

Thyroid Adenomas

Benign follicular neoplasms of the thyroid

Pathogenesis • morphology • diagnostic boundaries

A pathology lecture grounded in Robbins

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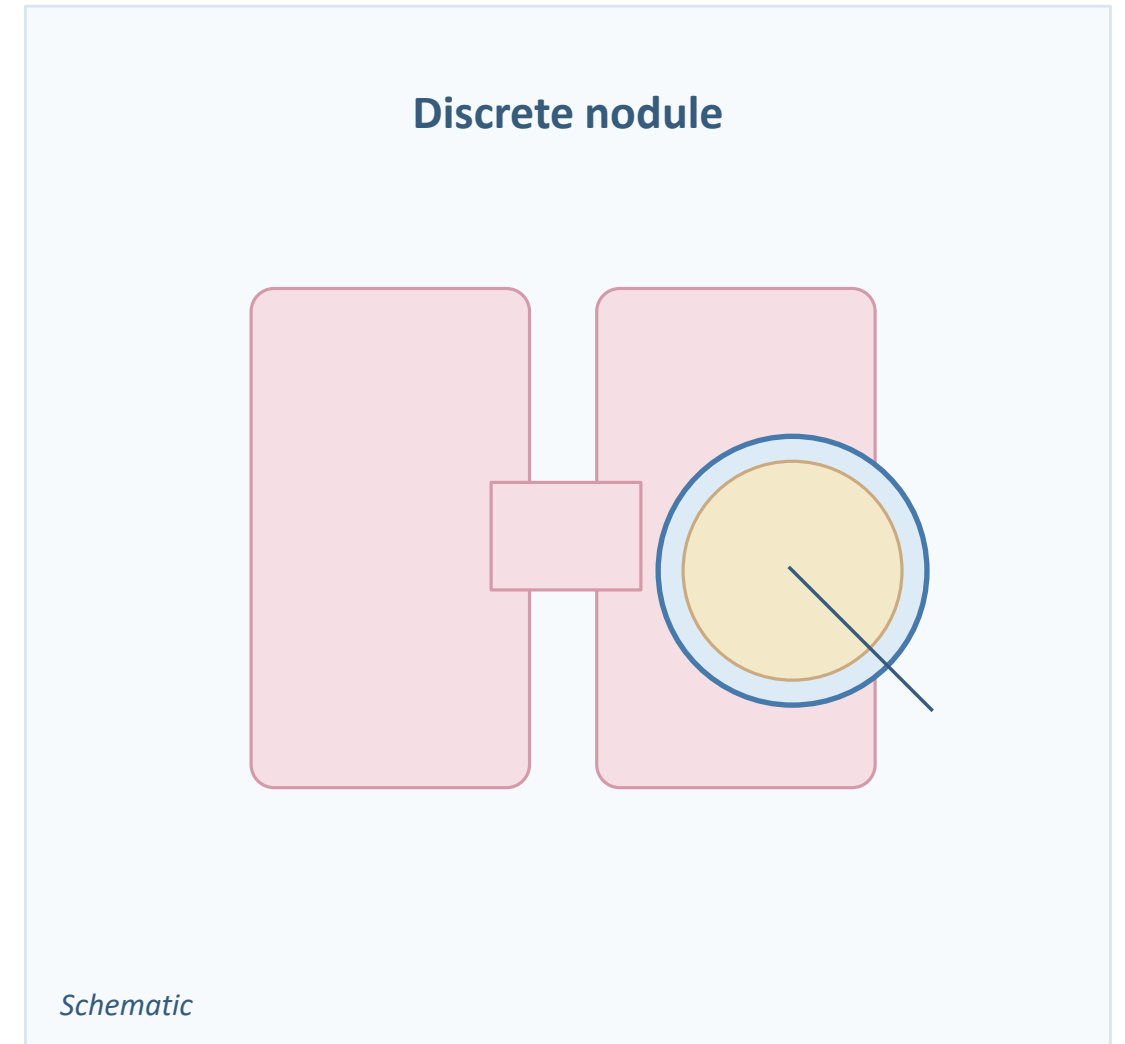
Learning objectives

- Classify a solitary thyroid nodule without equating it with malignancy
- Explain TSH-independent hormone secretion in toxic adenomas
- Recognize characteristic gross and microscopic morphology
- Apply the invasion-based distinction between adenoma and carcinoma
- Explain why FNA cannot confirm a follicular adenoma

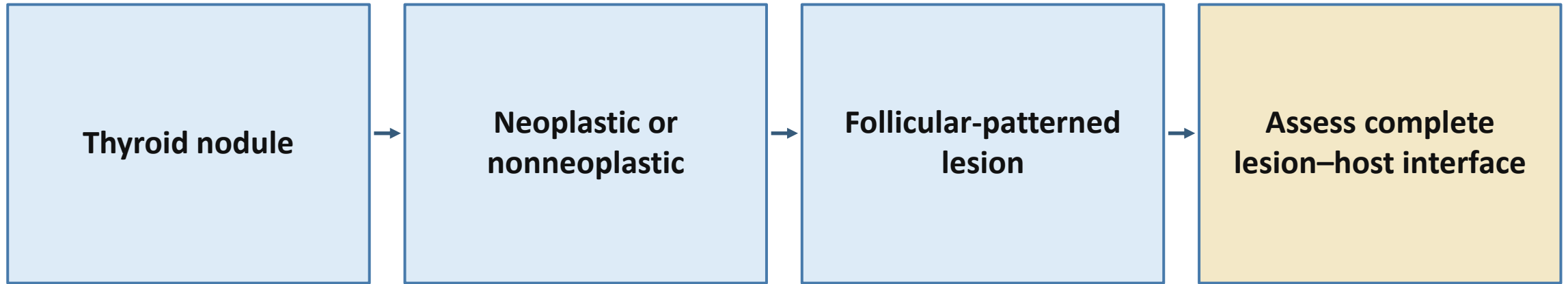
What is a follicular adenoma?

- A benign, discrete neoplasm of thyroid follicular epithelium
- Usually solitary, spherical or ovoid, and sharply circumscribed
- Most are nonfunctioning; A small minority are autonomous
- Diagnosis is established by tissue architecture and absence of invasion

Adenoma is a histologic diagnosis—not a synonym for any thyroid nodule.



Where does adenoma sit in thyroid pathology?



A clinical nodule is a presentation; Follicular adenoma is a specific diagnosis.

Solitary nodule $\neq$ solitary neoplasm

Clinical presentation

- Palpable or incidental focal thyroid swelling
- May be a cyst, nodular hyperplasia, thyroiditis, or neoplasm
- Physical examination cannot establish invasion

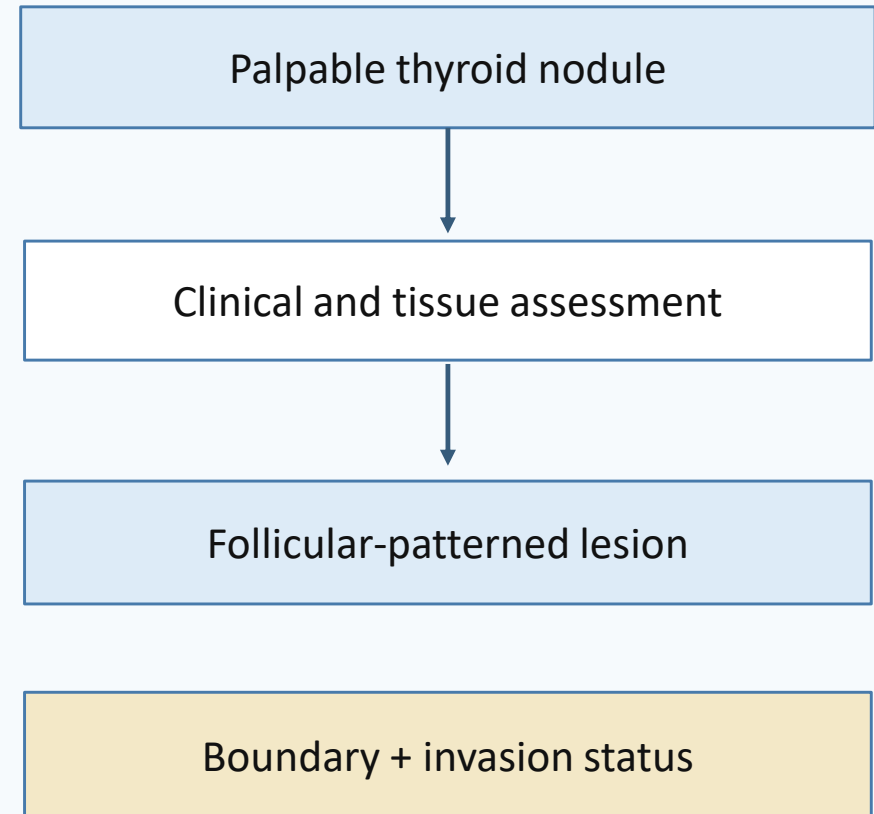
Histologic entity

- Follicular adenoma is a benign follicular-cell tumor
- Discrete growth with noninvasive interface
- Resection establishes a definitive diagnosis

Major questions for a thyroid nodule

- Is the lesion functional or nonfunctional?
- Is it a neoplasm or a nonneoplastic nodule?
- If follicular-patterned, is there capsular or vascular invasion?
- Which investigations inform—but do not replace—histology?

Answer these questions separately.



Two independent descriptive axes

Functional axis

- Nonfunctioning adenoma: Usual presentation
- Toxic adenoma: Autonomous hormone secretion
- Scintigraphic uptake reflects function

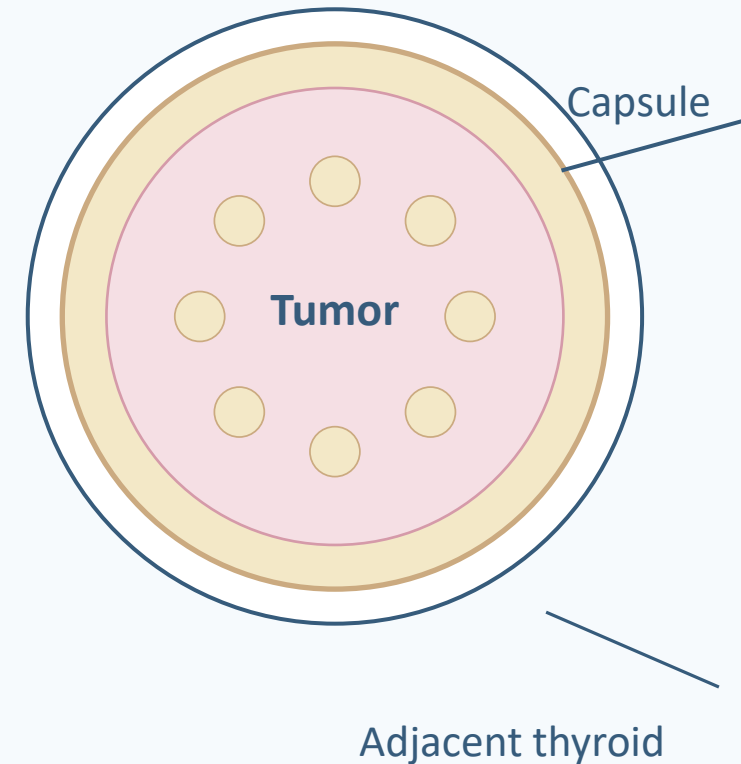
Biologic axis

- Adenoma: No invasion
- Follicular carcinoma: Invasion present
- Hot/cold status is not histologic classification

Why the boundary of a lesion matters

A noninvasive follicular proliferation is assessed at its periphery.

A bland central field alone does not tell whether tumor penetrates its capsule or vessels.

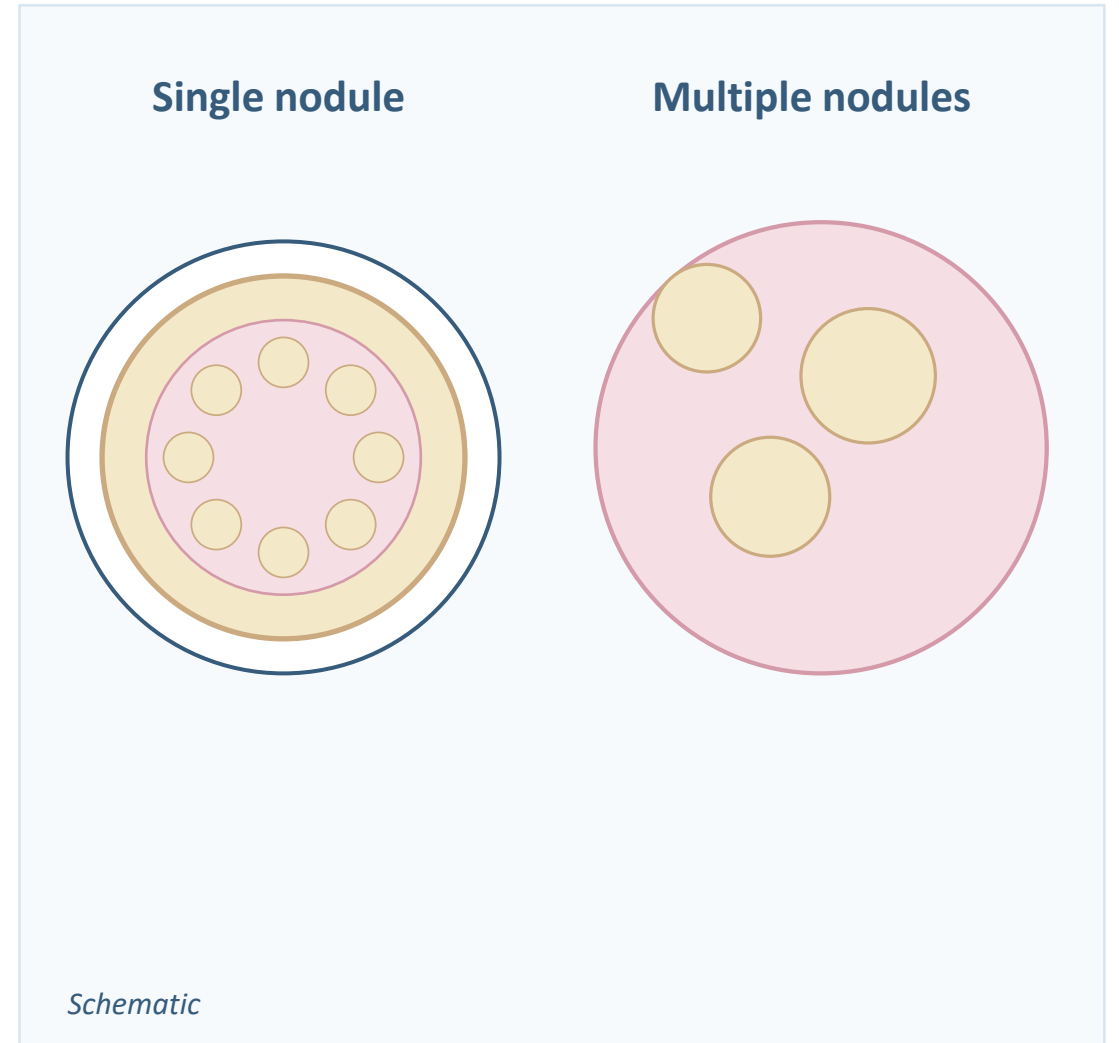


Schematic

Follicular nodular disease: Key mimic

- Often contains multiple nodules across the gland
- A dominant nodule may feel clinically solitary
- Nodules may show degeneration and variable follicles
- A distinct complete tumor capsule is often absent

Clinical multinodular goiter and true solitary adenoma can overlap in appearance.



Adenoma versus follicular nodular disease

Follicular adenoma

- Usually solitary
- Well circumscribed, often encapsulated
- Growth pattern typically distinct from background thyroid

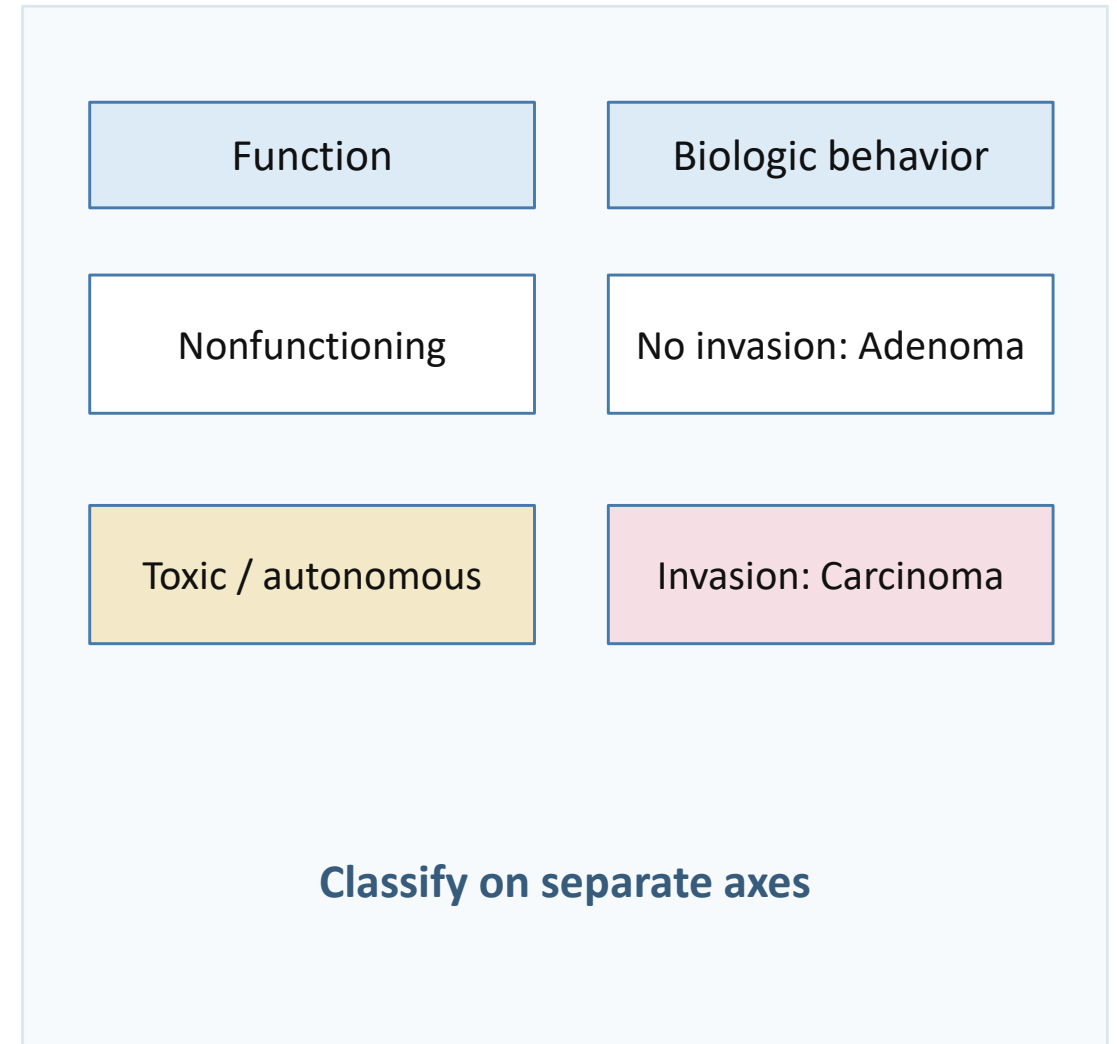
Follicular nodular disease

- Multiple nodules may coexist
- Dominant nodule may simulate neoplasm
- Heterogeneous follicles and secondary changes

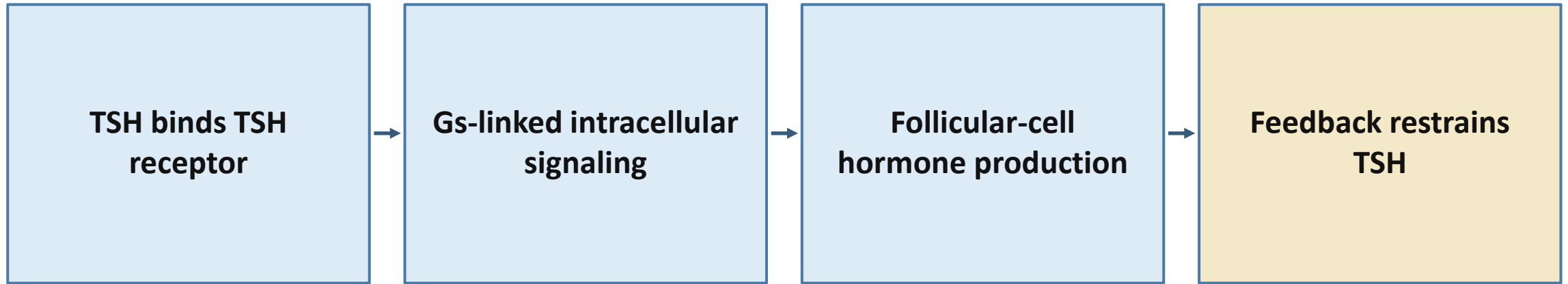
Functional classification of adenomas

- Most follicular adenomas do not cause thyrotoxicosis
- A small minority secrete thyroid hormone independently of TSH
- An autonomously functioning adenoma is called a toxic adenoma
- Hormone output and morphologic invasion are different properties

“Toxic” indicates hormone excess, not malignant behavior.



Normal TSH signaling: Conceptual overview

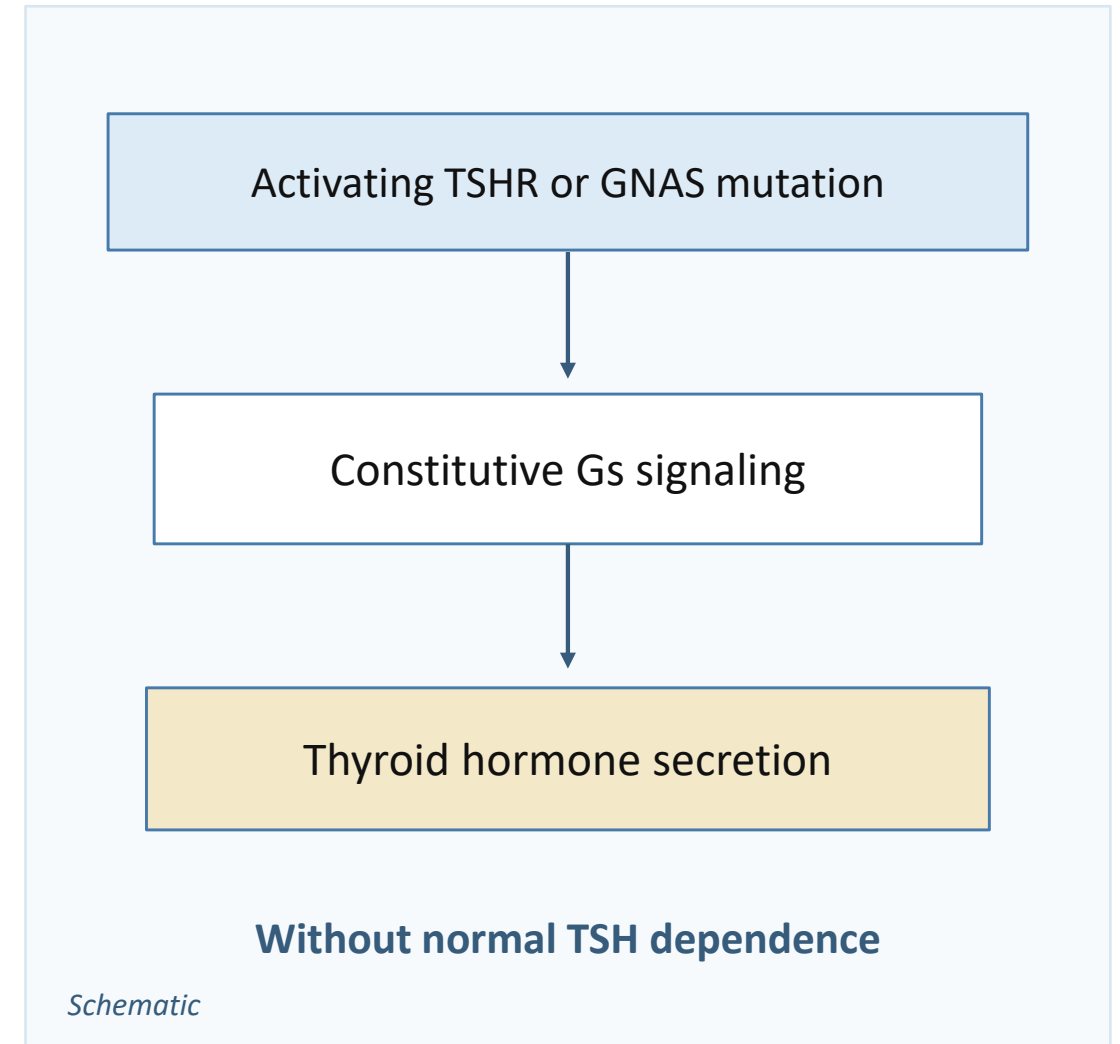


Constitutive signaling bypasses dependence on pituitary TSH.

Toxic adenomas arise through autonomy

- Somatic gain-of-function changes activate the TSH receptor pathway
- Activation occurs even when circulating TSH stimulation is reduced
- Follicular cells maintain thyroid hormone secretion
- Persistent autonomy can produce hyperthyroidism

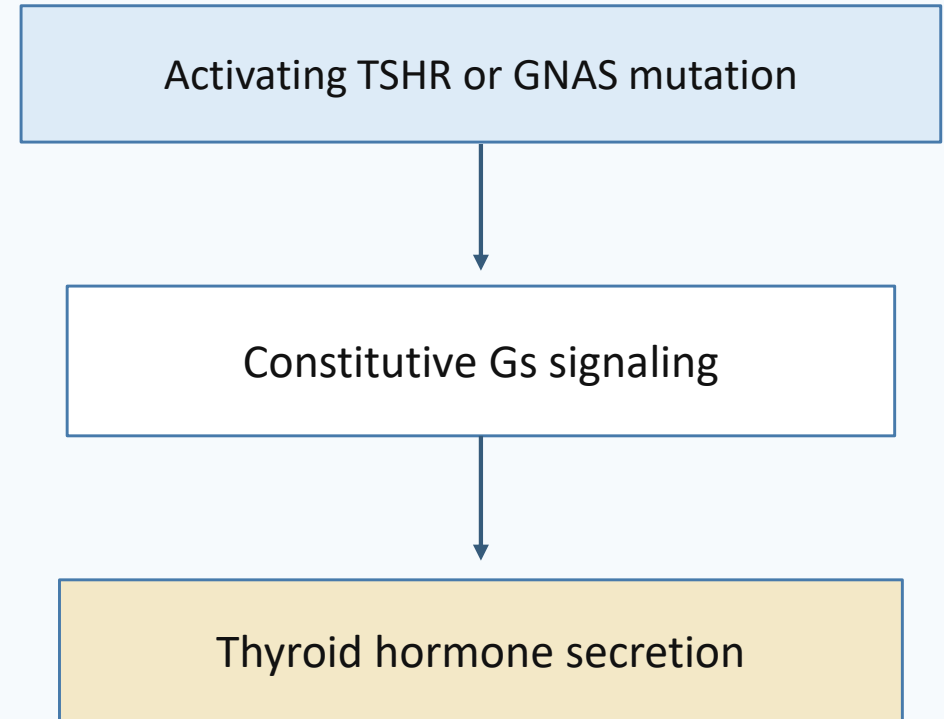
This is acquired follicular-cell signaling autonomy.



TSHR mutations

Activating TSHR variants can make the receptor signal without ordinary TSH stimulation.

TSHR encodes the thyroid-stimulating hormone receptor; Mutated receptors help drive autonomous hormone production.



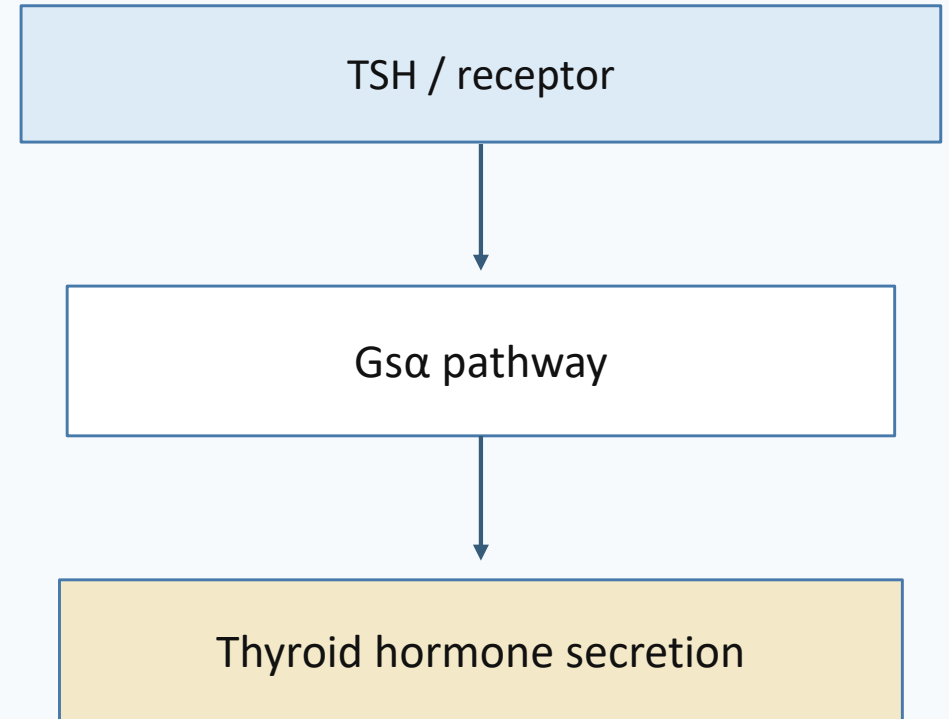
Without normal TSH dependence

Schematic

GNAS mutations

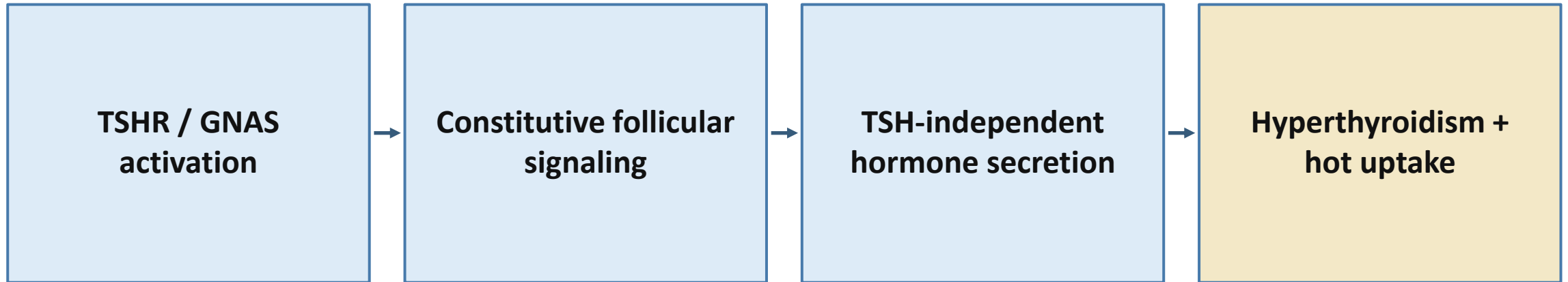
GNAS alterations can activate the Gs α signaling component downstream of TSHR.

The source describes GNAS as a less common activating mechanism than TSHR mutations.



Schematic

From molecular change to a hot nodule



The scan is functional evidence, not proof of a specific genetic variant.

Normal regulation versus autonomous secretion

Normal follicle

- TSH-dependent receptor activation
- Hormone output tracks pituitary stimulation
- Negative feedback acts through TSH

Toxic adenoma

- Signal persists with little TSH stimulation
- Hormone output becomes autonomous
- Nodule often appears “hot” on radionuclide study

What the molecular frequency means

- TSHR or GNAS mutations in 50%–80% of toxic adenomas
- This is a reported range, not a universal diagnostic sensitivity
- A mutation is not required to diagnose every toxic adenoma
- Molecular status does not replace the invasion assessment

Classify on separate axes

Function

Biologic behavior

Nonfunctioning

No invasion: Adenoma

Toxic / autonomous

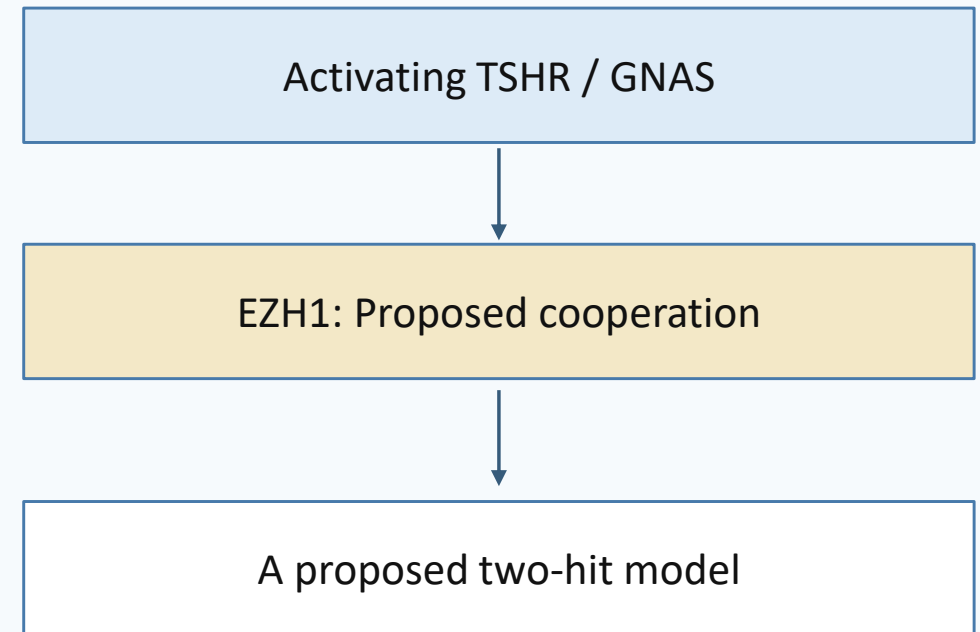
Invasion: Carcinoma

Source-specific proportion: Robbins, 11th ed., p. 987.

EZH1: A proposed second hit

A study proposed that EZH1 mutation may cooperate with an activating TSH pathway mutation.

This is a suggested two-hit model, not an established universal requirement for follicular adenoma.



Hypothesis—not an obligatory criterion

Schematic

Molecular association is not diagnostic proof

What Robbins supports

- Activating TSHR / GNAS changes in many toxic adenomas
- Suggested cooperating EZH1 alteration
- Those mutations are uncommon in follicular carcinomas

What it does not establish

- A molecular test is sufficient to diagnose adenoma
- Every adenoma has an EZH1 mutation
- Toxic adenomas commonly transform into carcinomas

Toxic adenoma is not regarded as a precursor of carcinoma

TSHR, GNAS, and EZH1 alterations described in toxic adenomas are rare in follicular carcinomas.

This distinction to argue against toxic adenomas as precancerous lesions.

Function

Biologic behavior

Nonfunctioning

No invasion: Adenoma

Toxic / autonomous

Invasion: Carcinoma

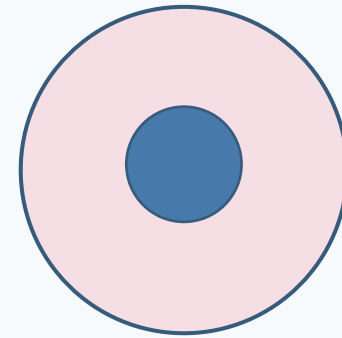
Classify on separate axes

Nonfunctioning adenomas: An important contrast

- Do not secrete enough thyroid hormone to produce overt thyrotoxicosis
- Often present as an isolated painless thyroid nodule
- Usually exhibit relatively low iodine uptake on scintigraphy
- “Cold” describes function and does not establish malignancy

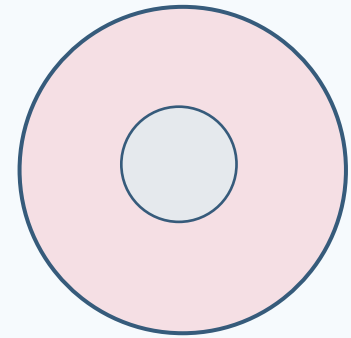
Do not infer benign or malignant histology from uptake alone.

Functional schematic—not a radionuclide scan



HOT

Relative uptake ↑



COLD

Relative uptake ↓

Schematic

Hot and cold: Interpret function correctly

Hot nodule

- Higher uptake on radionuclide imaging
- Suggests functional autonomy
- Much more likely to be benign, not guaranteed

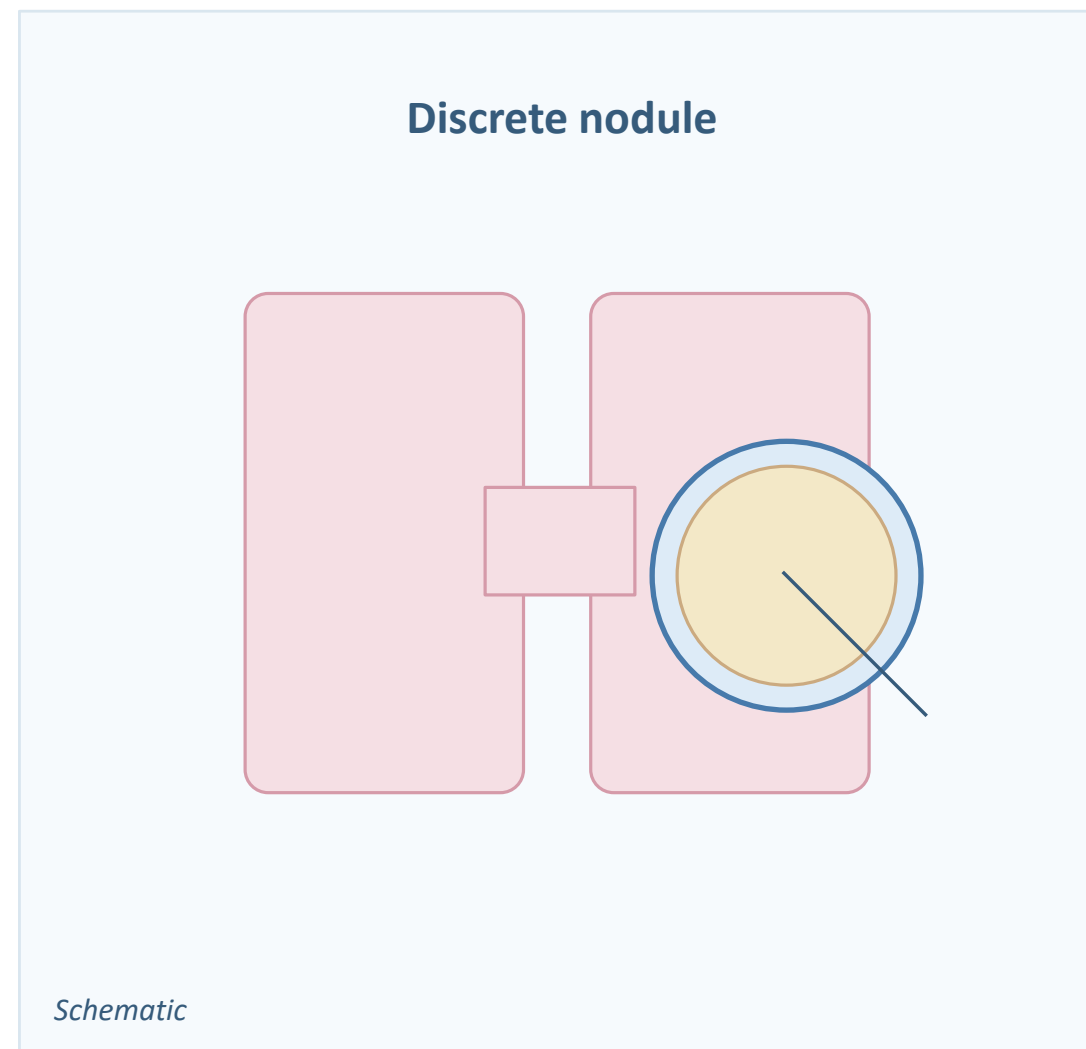
Cold nodule

- Reduced tracer uptake
- Typical of many nonfunctioning adenomas
- Also occurs in other benign or malignant nodules

Typical gross appearance

- Solitary, spherical or ovoid mass
- Clear separation from adjacent thyroid
- Often encircled by a fibrous capsule
- Can compress the surrounding thyroid parenchyma

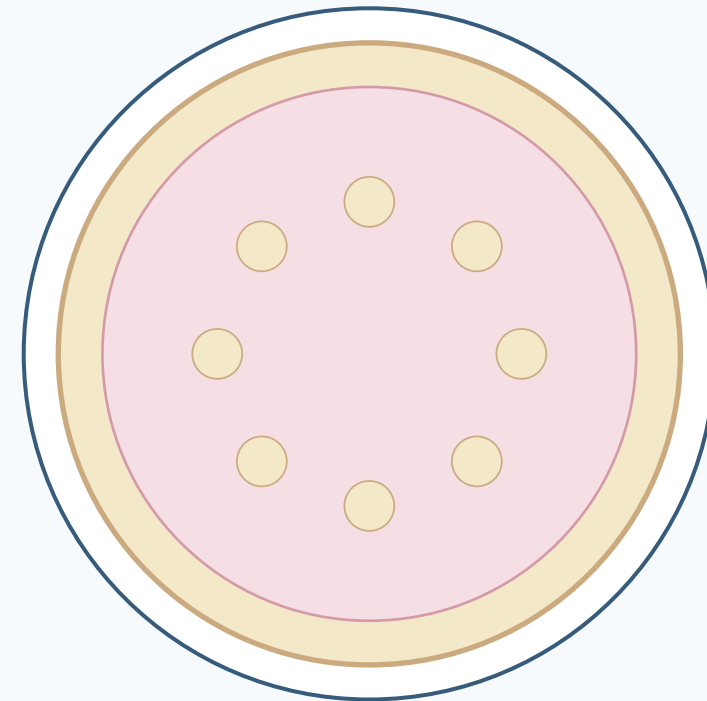
Schematic illustrates relationships; It is not a specimen photograph.



The adenoma often bulges on cut section

An expansile, well-demarcated neoplasm displaces neighboring thyroid tissue.

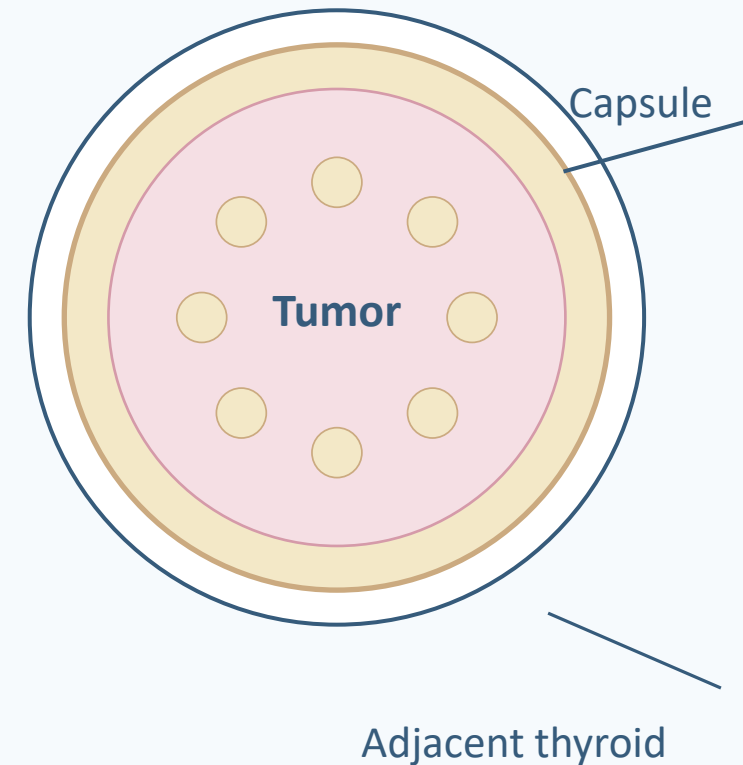
The lesion as bulging from a freshly resected cut surface and compressing adjacent thyroid.



Schematic Color depends on cellularity and colloid

The capsule is a structural clue

- A fibrous capsule often sharply separates tumor from normal thyroid
- The capsule encircles many—but not all—adenomas
- Tumor–capsule–thyroid relationships must be examined carefully
- An intact capsule supports, but does not alone prove, benign behavior



Schematic

Capsular integrity requires histologic evaluation.

Encapsulated versus unencapsulated adenoma

Encapsulated pattern

- Well-formed continuous peripheral fibrous tissue
- Clear lesion–host boundary
- Capsular invasion must be excluded

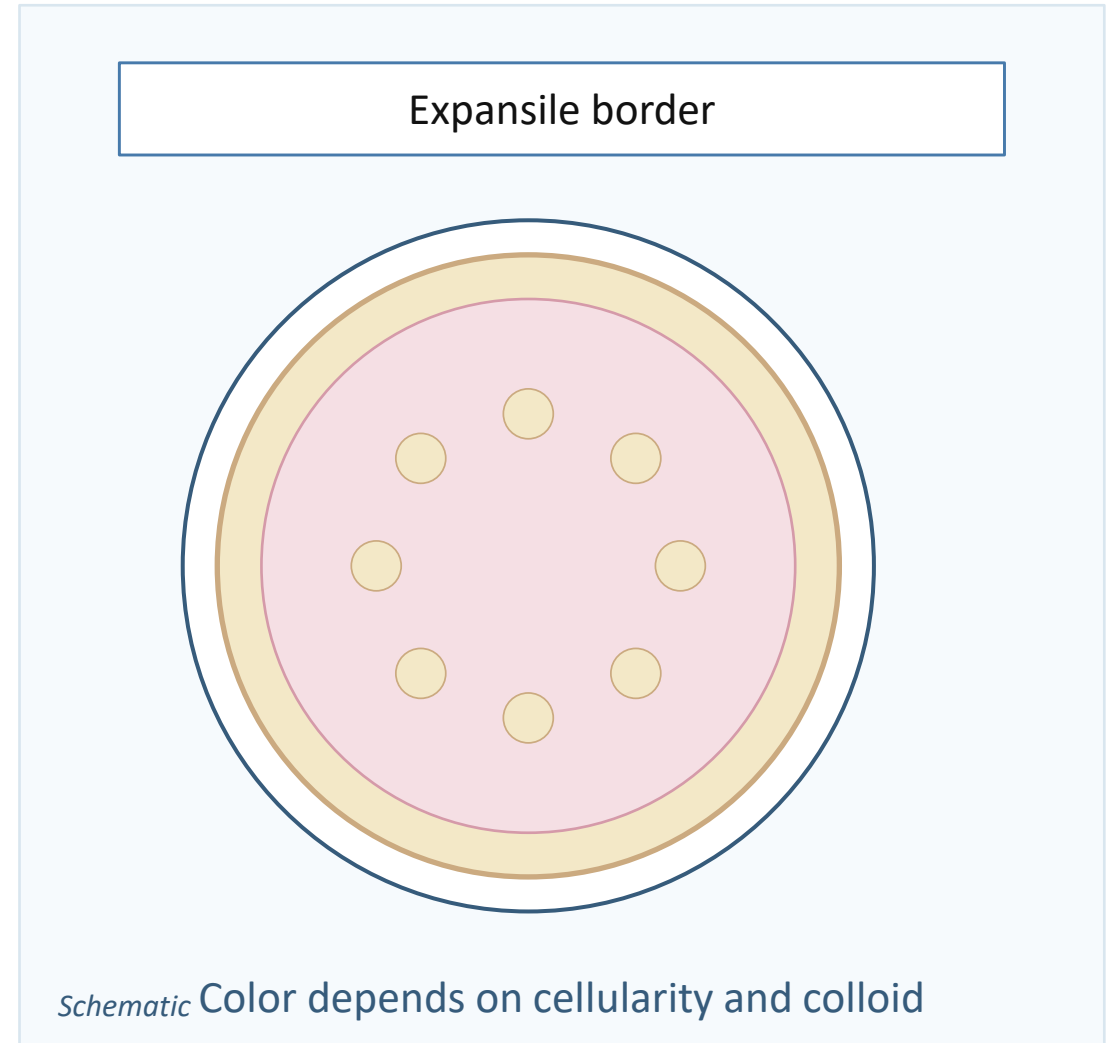
Circumscribed without full capsule

- Capsule is not necessarily present in every adenoma
- Absence of infiltrative growth remains essential
- Peripheral interface still determines diagnosis

Why tumor color varies

- Cut surfaces may appear gray-white, tan, or red-brown
- Cellularity and stored colloid influence the appearance
- Gross color is not a reliable discriminator of malignancy
- Interpret color alongside encapsulation and growth pattern

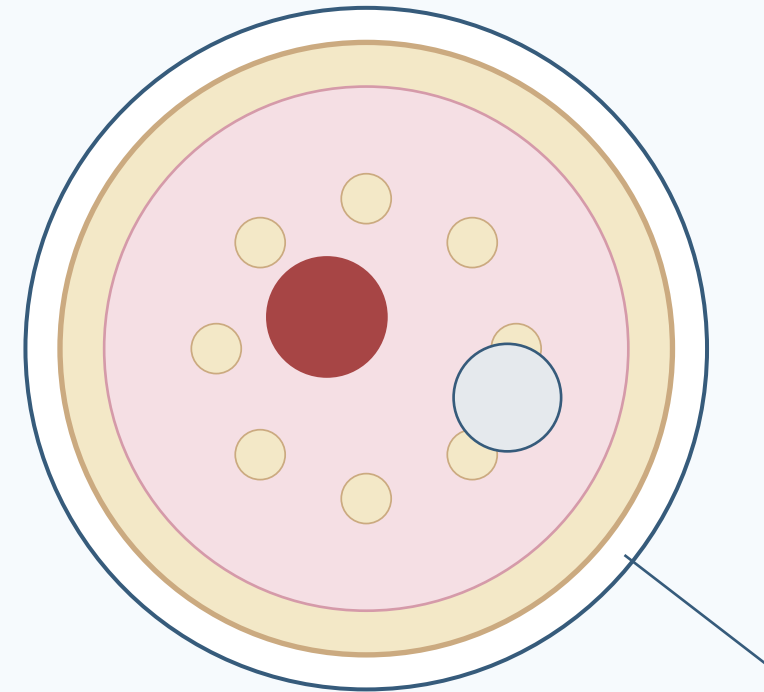
Macroscopic variation alone does not determine biologic behavior.



Secondary changes may dominate grossly

- Hemorrhage
- Fibrosis
- Calcification
- Cystic change
- Large adenomas particularly may display degenerative areas

These changes are also seen in follicular nodular disease.



Secondary changes may coexist

Schematic

Secondary change is not invasion

Common degenerative findings

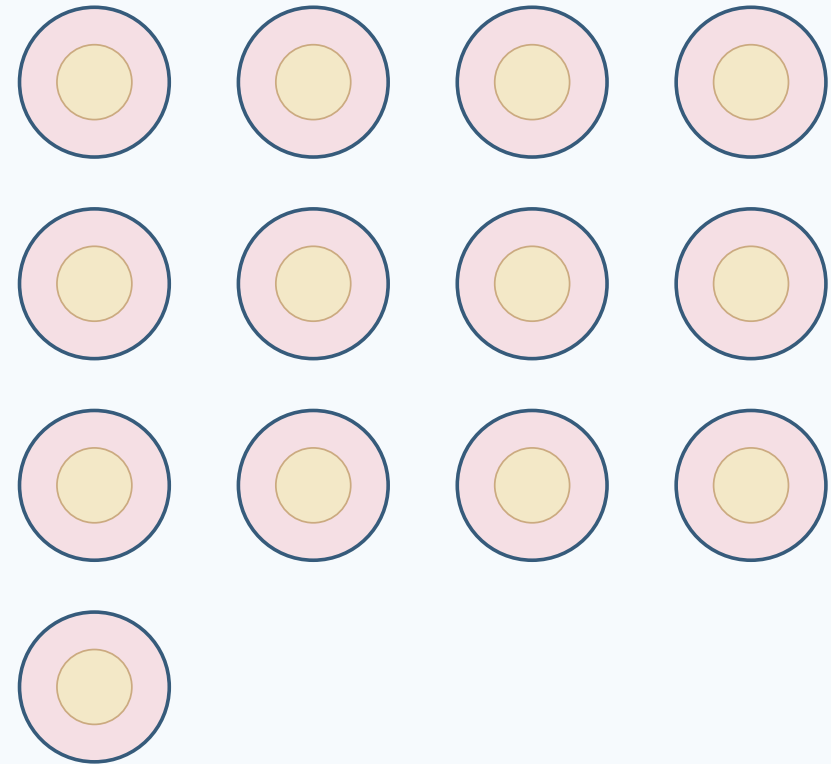
- Hemorrhage within an adenoma
- Fibrotic or calcified foci
- Cystic breakdown in a larger nodule

Findings requiring tumor-border review

- Definite extension through capsule
- True vascular invasion
- Infiltration of adjacent thyroid

Microscopic architecture: Follicles

- Well-differentiated follicular epithelial cells form follicles
- Follicles may contain eosinophilic colloid
- Architecture often differs from that of adjacent nonneoplastic thyroid
- Peripheral relationship is needed to interpret the central pattern



Follicles containing colloid

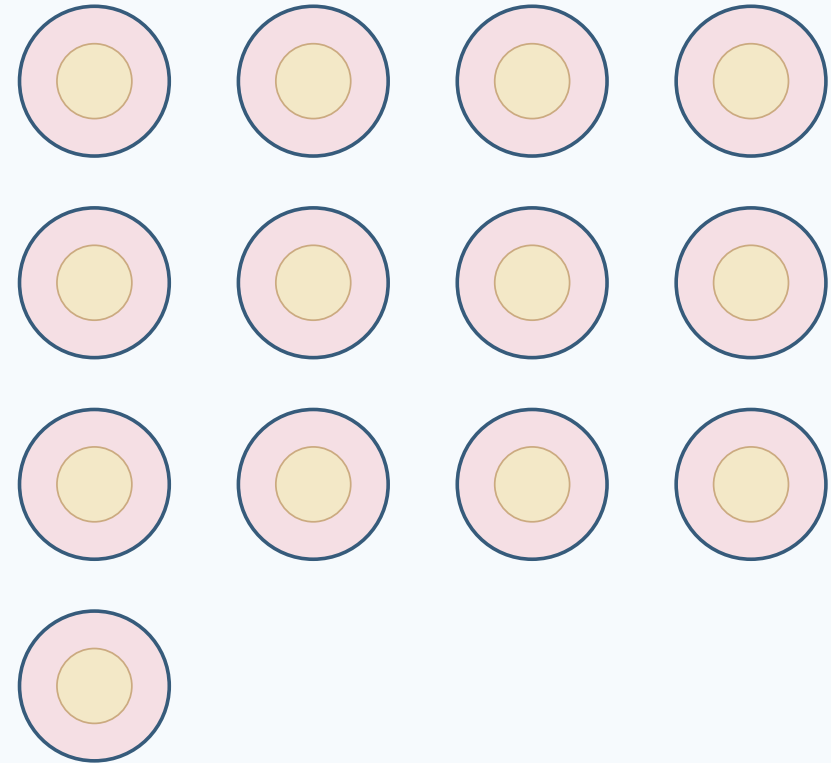
Schematic — not histology

Original editable schematic; Not an H&E photomicrograph.

Follicular uniformity is characteristic

Neoplastic follicles often show a relatively monotonous architecture.

The source describes follicles that may resemble normal thyroid but form a growth pattern distinct from the surrounding gland.



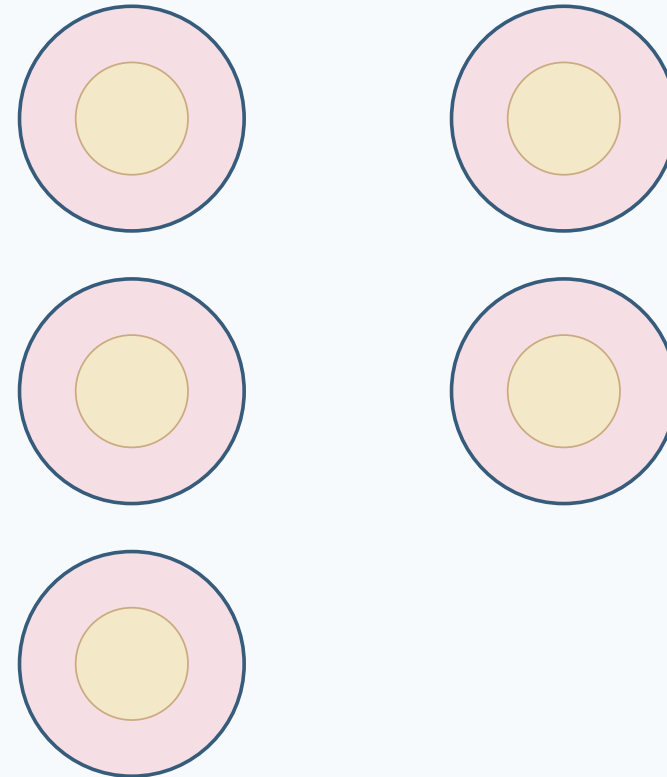
Follicles containing colloid

Schematic — not histology

Cytology is usually bland

- Cells typically vary little in size and shape
- Nuclear morphology is comparatively uniform
- Marked atypia is not a defining feature of ordinary adenoma
- Bland appearance cannot by itself exclude follicular carcinoma

Review the tumor margin even when nuclei appear innocuous.



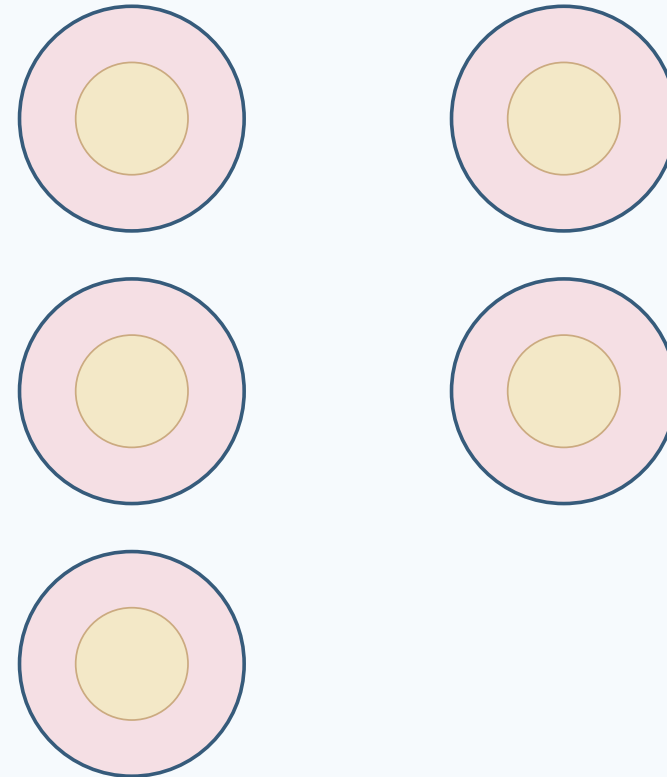
Follicles containing colloid

Schematic — not histology

Mitotic figures are typically rare

Low mitotic activity supports the conventional benign cytologic impression.

Marked activity prompts greater suspicion and more careful evaluation; This is not itself a substitute for demonstrating invasion.



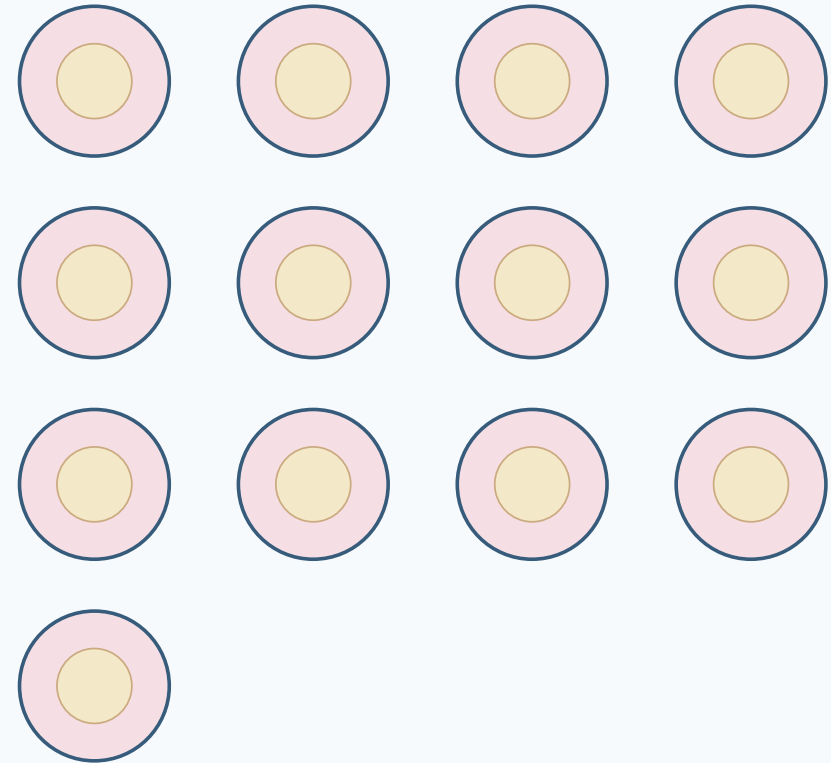
Follicles containing colloid

Schematic — not histology

Colloid is a variable constituent

- Follicles may contain pink, proteinaceous colloid
- Cellularity and colloid contribute to gross color and consistency
- Follicular size and colloid amount can vary among lesions
- Colloid-containing follicles alone do not establish a neoplasm

Evaluate pattern, border, and surrounding parenchyma.



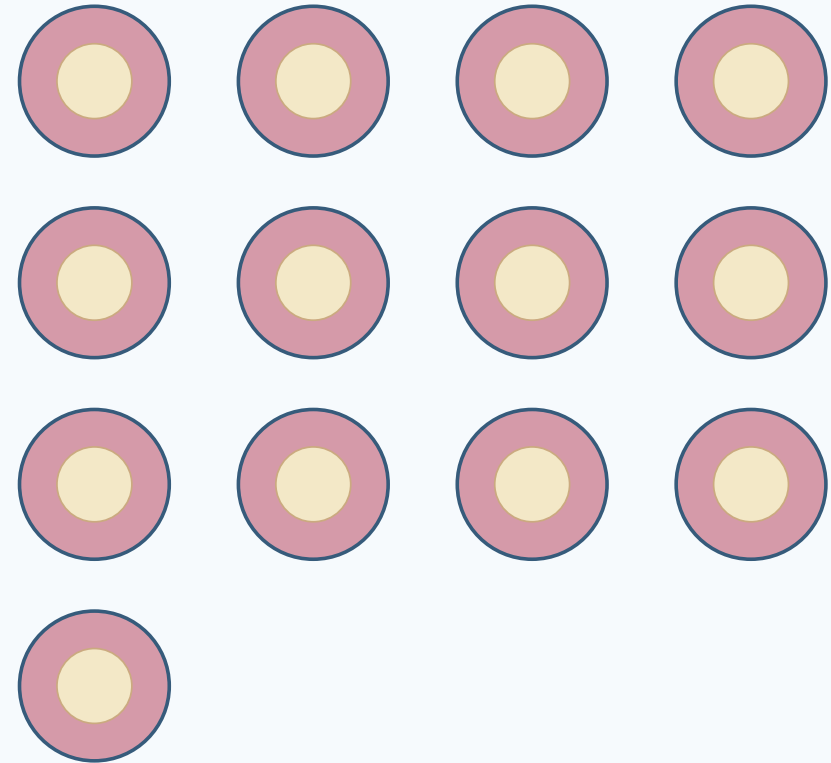
Follicles containing colloid

Schematic — not histology

Oncocytic change in an adenoma

- Some tumor cells have abundant granular eosinophilic cytoplasm
- This cytoplasmic phenotype is termed oncocytic change
- An oncocytic adenoma
- Oncocytic cytoplasm alone does not demonstrate malignancy

Diagnosis still depends on complete structural assessment.



Oncocytic cytoplasm (conceptual)

Schematic — not histology

Architecture and cytology answer different questions

Central tumor fields

- Follicular growth pattern
- Colloid formation
- Uniform cells and rare mitoses
- Possible oncocytic cytoplasm

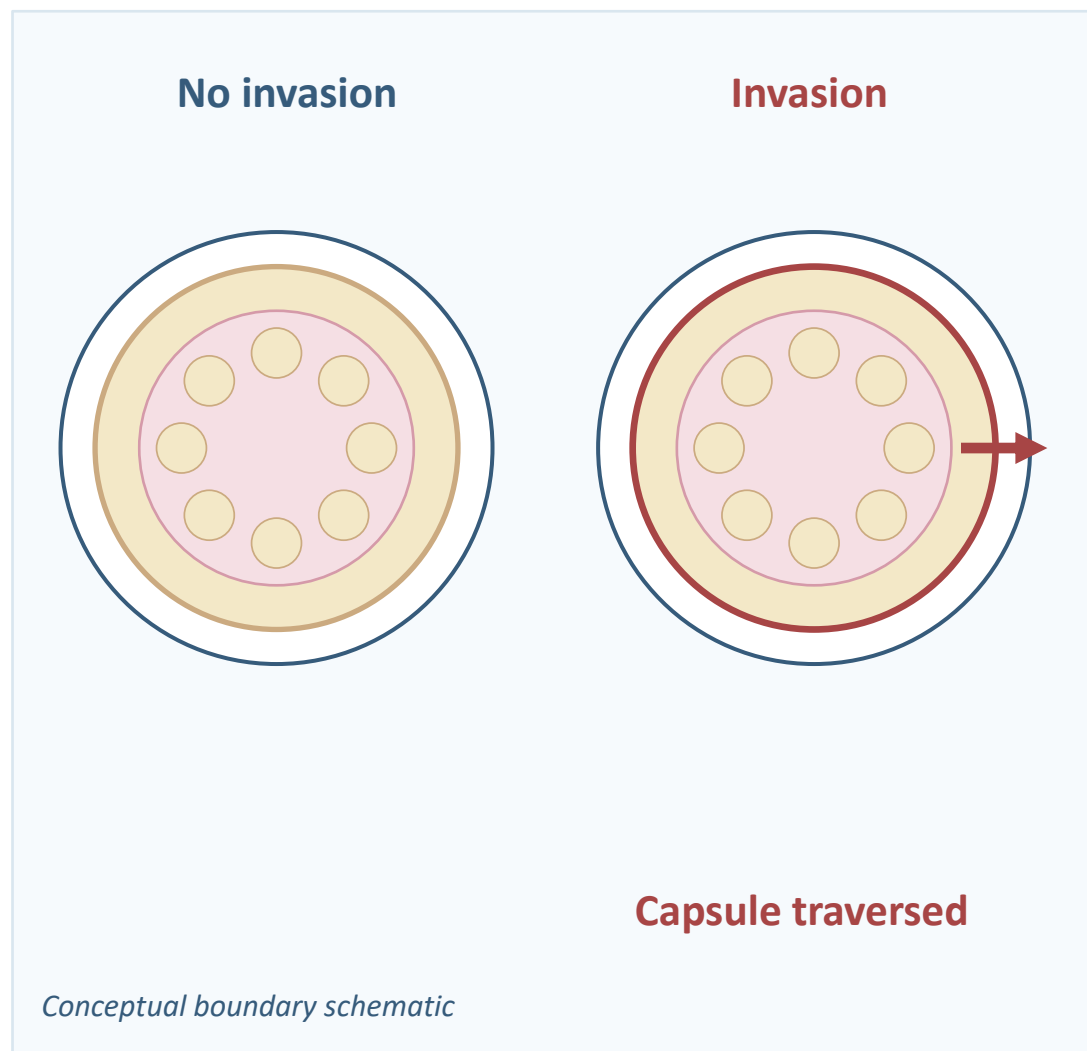
Tumor periphery

- Presence / character of capsule
- Complete versus penetrative interface
- Vascular and intrathyroidal invasion
- Required for final biologic classification

The decisive distinction: Invasion

Follicular carcinoma exhibits capsular, vascular, or intrathyroidal invasion.

An adenoma must be circumscribed and show no invasion; The absence of invasion cannot be established by routine cytology.



Adenoma and carcinoma may look alike centrally

Follicular adenoma

- Follicular cells can look bland
- Encapsulated or sharply circumscribed
- No capsular, vascular, or intrathyroidal invasion

Follicular carcinoma

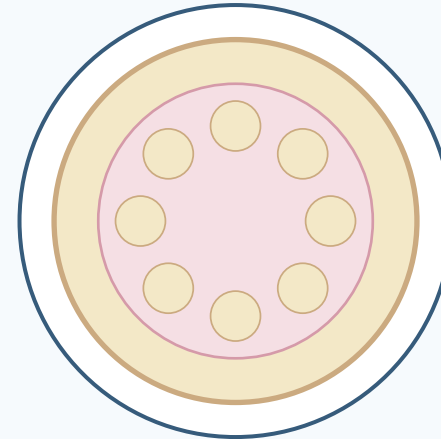
- May also exhibit differentiated follicles
- Invasion establishes malignant behavior
- Requires deliberate histologic study of tumor edge

Capsular invasion: What is the question?

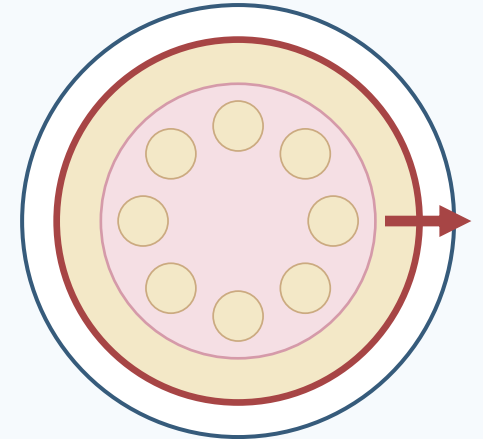
Does neoplastic tissue actually penetrate the capsule?

Tangential sections and irregular contours require cautious interpretation. The schematic distinguishes intact from penetrated capsule.

No invasion



Invasion



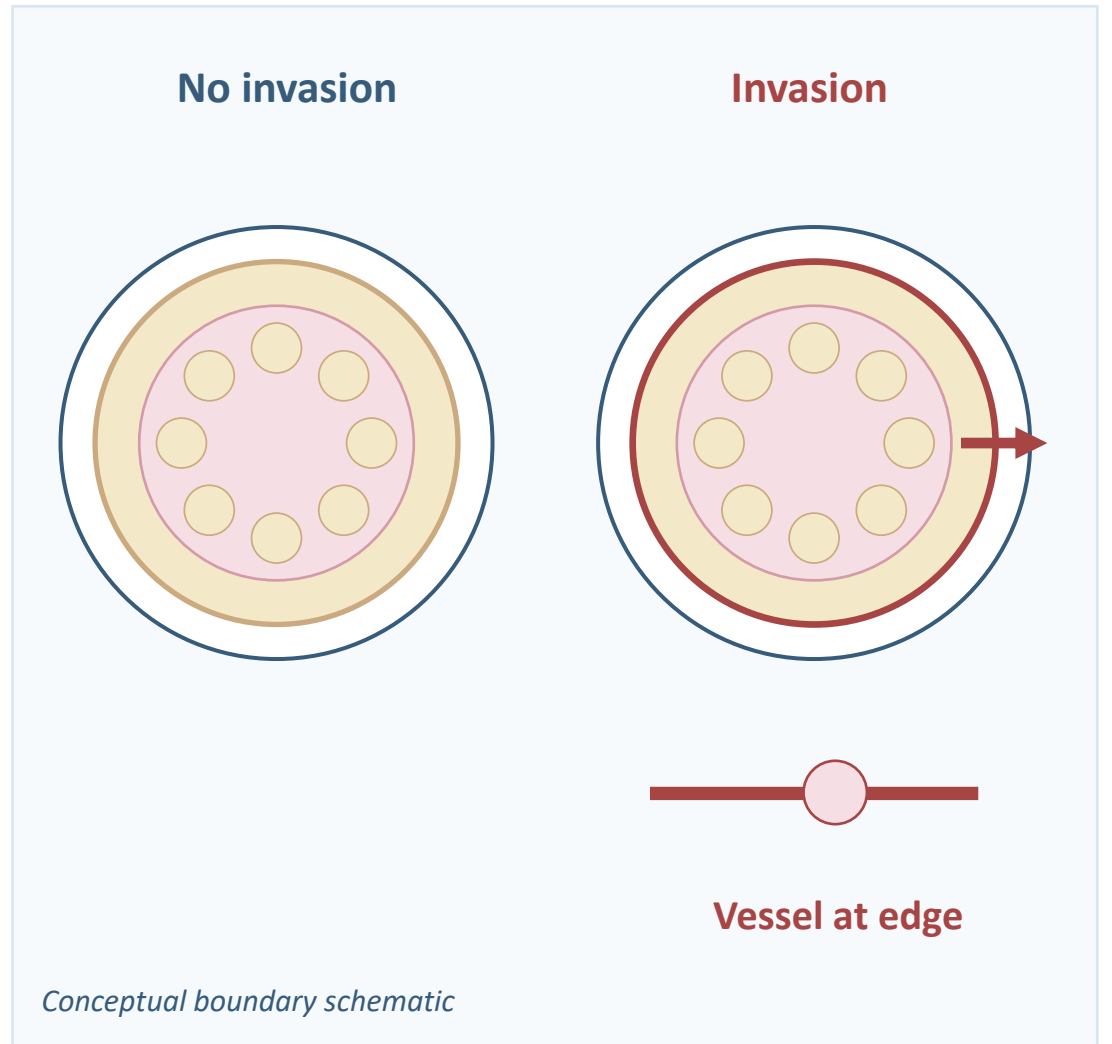
Capsule traversed

Conceptual boundary schematic

Vascular invasion: What is the question?

Are neoplastic cells invading vessels at or beyond the tumor periphery?

Vascular invasion as a diagnostic feature of follicular carcinoma; Central bland histology does not negate it.

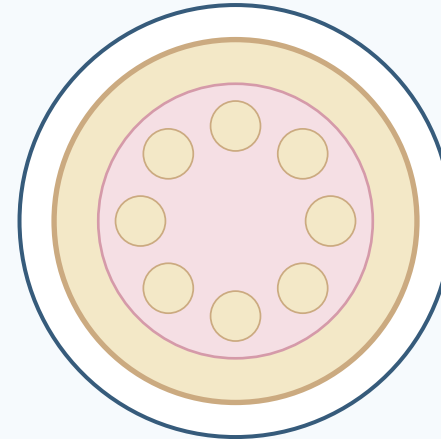


Intrathyroidal invasion: What is the question?

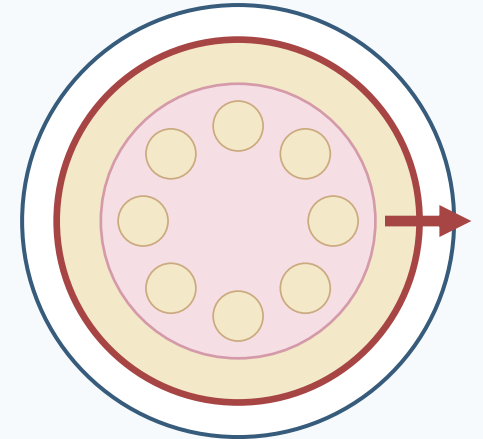
**Does the tumor infiltrate
surrounding nonneoplastic thyroid?**

Circumscription without invasion is required for adenoma, even when no complete fibrous capsule is visible.

No invasion



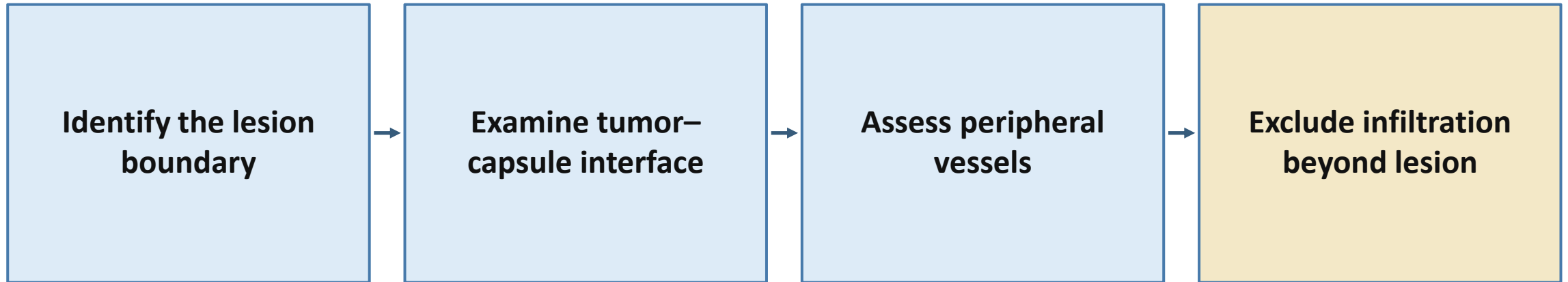
Invasion



Infiltration outside lesion

Conceptual boundary schematic

A systematic peripheral sampling logic

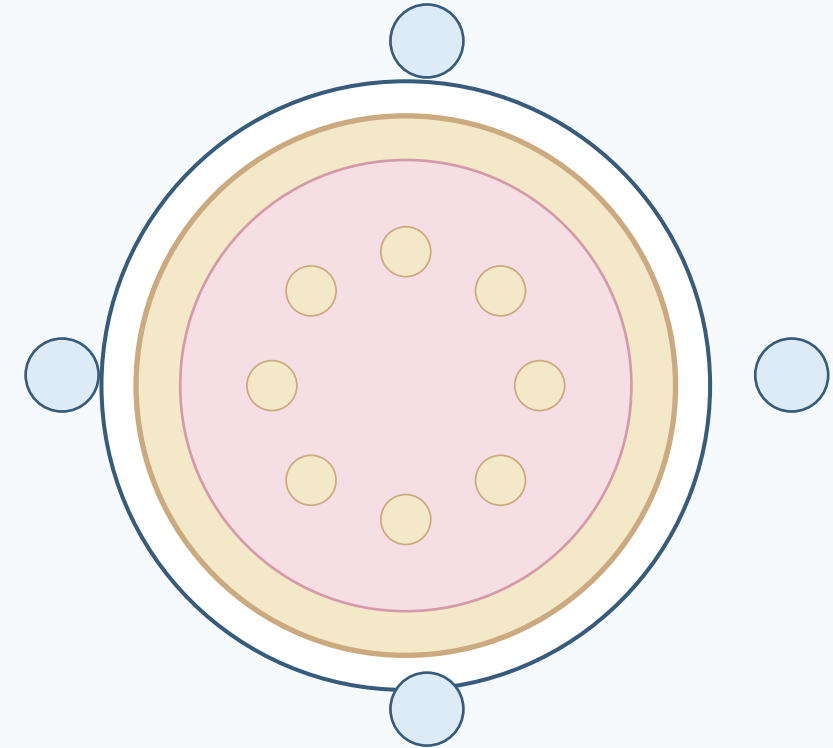


This is a conceptual checklist, not a prescribed specimen-block count.

Why focal invasion can be missed

- A lesion is three-dimensional; Each histologic section is only a plane
- The center cannot reveal every peripheral tumor–host relationship
- The concerning focus may be small relative to the tumor circumference
- Adequate sampling of the interface is therefore critical

A reassuring single field does not constitute full exclusion of invasion.



Inspect the full interface, not only the center

Schematic

Concerning histology versus proven carcinoma

Raises suspicion

- Increased cellularity
- Notably elevated mitotic activity
- Necrosis
- Atypical architecture

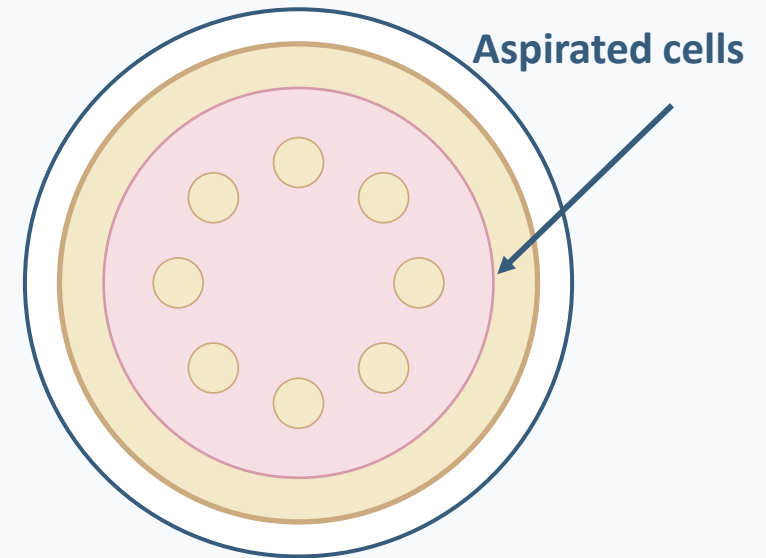
Diagnostic distinction in the source

- Capsular invasion
- Vascular invasion
- Intrathyroidal infiltration
- These findings require tissue architecture

What FNA can show

- Follicular epithelial cells and colloid in an aspirated sample
- Cytologic architecture and nuclear characteristics
- Suspicious features prompting further diagnostic workup
- Useful information for clinical nodule triage

FNA samples cells, not the complete tumor boundary.



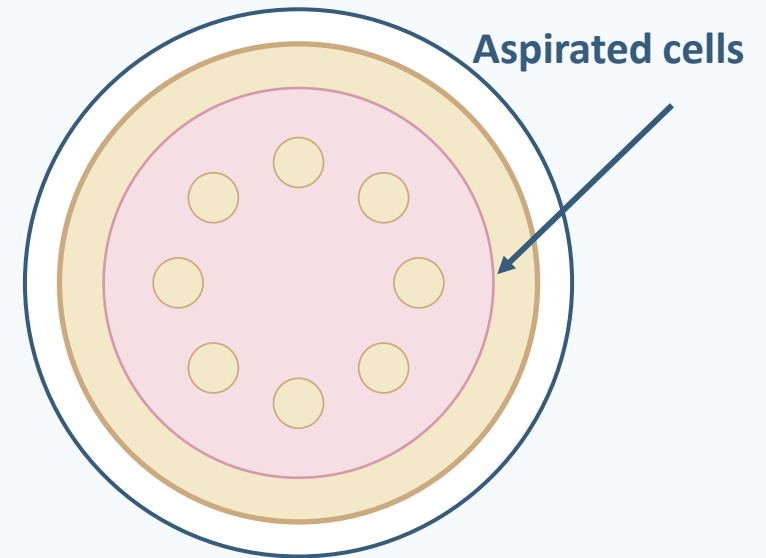
No complete capsule in aspirate

Schematic

What FNA cannot establish

Follicular adenoma versus follicular carcinoma cannot be definitively distinguished by FNA alone.

Capsular integrity and vascular invasion require evaluation of a resected lesion.



No complete capsule in aspirate

Schematic

Ultrasound, FNA and resection

Preoperative evaluation

- Ultrasound characterizes the nodule
- Suspicious features guide FNA selection
- FNA may classify many nodules but leaves some indeterminate

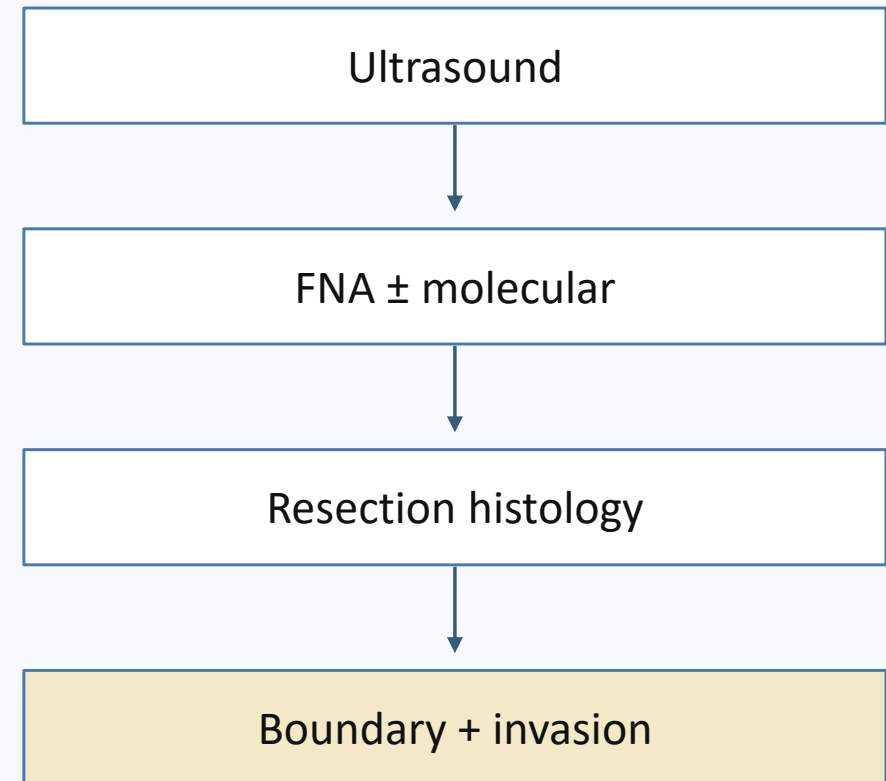
Definitive tissue diagnosis

- Histology demonstrates architecture
- Peripheral interface can be inspected
- Adenoma requires exclusion of invasion

Ultrasound provides risk information

- Nodule composition and contour can be documented
- Hypoechogenicity and irregular margins may be suspicious
- Imaging can guide decisions about FNA
- Ultrasound cannot directly prove absent microscopic capsular invasion

No ultrasound pattern alone confirms follicular adenoma.

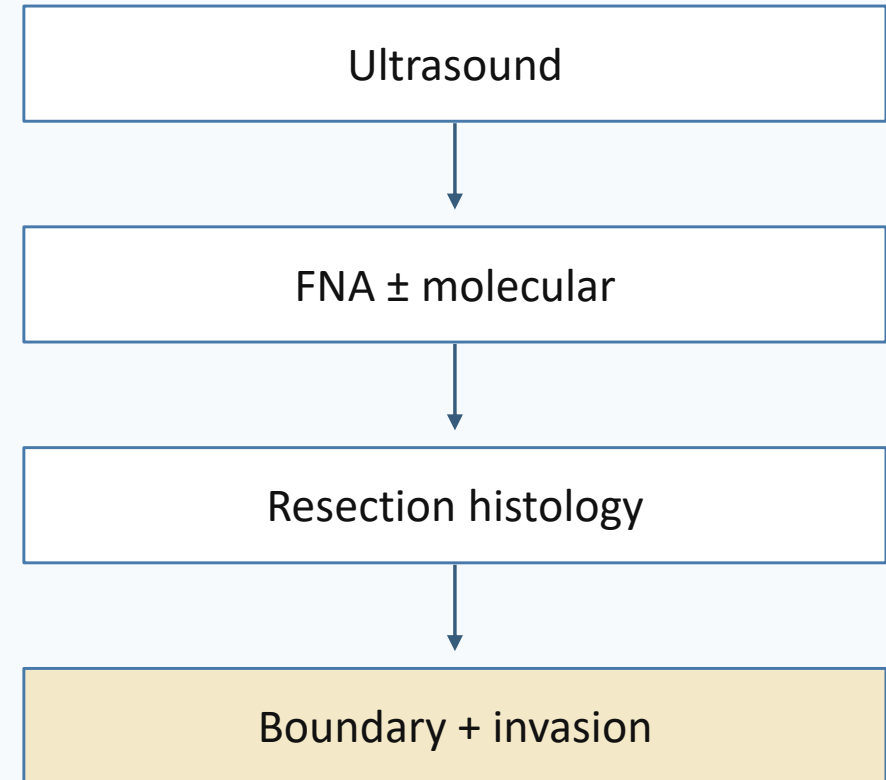


Conceptual diagnostic sequence

Molecular assessment: A supporting role

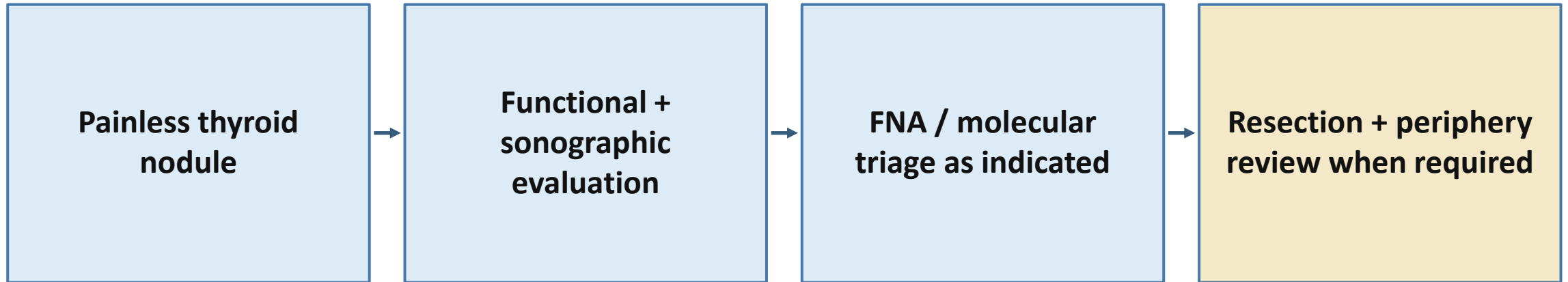
- Indeterminate thyroid nodules can be evaluated with molecular diagnostic tests
- These studies may help select nodules needing further surgery
- Molecular results are adjunctive to morphology
- The textbook does not supply a single universal marker of follicular adenoma

Do not confuse triage performance with proof of absent invasion.



Conceptual diagnostic sequence

Clinical-to-pathology diagnostic pathway

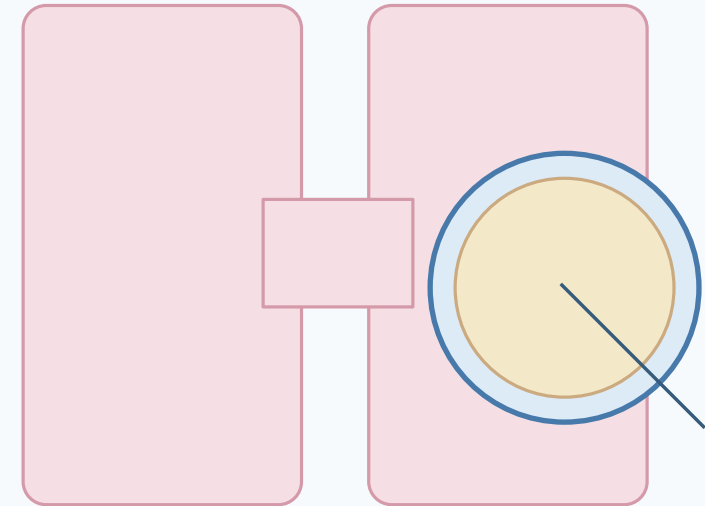


The pathway illustrates principle, not a substitute for current local clinical guidelines.

Most adenomas present as a mass

- Often painless
- Frequently found on routine physical examination
- May be incidentally detected during radiologic investigation
- Clinical features overlap with many benign and malignant nodules

Discrete nodule



Schematic

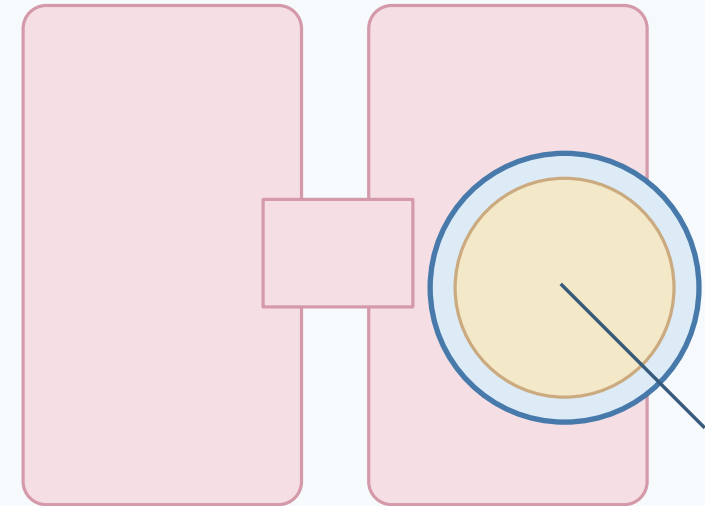
Symptoms do not establish an invasion status.

Larger lesions may cause dysphagia

An expanding thyroid mass can exert pressure on adjacent cervical structures.

Difficulty swallowing as one possible local symptom of a larger adenoma.

Discrete nodule



Expansile mass → local pressure

Schematic

Clinical phenotype: Nonfunctioning versus toxic

Nonfunctioning follicular adenoma

- Typically euthyroid clinical presentation
- Painless nodule or incidental discovery
- Often reduced radionuclide uptake

Toxic follicular adenoma

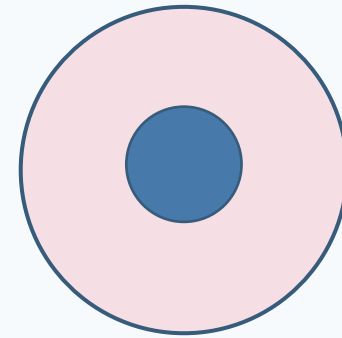
- Autonomous thyroid hormone secretion
- Can cause clinical thyrotoxicosis
- Typically functionally “hot”

Functional imaging: What to conclude

- Hot nodule: Autonomous uptake is favored
- Cold nodule: Reduced iodine uptake is identified
- Hot nodules are much more likely to be benign
- A cold nodule does not by itself prove carcinoma

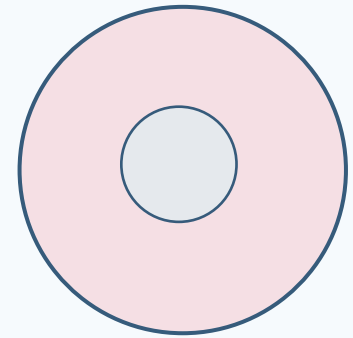
Scintigraphy assesses function rather than capsular integrity.

Functional schematic—not a radionuclide scan



HOT

Relative uptake ↑



COLD

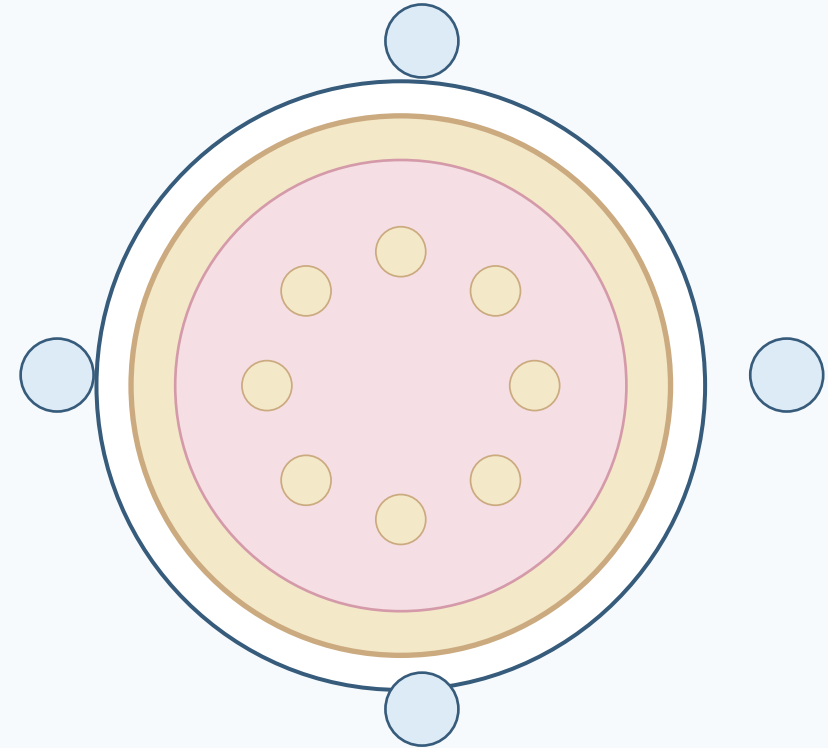
Relative uptake ↓

Schematic

Resection allows definitive classification

The examined specimen permits assessment of the tumor boundary and any vascular invasion.

Definitive adenoma diagnosis requires careful histologic examination of the excised lesion.



Inspect the full interface, not only the center

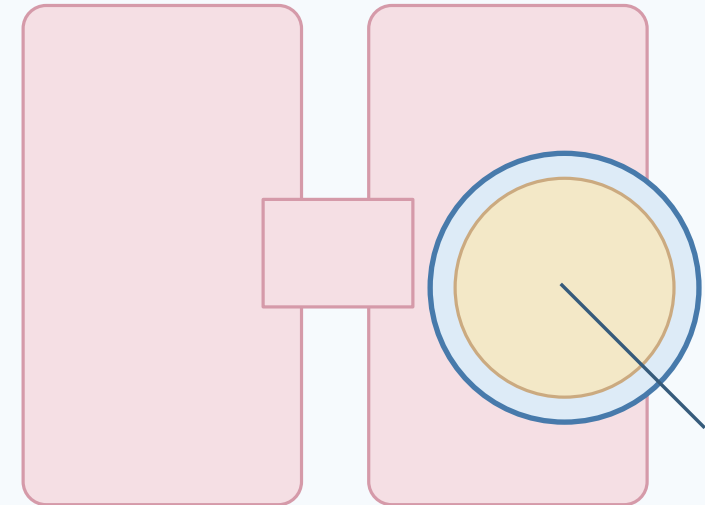
Schematic

Prognosis after a confirmed adenoma

- Follicular adenoma is a benign neoplasm
- It does not metastasize
- Recurrence is not expected for a definitively diagnosed, adequately treated lesion
- The expected prognosis is excellent

These statements apply to a securely established adenoma, not an indeterminate nodule.

Discrete nodule



Schematic

Why adenoma and carcinoma must not be conflated

Shared appearances

- Follicular epithelial differentiation
- Sometimes a solitary circumscribed thyroid mass
- A similar cytologic appearance on FNA

Essential difference

- Adenoma lacks invasion
- Carcinoma demonstrates invasion
- Resection histology establishes the distinction

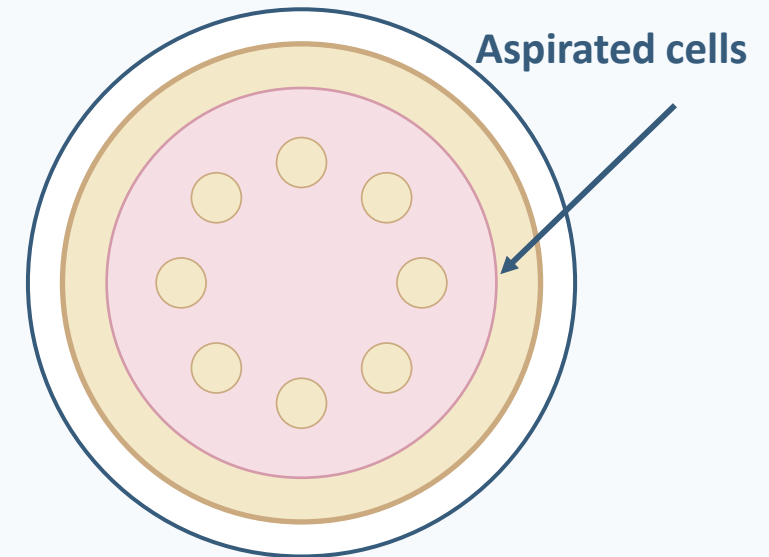
Case 1: A bland follicular aspirate

An asymptomatic adult has a well-defined thyroid nodule. FNA yields uniform follicular cells and colloid.

Interpretation question

Can the aspirate certify follicular adenoma?

No. The diagnosis requires assessment of the resected lesion–host interface for invasion.



No complete capsule in aspirate

Schematic

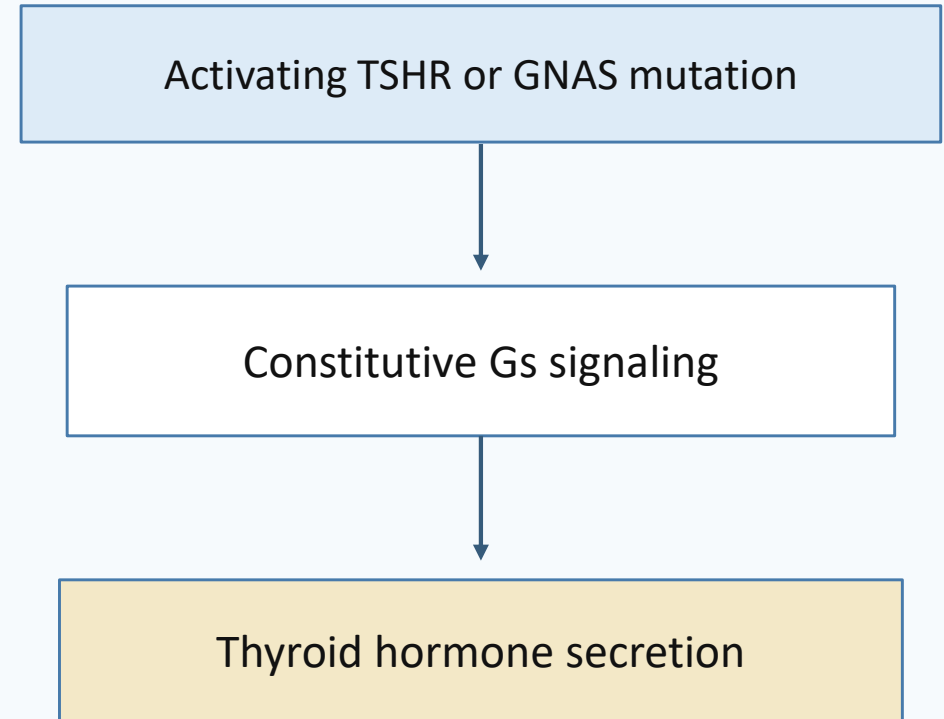
Case 2: A functionally hot nodule

A patient with thyrotoxicosis has one focally hyperfunctioning thyroid nodule on radionuclide imaging.

Interpretation question

Which mechanism is biologically plausible?

Activating TSHR or GNAS pathway alteration causing hormone secretion independent of TSH.



Without normal TSH dependence

Schematic

Case 3: A focal capsular breach

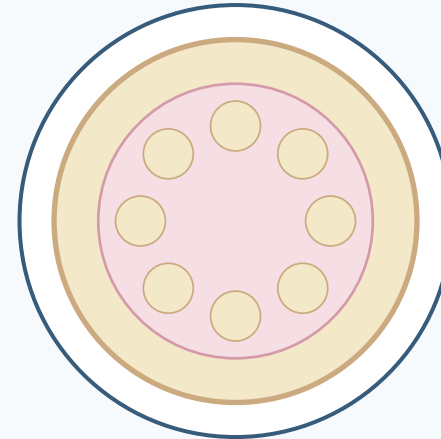
A resected follicular-patterned tumor contains bland follicles centrally, but one peripheral field shows unequivocal capsular invasion.

Interpretation question

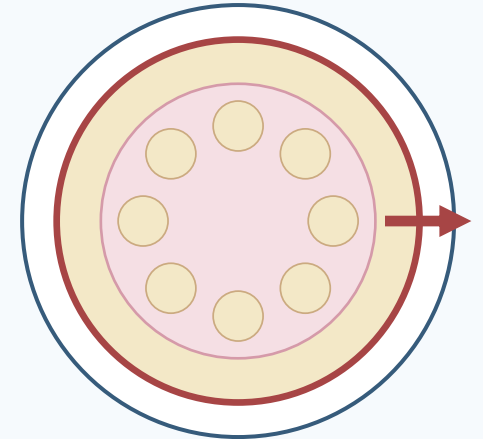
Does bland cytology retain an adenoma diagnosis?

No. Demonstrated invasion overrides bland cytologic appearance and raises carcinoma classification.

No invasion



Invasion



Capsule traversed

Conceptual boundary schematic

Case 4: Dominant nodule in a large gland

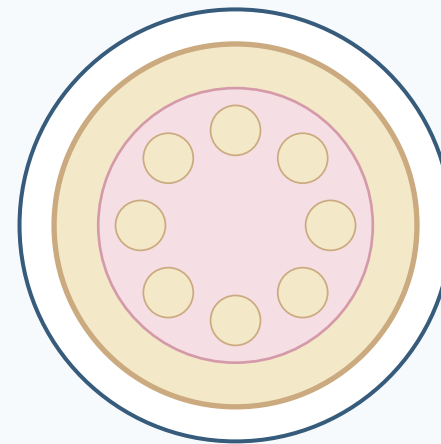
A palpable dominant nodule is present, but examination reveals several other nodules with heterogeneous architecture.

Interpretation question

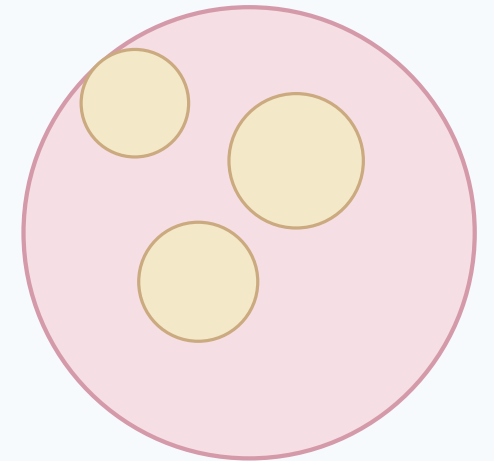
What is a key differential for a “solitary” adenoma?

Follicular nodular disease (multinodular goiter) with a dominant nodule.

Single nodule



Multiple nodules



Schematic

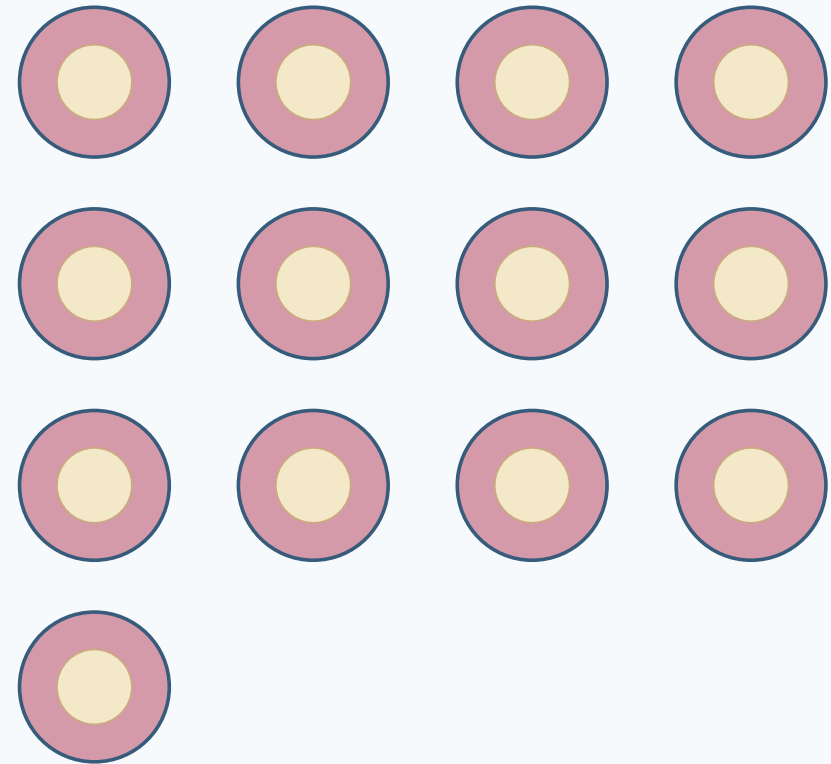
Case 5: Oncocytic cells

A well-circumscribed follicular tumor shows abundant granular eosinophilic cytoplasm. No invasion is identified after peripheral assessment.

Interpretation question

What does the oncocytic phenotype indicate?

Oncocytic change; It does not alone establish malignancy.



Oncocytic cytoplasm (conceptual)

Schematic — not histology

Decision framework: What each modality contributes

Method	Can support	Cannot by itself prove
Clinical assessment	Nodule / pressure / thyrotoxicosis	Adenoma versus carcinoma
Radionuclide scan	Functional activity (hot / cold)	Absence of invasion
Ultrasound	Nodule architecture and suspicious features	Microscopic capsular status
FNA	Cytology and triage	Capsular / vascular invasion
Resection histology	Tumor boundary and invasion status	—

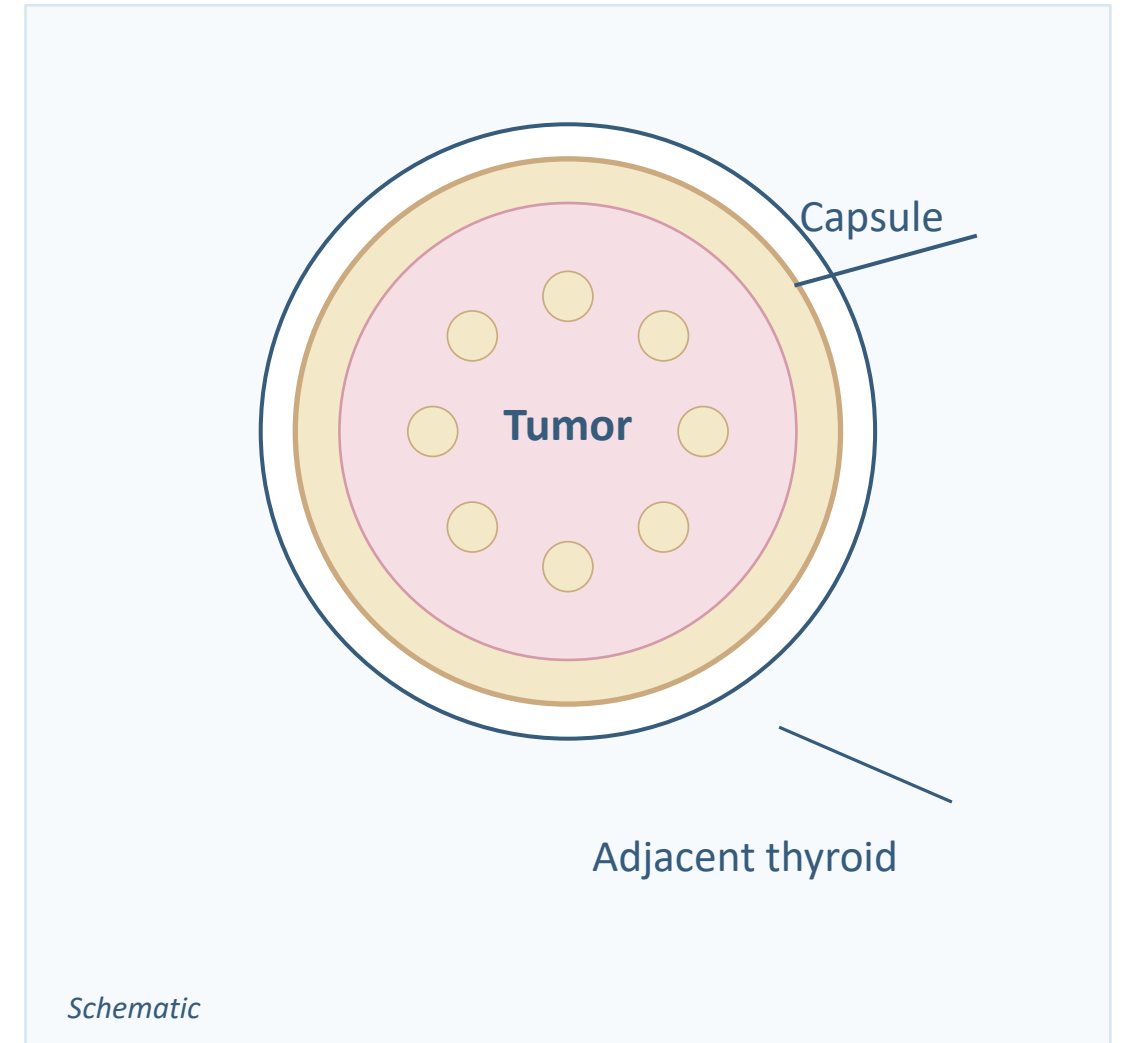
Adenoma versus principal mimics

Feature	Follicular adenoma	Follicular nodular disease	Follicular carcinoma
Distribution	Usually solitary	Typically multinodular	May be solitary
Capsule	Often present	Usually no distinct complete tumor capsule	May be present
Follicles	Relatively uniform	Variable / heterogeneous	May look differentiated
Invasion	Absent	Not a criterion of a benign nodule	Present by definition

Five defining checkpoints

- Follicular-cell neoplasm, commonly solitary
- Well-circumscribed, often encapsulated mass
- Follicles often uniform, with bland cytology
- Most are nonfunctional; A minority are toxic
- No capsular, vascular, or intrathyroidal invasion

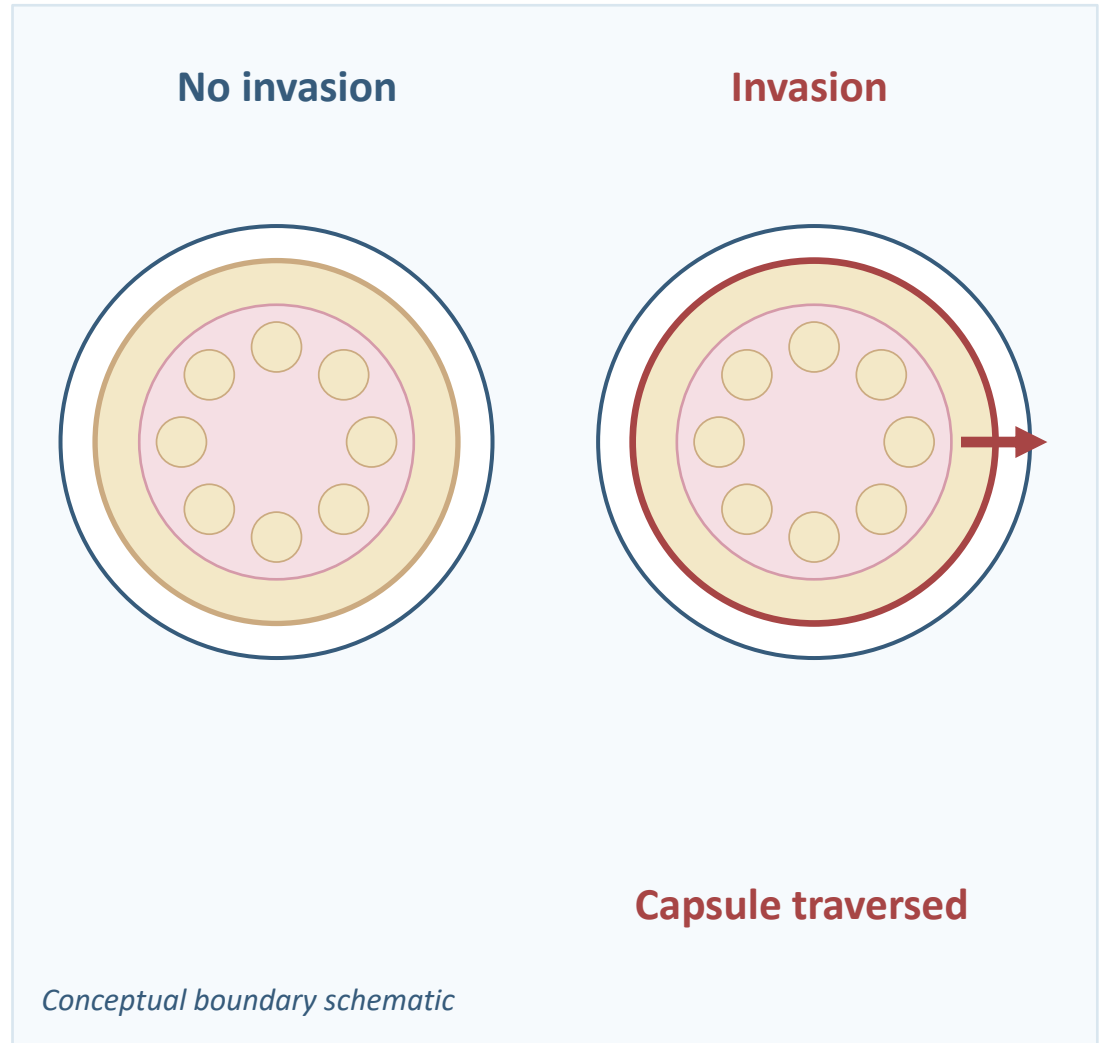
Adenoma is confirmed by the complete morphologic interpretation.



Final diagnostic principle

A beautiful central micrograph does not substitute for examining the tumor boundary.

The diagnosis of follicular adenoma ultimately rests on circumscription without invasion.



Source and visual provenance

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Chapter 24, “Thyroid Adenomas,” pp. 987–988.
- Parent context: “Neoplasms of the Thyroid” and “Follicular Nodular Disease,” Chapter 24.
- All diagrams are original, editable teaching schematics; no diagnostic specimen images are reproduced.
- TSHR/GNAS frequencies and EZH1 two-hit discussion are reported as stated in the supplied edition.