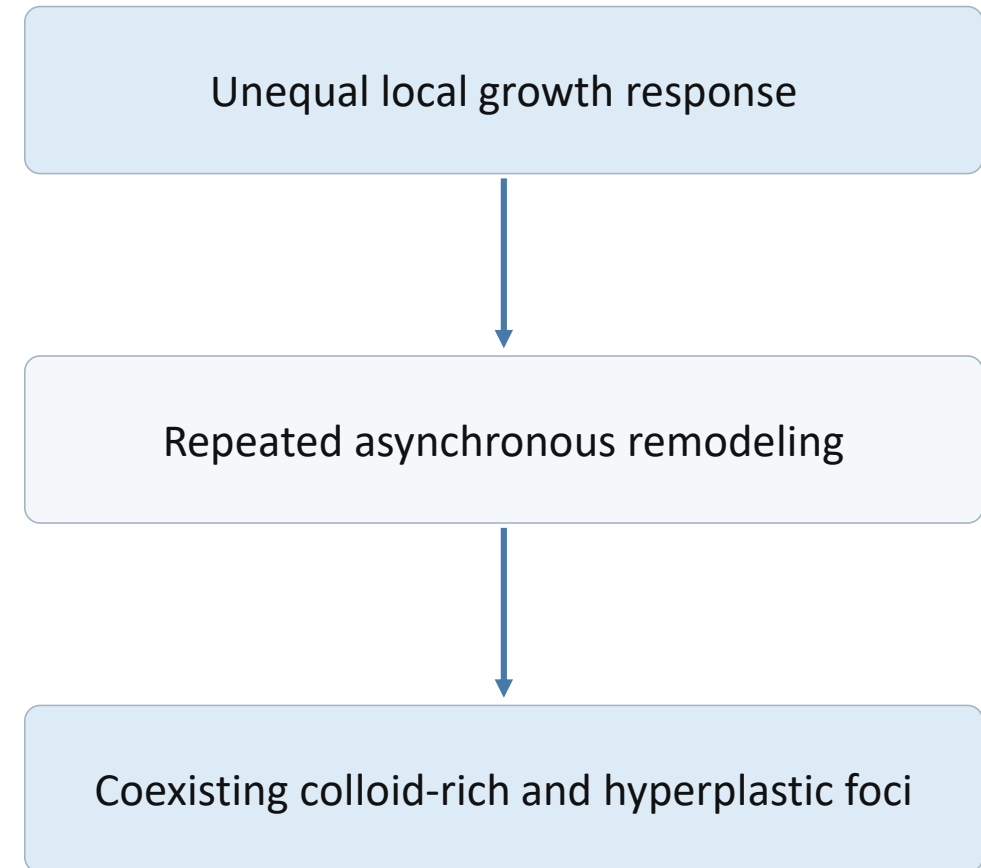
- Foci of follicular proliferation persist alongside more inactive regions.
- Crowded cells contrast with nearby colloid-distended follicles.
- A multifocal rather than uniformly hyperplastic pattern is characteristic.



The microscopically mixed pattern has a cause

Regional proliferative and involutional histories differ.

- Variable cellular responsiveness creates distinct growth trajectories.
- Repeated episodes expose individual nodules to nonuniform tissue stress.
- Thus the histology recapitulates the disease pathogenesis.



Degenerative changes have histologic correlates

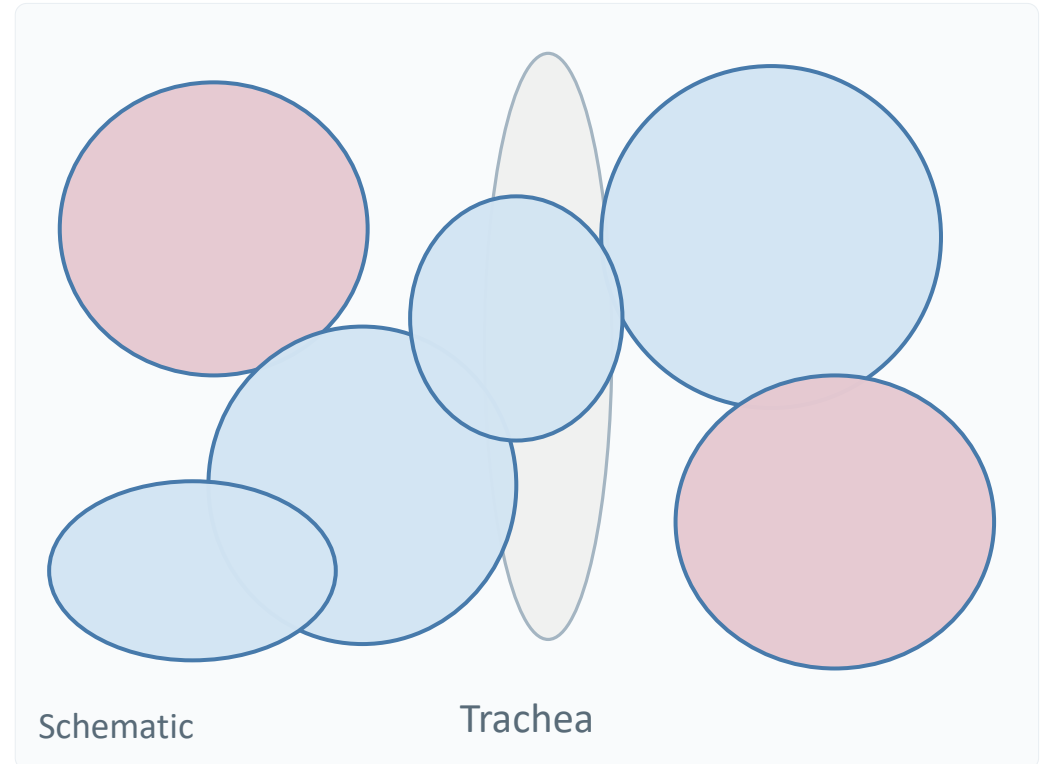
Old lesions may show hemorrhage, scar, calcification and cyst formation.

Follicular changes	Regressive changes
Colloid-rich lumens	Hemorrhage
Flattened lining epithelium	Fibrosis and calcification
Intermixed hyperplastic foci	Cystic degeneration

Absence of a discrete capsule is important

Prominent encapsulation between nodules and residual parenchyma is not a defining feature.

- Multiple nodules blend into a remodeled gland.
- Residual thyroid may be compressed without a continuous tumor capsule.
- This architecture helps distinguish follicular nodular disease from many adenomas.



Follicular nodular disease: The histologic term

This designation emphasizes the overall benign follicular remodeling pattern.

- The clinical phrase multinodular goiter describes the gland-level appearance.
- The histologic label highlights nonuniform follicles, colloid and secondary change.
- Terminology avoids automatically labeling each nodule a separate neoplasm.

Clinical ↔ histologic

Multinodular goiter ↔ follicular nodular disease

Diffuse versus multinodular goiter

The distinction is mainly the evolution from symmetric to irregular architecture.

Diffuse simple goiter	Multinodular goiter
Relatively symmetric enlargement	Asymmetric nodular enlargement
Hyperplastic and colloid phases	Mixed activity and degeneration
Often less extreme growth	Potentially extreme growth

Multinodular goiter versus follicular adenoma

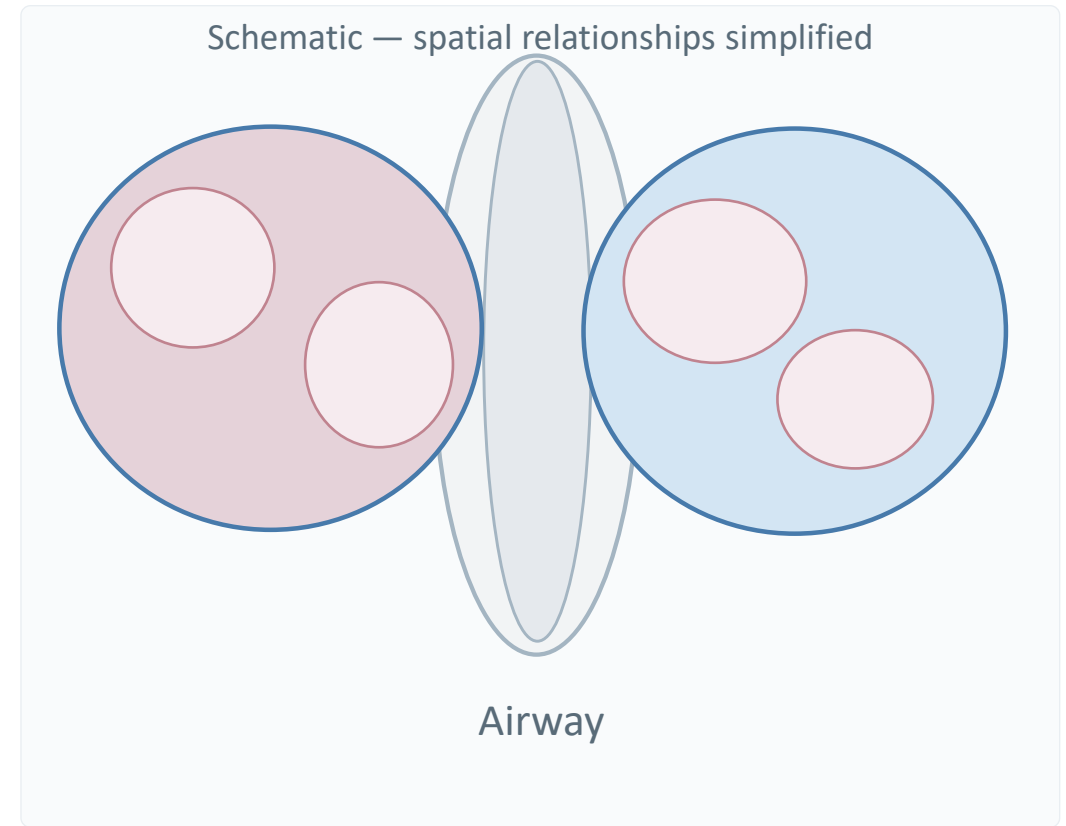
The presence of multiple nodules and lack of a consistent capsule favor follicular nodular disease.

Follicular nodular disease	Follicular adenoma
Multiple variably sized nodules	Usually solitary lesion
No prominent uniform capsule	Typically sharply circumscribed
Heterogeneous follicular patterns	Often a well-defined capsule

Clinical manifestations are mainly compressive

Gland volume and location explain much of the clinical presentation.

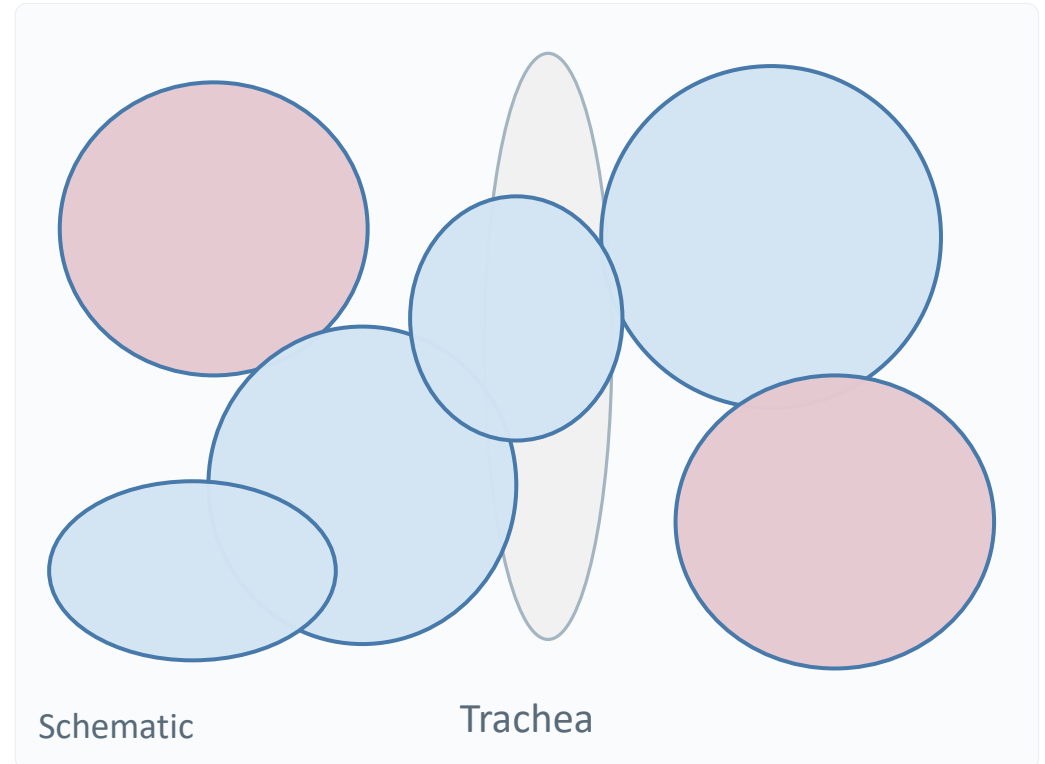
- Cosmetic enlargement can be the initial concern.
- Tracheal, esophageal and vascular compression can dominate symptoms.
- Functional hyperthyroidism is a distinct possibility in some patients.



Visible swelling is a consequence, not a diagnosis

Neck contour changes reflect enlarged thyroid tissue.

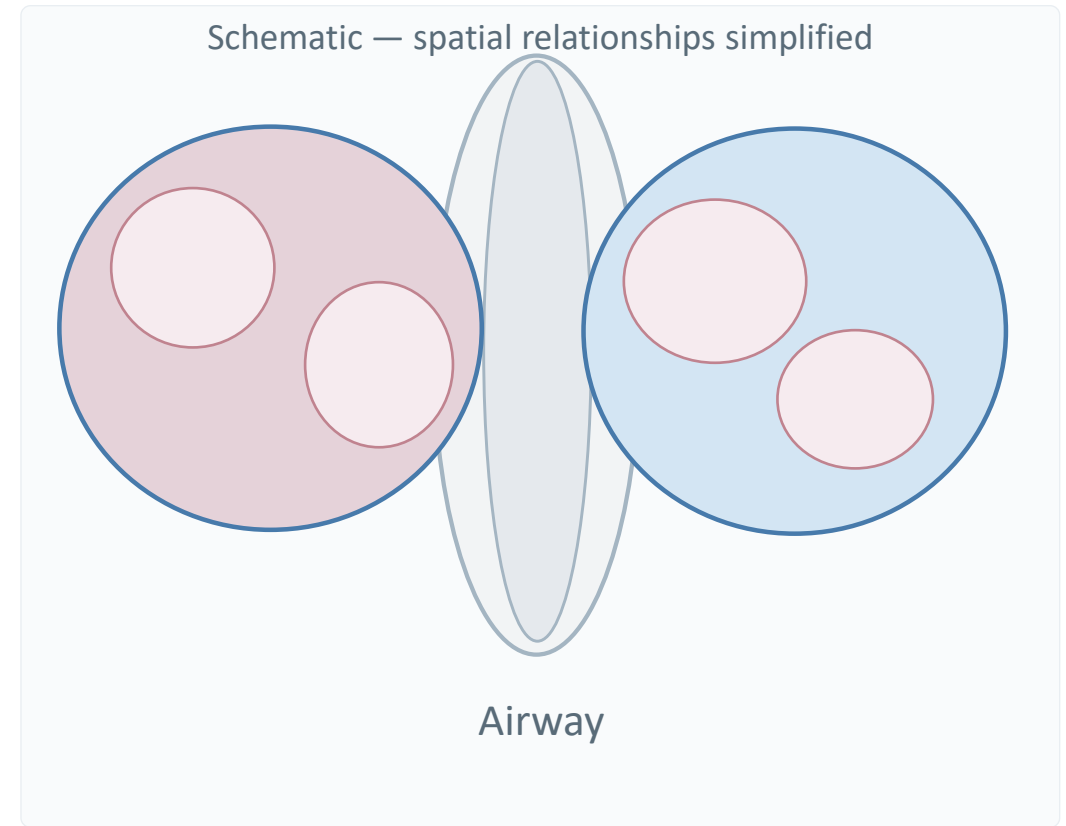
- Multilobulated nodules may produce an irregular visible mass.
- Cosmetic prominence does not reliably indicate hormone output.
- A visible dominant prominence does not establish that the nodule is neoplastic.



Airway obstruction requires recognition

Large goiters may physically narrow the airway.

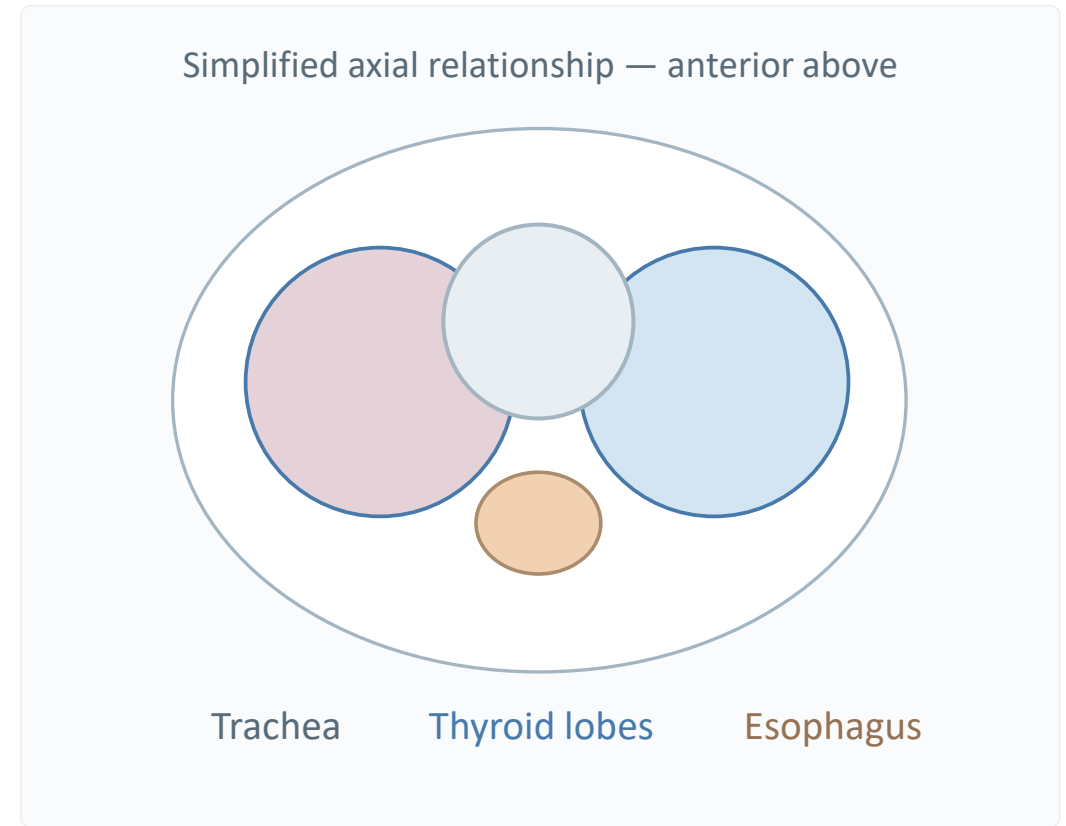
- Tracheal compression may arise from lateral or deep gland growth.
- Respiratory complaints should be interpreted in relation to gland extent.
- Airway obstruction as a major mass effect.



Dysphagia localizes the mass effect

The enlarged thyroid can compromise adjacent swallowing structures.

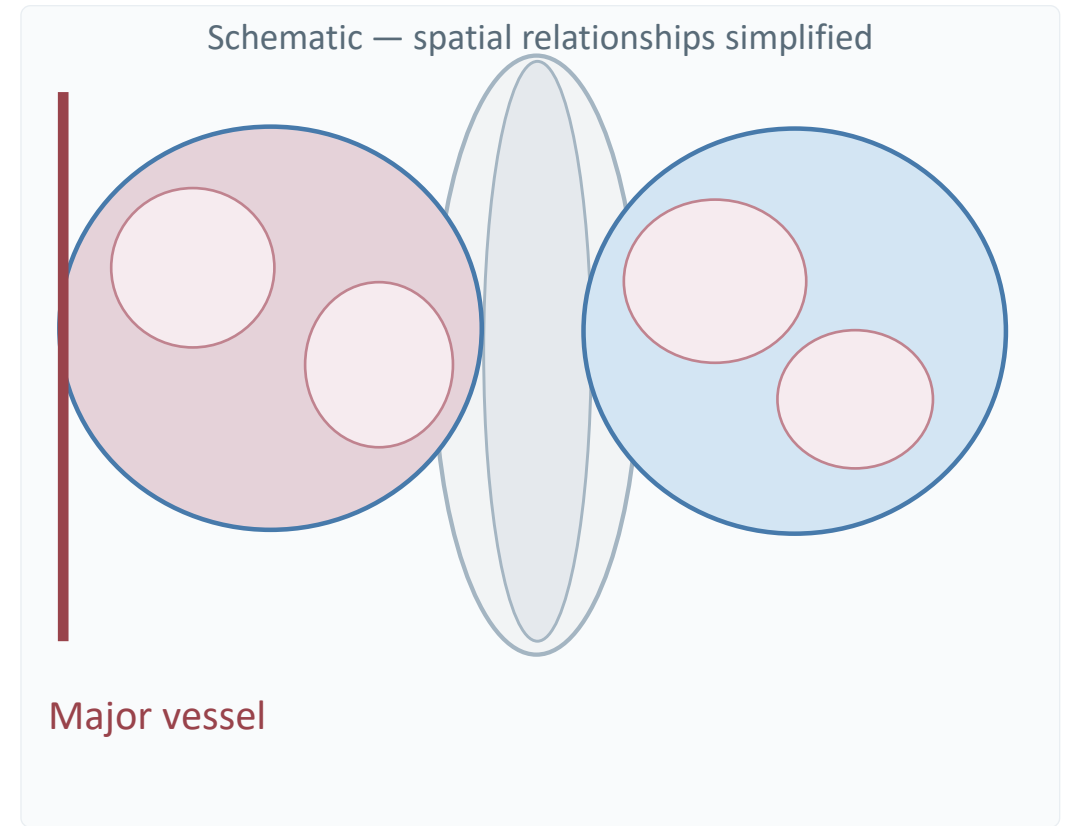
- Esophageal compression explains the symptom mechanistically.
- Deep or retrotracheal extension makes location clinically relevant.
- This symptom does not itself establish malignancy.



Vascular compression can be consequential

A large cervical or intrathoracic gland can compress major neck and upper-thoracic veins.

- Superior vena cava syndrome as a possible complication.
- Thoracic extension can alter the relationship to major vessels.
- The vascular manifestation reflects a space-occupying effect.



Most multinodular goiters are euthyroid

Normal hormone status is common despite substantial gland enlargement.

- Compensatory thyroid growth may maintain hormone supply.
- Mass effects can therefore predominate without thyrotoxicosis.
- Function needs clinical and biochemical correlation.

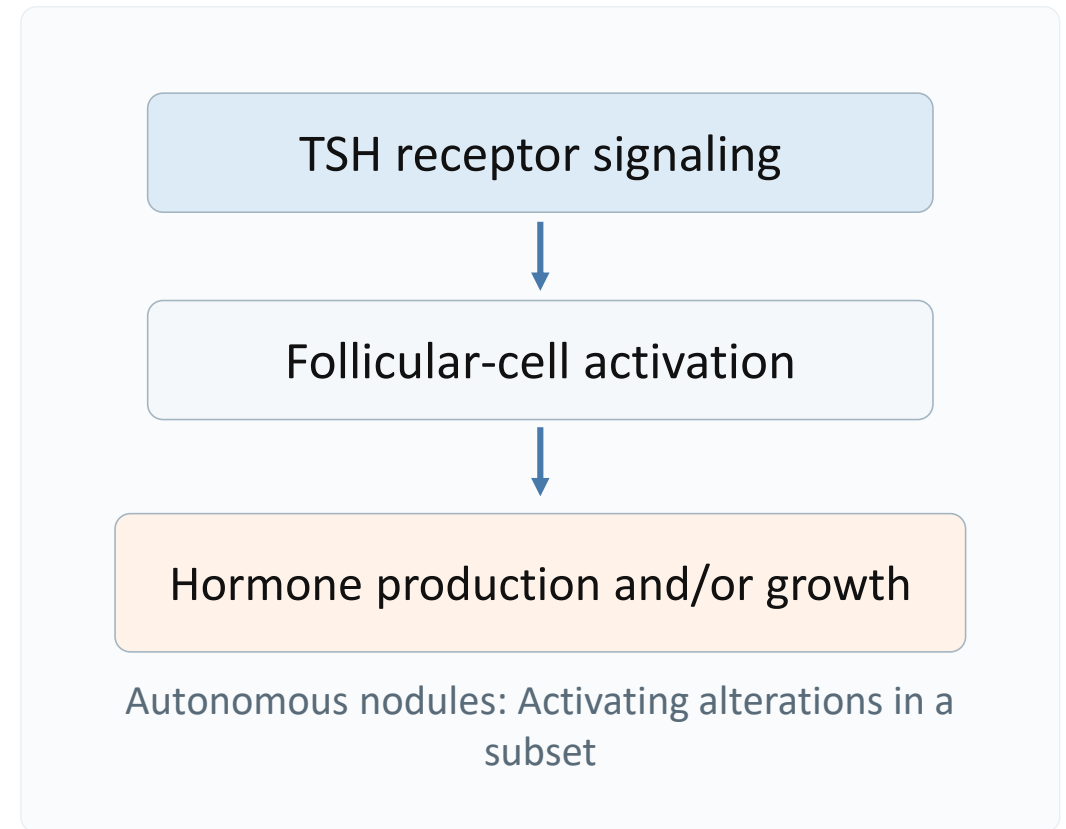
Common pattern

Enlarged, multinodular gland with preserved thyroid function.

Toxic multinodular goiter: Plummer disease

Autonomous functioning regions may produce hyperthyroidism.

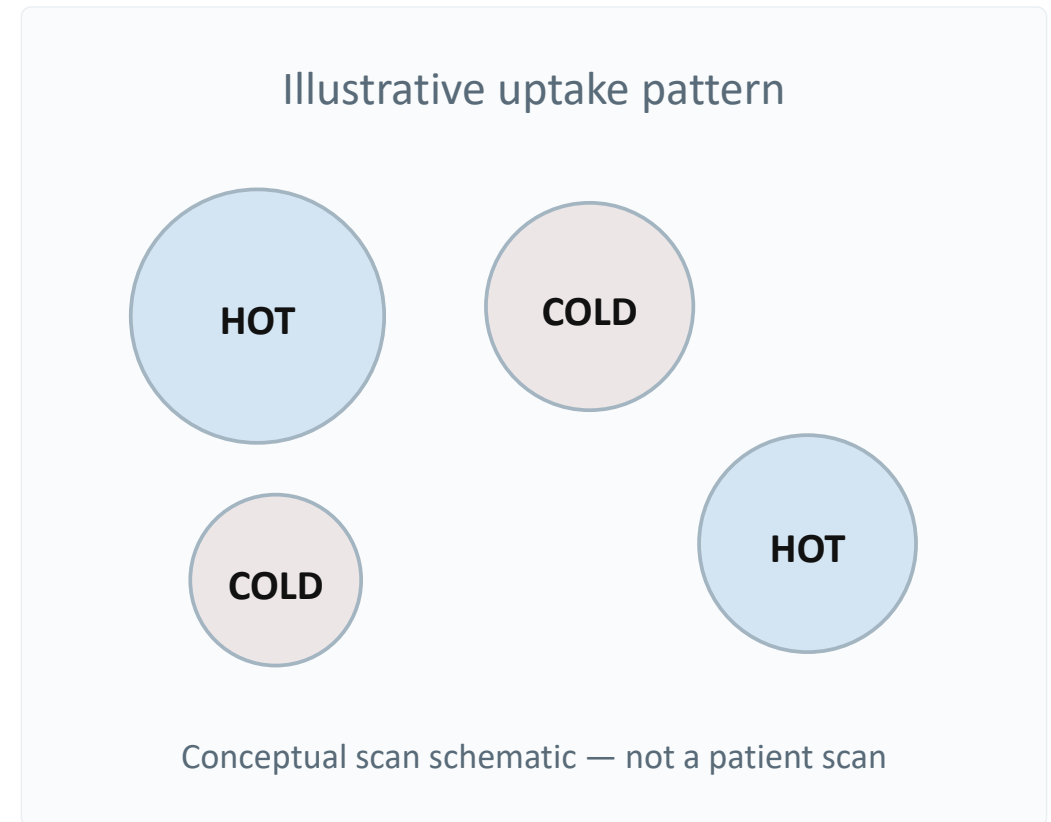
- Overactive nodules need not depend on ordinary TSH stimulation.
- The gland may simultaneously contain less active nodules.
- Toxic disease is a functional subset, not the definition of all multinodular goiters.



Radioiodine uptake is heterogeneous

A multinodular gland may contain both high-uptake and low-uptake areas.

- Autonomous hot nodules exhibit increased radionuclide uptake.
- Nonfunctioning cold nodules show comparatively reduced uptake.
- The scan pattern reflects functional heterogeneity, not automatically malignancy.



Hot and cold nodules answer different questions

Radionuclide behavior addresses function; It is not a complete tissue diagnosis.

Hot nodule

Higher radioactive iodine uptake

Often autonomous functional activity

Generally more likely benign

Cold nodule

Lower radioactive iodine uptake

Nonfunctioning tissue region

May warrant suspicious-nodule workup

Malignancy risk is low but not absent

Carcinomas can occur within a multinodular gland.

- Low malignancy incidence in long-standing multinodular goiter.
- A background diagnosis of goiter does not exempt a suspicious nodule.
- Assessment is guided by concerning features, not the goiter label alone.

Low risk ≠ zero risk

A suspicious focal nodule requires assessment despite an otherwise benign multinodular background.

Sudden changes and hoarseness warrant concern

Changes in the clinical course can signal a process requiring separate assessment.

- Sudden changes in size or symptoms.
- New hoarseness is an example of a concerning symptom.
- These findings are warning signs rather than proof of carcinoma.

Clinical warning

Sudden enlargement, altered symptoms or hoarseness: Reassess for a suspicious lesion.

Suspicious ultrasound features modify evaluation

Focal sonographic abnormalities help select nodules for further assessment.

Background goiter	Suspicious focus
Multiple nodules can be benign	Concerning sonographic morphology
Overall architecture heterogeneous	Possible clinical change
Many patients euthyroid	Targeted diagnostic consideration

Fine-needle aspiration may clarify selected nodules

Aspirating selected cold or suspicious nodules can help identify neoplasia.

- The source describes FNA as helpful for evaluation of cold nodules.
- Cytology distinguishes benign and malignant processes in many—but not all—cases.
- Indeterminate results may require additional assessment.

Identify clinically / sonographically concerning nodule



Review functional imaging when relevant



Consider targeted FNA



Interpret cytology with limitations

No single finding resolves every thyroid nodule

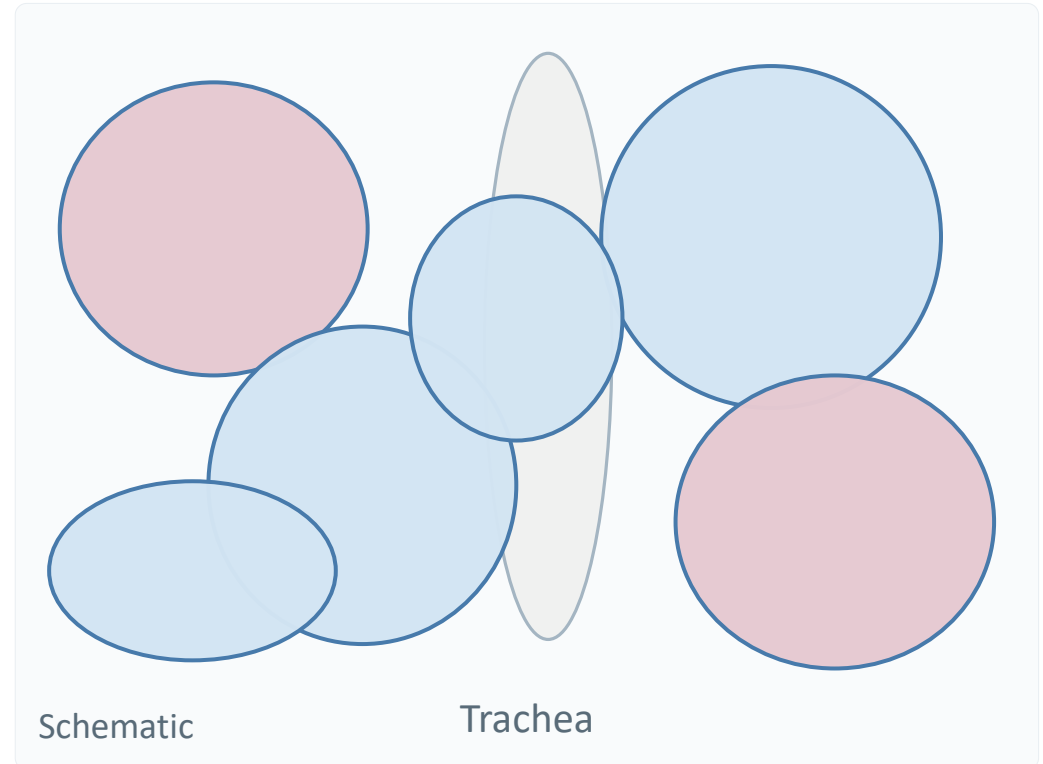
A nodule may look dominant, appear cold or yield indeterminate cytology.

What each test contributes	What it cannot guarantee
Symptoms: Mass effects and change	Clinical examination: Not histology
Ultrasound: Nodule morphology	Imaging: Not definitive cancer diagnosis
FNA: Sampled cellular features	Cytology: Sometimes indeterminate

Morphologic synthesis: Diagnose the whole gland

Pathology interpretation combines nodules, adjacent thyroid and regressive changes.

- Document multinodular architecture and follicular heterogeneity.
- Correlate colloid-rich follicles, hyperplasia and degenerative changes.
- Examine any discrete suspicious focus separately from background nodular disease.



Case 1: An enlarging gland with dysphagia

An older patient has a long-standing irregular neck mass and increasing swallowing difficulty.

Discuss

- Which anatomic mechanism best explains the symptom?
- What gross pattern would support multinodular goiter?
- Does dysphagia alone establish a malignant lesion?

Interpretation

Esophageal compression from a multilobulated enlarged gland explains dysphagia. An asymmetric gland with variably sized colloid-rich nodules supports multinodular goiter. Dysphagia alone is not proof of cancer.

Case 2: Functional heterogeneity

A multinodular gland shows uneven radioiodine uptake with both hot and cold foci.

Discuss

- What explains a functional hot focus?
- Would every nodule need the same hormone output?
- What additional issue arises with a suspicious cold focus?

Interpretation

An autonomously functioning focus can increase uptake and hormone secretion. Functional states vary across nodules. A suspicious cold nodule should be evaluated on its own merits, including targeted sampling when indicated.

Case 3: A prominent solitary-appearing nodule

A clinically dominant nodule is found in an irregular thyroid with additional small nodules.

Discuss

- Which findings favor follicular nodular disease over adenoma?
- Why is attention to the surrounding gland essential?
- What would raise concern for a coexisting neoplasm?

Interpretation

Multiple background nodules, variable follicles and no uniform capsule favor follicular nodular disease. Concerning ultrasound features, rapid change or new hoarseness require further assessment.

Diagnostic contrasts worth retaining

Interpret functional, gross and microscopic evidence as complementary—not interchangeable.

Structure	Function	Focal risk
Asymmetric multinodularity	Usually euthyroid	Suspicious ultrasound
Variable follicles	Sometimes autonomous hot foci	Clinical warning signs
No uniform capsule	Toxic subset possible	Targeted evaluation

Five linked conclusions

The core diagnostic model integrates the long-standing process and its consequences.

- Repeated follicular hyperplasia and involution create irregular nodules.
- Mixed polyclonal and monoclonal nodules, with autonomy in some, explain heterogeneity.
- Gross colloid-rich and degenerative changes mirror the microscopic mosaic.
- Compressive effects dominate; Most patients remain euthyroid.
- Suspicious nodules must be investigated despite low overall cancer risk.

Textbook source and verification boundary

Primary reference used throughout this presentation.

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026).
- Chapter 24, The Endocrine System; Diffuse and Multinodular Goiter, pp. 985–987.
- Adjacent Neoplasms of the Thyroid / Thyroid Adenomas: contextual comparison, pp. 987–988.
- Supplied Markdown conversion used; original chapter PDF and textbook figures were unavailable for image-level comparison.