

Papillary Carcinoma of the Thyroid

Morphology • molecular pathogenesis • clinicopathologic reasoning

Thyroid pathology: a structured diagnostic and molecular approach

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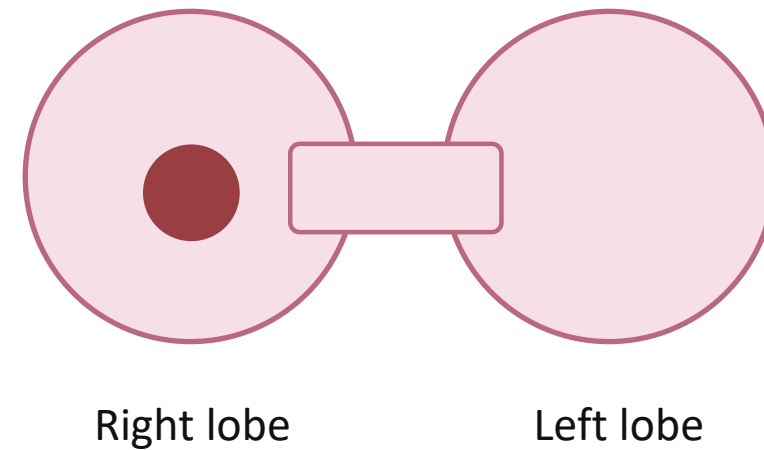
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Learning objectives

- Recognize the nuclear and architectural hallmarks of conventional PTC.
- Connect BRAF and kinase-fusion drivers to MAPK signaling.
- Explain lymphatic dissemination, clinical presentation and prognosis.
- Distinguish conventional PTC from key follicular-patterned mimics.

PTC is a follicular epithelial malignancy

- Arises from thyroid follicular epithelium, not parafollicular C cells.
- Belongs to the differentiated thyroid carcinomas.
- Characteristic nuclear changes are central to recognition.



Thyroid anatomy — simplified schematic

Thyroid carcinoma: Diagnostic context

Tumor family	Differentiation / origin	Key distinction
Papillary	Follicular epithelial	Papillae; defining nuclear features
Follicular / oncocytic	Follicular epithelial	Capsular or vascular invasion
High-grade / anaplastic	Follicular epithelial	High-grade morphology / dedifferentiation
Medullary	Parafollicular C cell	Neuroendocrine; calcitonin

Papillary carcinoma dominates thyroid malignancies

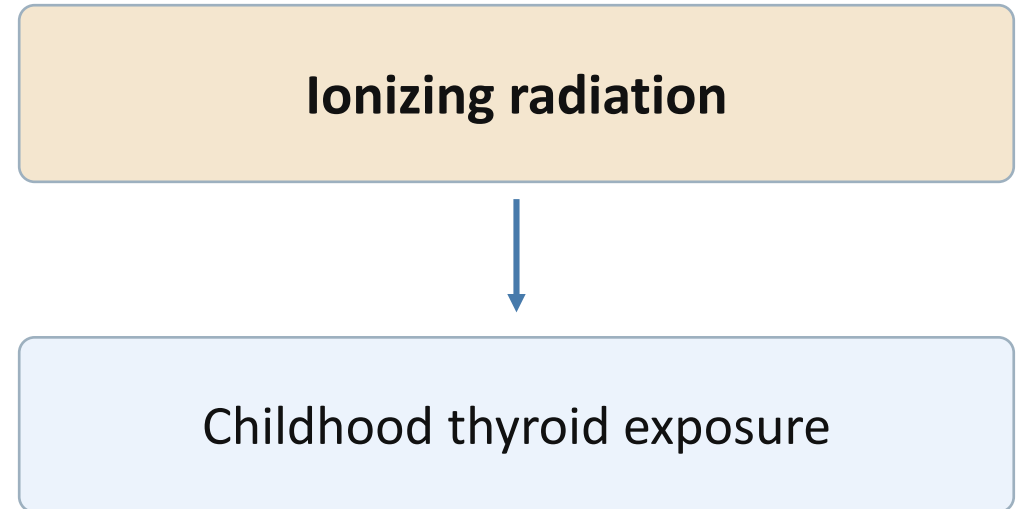
- Accounts for nearly 85% of thyroid cancers in the United States.
- Its high frequency largely determines the clinical face of thyroid cancer.
- Small, localized PTCs contribute to overall favorable thyroid cancer outcomes.

PTC can occur throughout life

- Occurs across the age spectrum.
- Most often presents between 25 and 50 years of age.
- Age also informs prognosis: Outcomes are generally less favorable after 55.

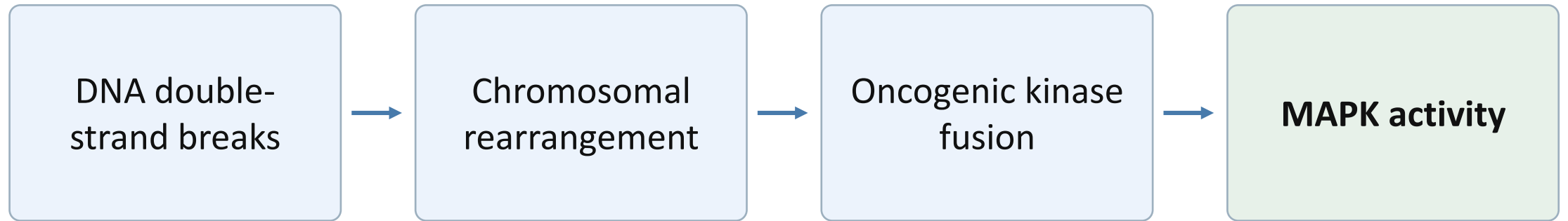
Ionizing radiation is an important risk exposure

- PTC predominates among thyroid cancers associated with prior radiation.
- Exposure in the first two decades of life is particularly relevant.
- Historical radiation-related childhood PTC provides etiologic evidence.



Exposure association — conceptual

A plausible mechanism for radiation-associated fusions



The text proposes that radiation-related DNA breaks may help explain the increased fusion frequency in radiation-associated PTC.

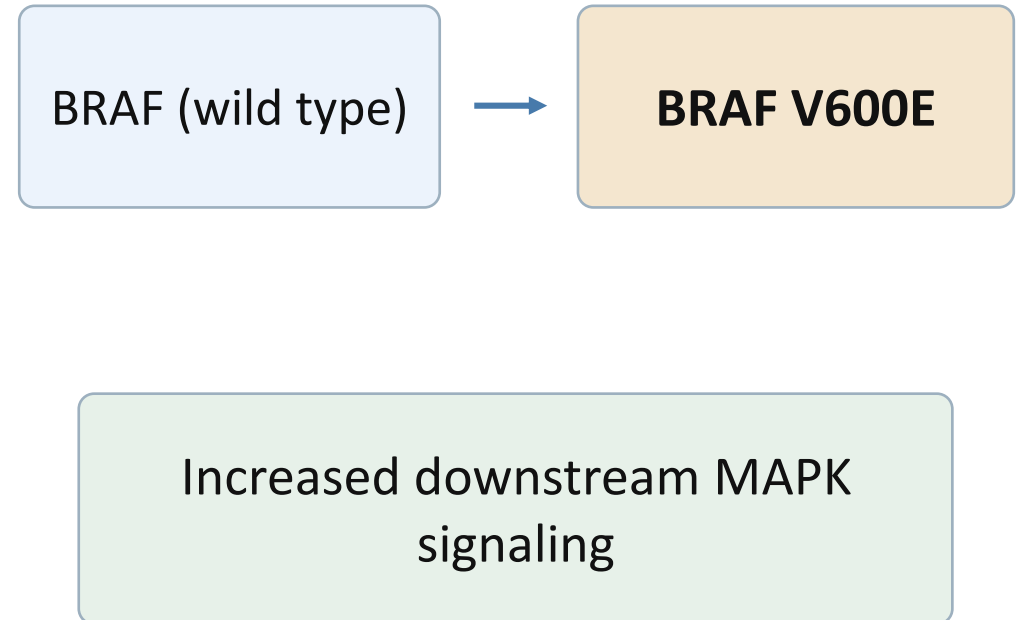
Conceptual mechanism — editable schematic

PTC development involves oncogenic driver events

- Conventional PTC is associated with activating BRAF point mutations.
- Rearrangements involving RET, NTRK or BRAF are another driver class.
- These pathways promote growth signaling in follicular epithelial cells.

BRAFV600E activates a signaling kinase

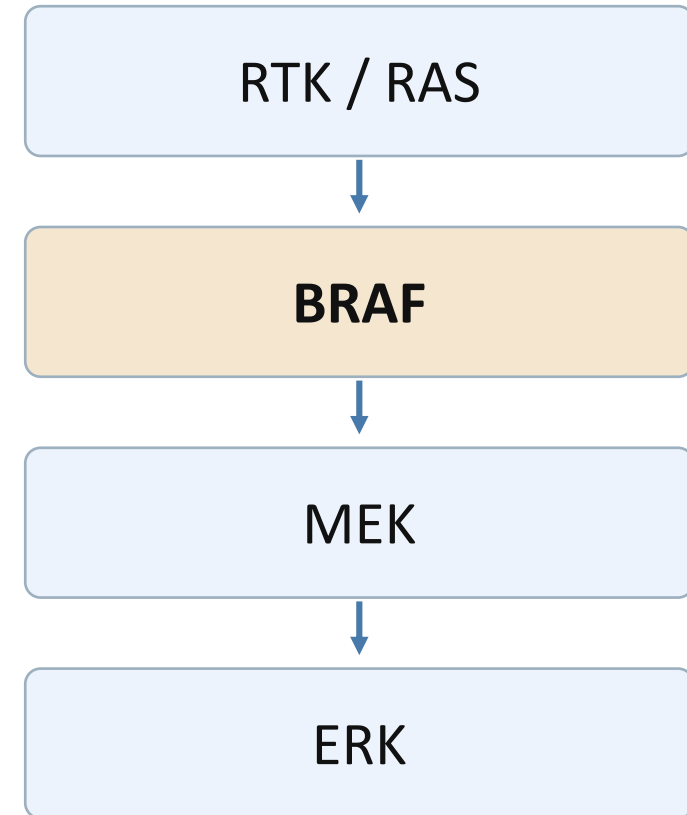
- BRAF V600E in up to 80% of conventional PTCs.
- The alteration substitutes glutamate for valine at codon 600.
- It produces gain of function in a serine/threonine kinase.



Driver-mutation schematic

BRAF lies within the MAPK signaling pathway

- The canonical cascade links upstream receptor/RAS signaling to BRAF.
- BRAF activates MEK, which activates ERK.
- The downstream response influences proliferation and differentiation.



Schematic MAPK signaling

A driver mutation is not a histologic diagnosis

- BRAF V600E occurs in PTC and in other malignancies.
- Molecular evidence should be interpreted with cytomorphology and clinical context.
- PTC recognition remains anchored in its characteristic nuclear changes.

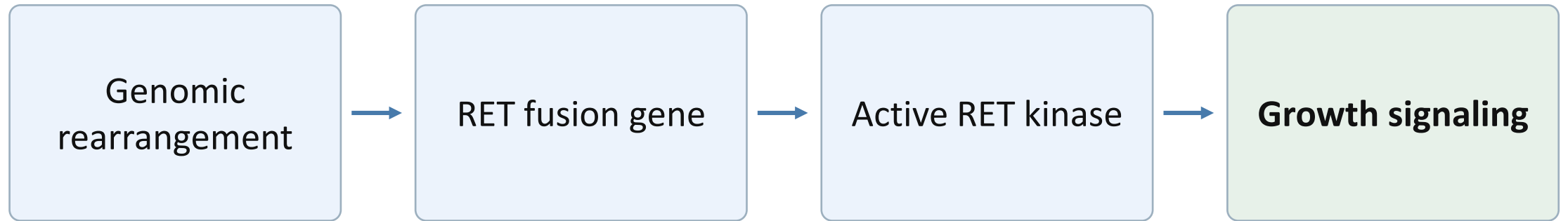
BRAF is linked to altered thyroid differentiation

- The source associates BRAF-mutant conventional PTC with reduced differentiation markers.
- Examples include thyroglobulin and thyroid peroxidase.
- This association helps connect oncogenic signaling with tumor phenotype.

BRAF status and adverse behavior: Interpret cautiously

- A possible association with extrathyroidal extension.
- A possible association with recurrence is also noted.
- These are probabilistic associations, not deterministic outcome predictions.

RET fusions create constitutive kinase signaling

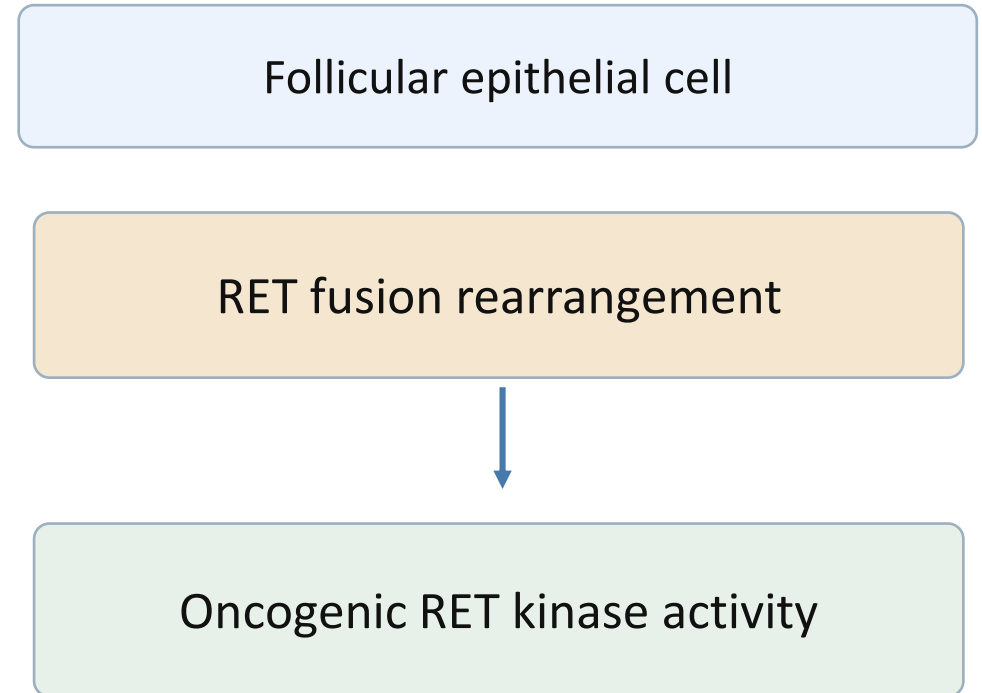


The rearrangement produces a fusion kinase active without normal physiological regulation.

Conceptual mechanism — editable schematic

RET is an unusual oncogenic kinase in follicular cells

- Normal thyroid follicular cells do not usually express RET.
- Rearrangements can activate the RET tyrosine kinase in PTC.
- CCDC6 is a common RET fusion partner.



Molecular schematic

NTRK rearrangements form another driver class

- NTRK1 and NTRK3 encode receptor tyrosine kinases.
- Gene rearrangements can produce constitutively active fusion proteins.
- The source notes these rearrangements particularly in some childhood PTCs.

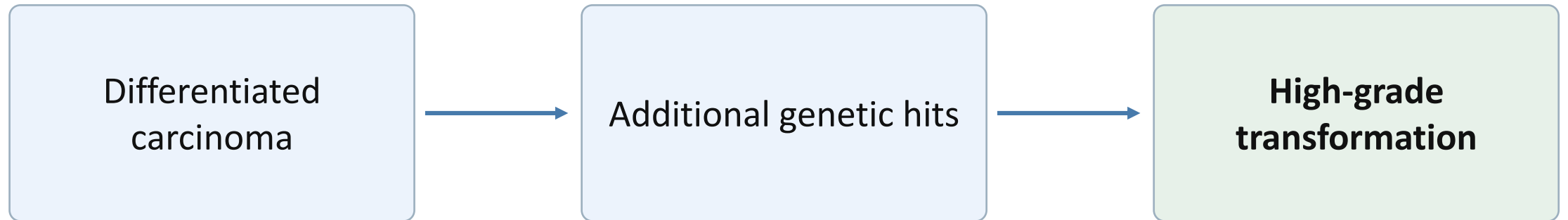
Conventional PTC: Two driver patterns

Molecular pattern	Example	Functional interpretation
Activating point mutation	BRAF V600E	Activated BRAF serine/threonine kinase
Oncogenic gene fusion	RET fusion	Constitutively active receptor tyrosine kinase
Oncogenic gene fusion	NTRK1 / NTRK3	Constitutively active fusion kinase
Oncogenic gene fusion	BRAF fusion	BRAF pathway deregulation

BRAF-like versus RAS-like follicular neoplasms

Conventional PTC	Follicular-patterned neoplasms
Frequently BRAF V600E or kinase fusions	Often RAS mutations or related alterations
Conventional papillary architecture is common	Follicular architecture may predominate
Thyroid differentiation markers may be reduced with BRAF	RAS-associated tumors often retain differentiation markers
Lymphatic spread characteristic	Vascular spread important when invasive

Additional mutations underlie higher-grade progression

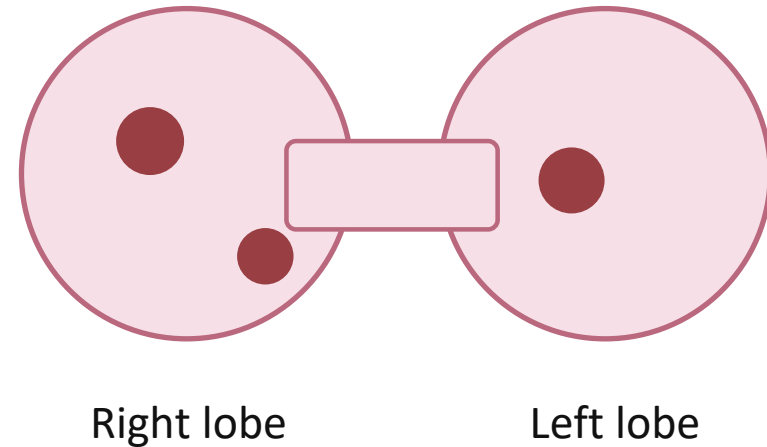


The source names TERT promoter and TP53 alterations in aggressive thyroid carcinomas. This is context, not a defining step for conventional PTC.

Conceptual mechanism — editable schematic

Conventional PTC may be solitary or multifocal

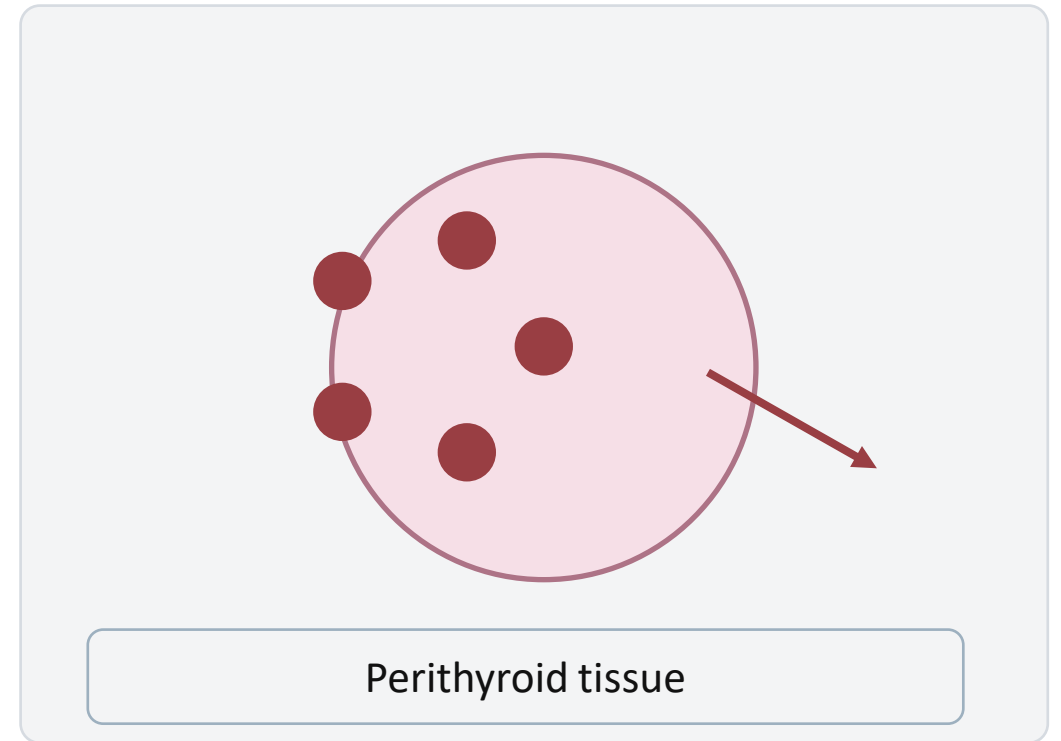
- Some glands contain a single dominant primary lesion.
- Others show multiple geographically separate foci.
- Multifocality is a gross distribution, not proof of extrathyroidal invasion.



Multifocal nodules — schematic

Tumor margins may be circumscribed or infiltrative

- Well-circumscribed lesions can have recognizable borders.
- Other PTCs permeate adjacent thyroid parenchyma.
- Margin assessment requires examination of tumor–thyroid interfaces.



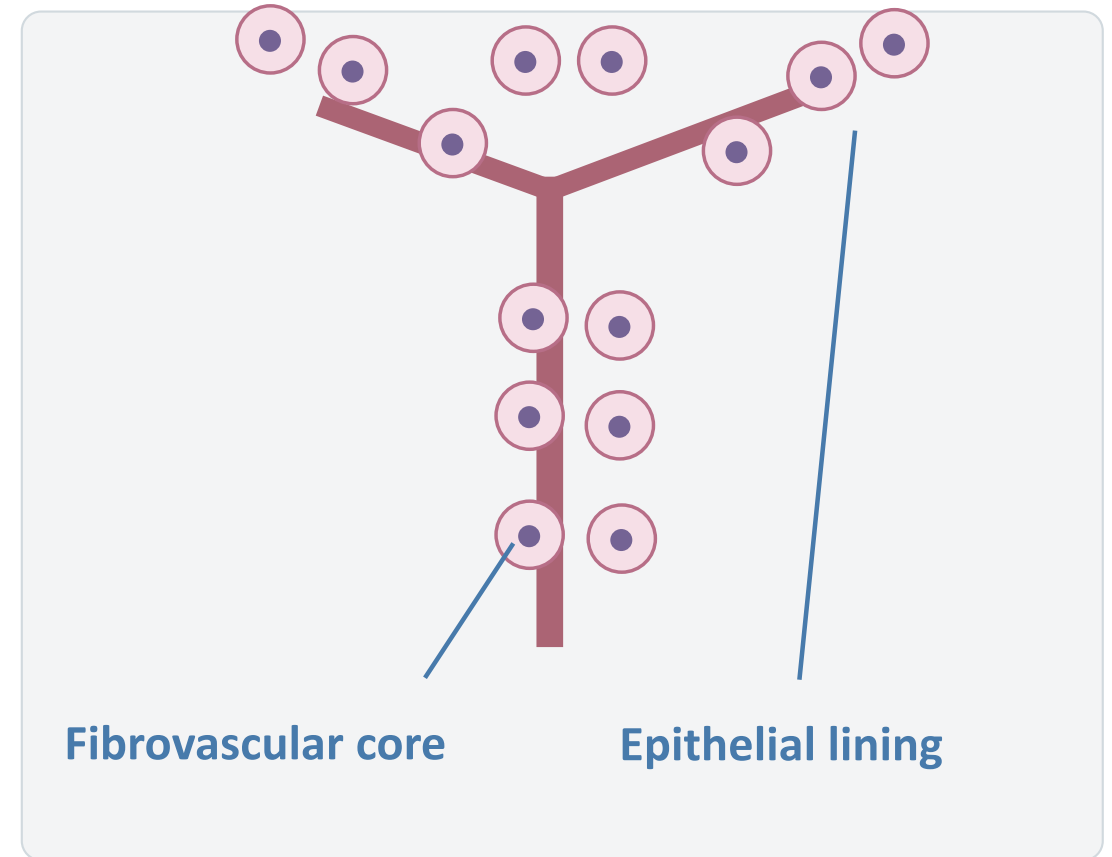
Simplified tissue schematic

Gross appearance can include secondary changes

- Areas of fibrosis may be present.
- Calcification is common enough to be a characteristic gross feature.
- Cystic change may alter the tumor's apparent architecture.
- Papillary foci may be visible on the cut surface.

True papillae have fibrovascular stalks

- Branching epithelial projections contain a central fibrovascular core.
- The epithelial covering may range from one to several cell layers.
- Branching complexity distinguishes the pattern from a simple follicle.



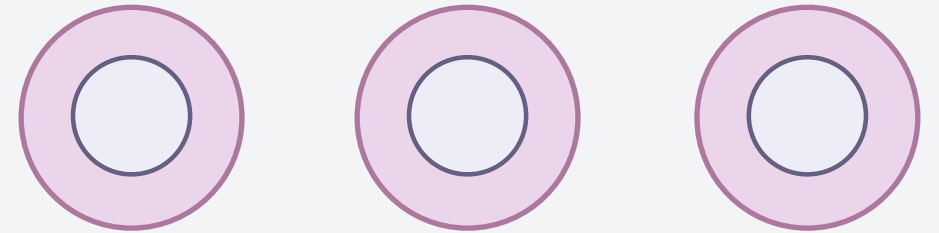
Schematic, not H&E micrograph

Architecture alone does not fully define PTC

- Well-formed branching papillae strongly support conventional PTC.
- Characteristic nuclear morphology remains essential.
- Papillary-type nuclear changes also occur in follicular-patterned lesions.

Optically clear nuclei are a defining feature

- Chromatin appears finely dispersed and pale.
- The empty-looking nucleus is termed ground-glass or Orphan Annie eye.
- Assess nuclear clearing alongside other nuclear membrane changes.

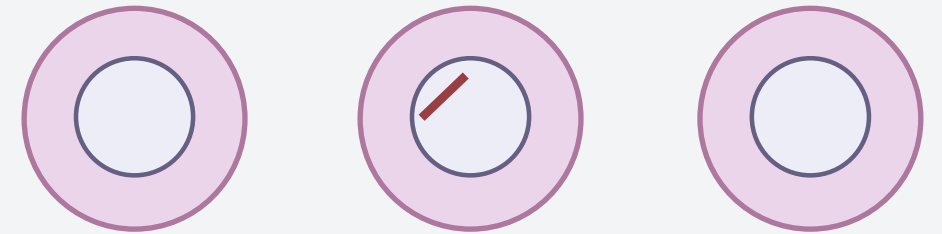


Pale, finely dispersed chromatin

Schematic cell nuclei — not histology

Nuclear grooves reflect membrane irregularity

- Nuclear contours show folds or longitudinal indentations.
- Grooves may create a coffee-bean appearance.
- They form part of a constellation of diagnostic nuclear changes.

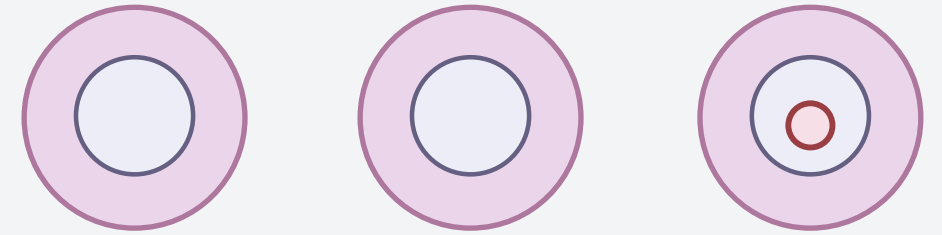


Longitudinal nuclear membrane infolding

Schematic cell nuclei — not histology

Intranuclear pseudoinclusions are cytoplasmic invaginations

- Cytoplasm appears to extend into the nucleus.
- Pseudoinclusions are enclosed by the nuclear membrane.
- They support PTC when accompanied by the expected nuclear phenotype.

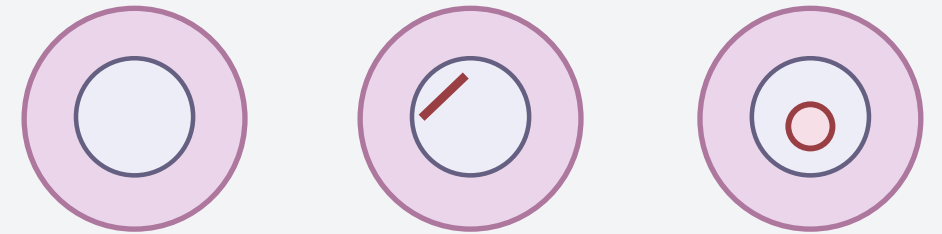


Cytoplasm appears invaginated into nucleus

Schematic cell nuclei — not histology

Interpret nuclear features as a combined pattern

- Nuclear enlargement, overlap and clearing occur together.
- Nuclear membrane wrinkling and grooves add specificity.
- Pseudoinclusions provide a further characteristic clue.

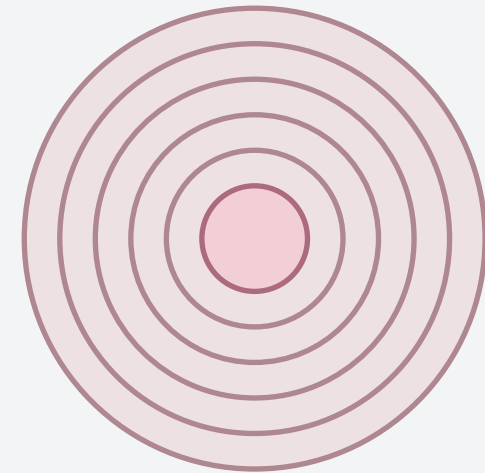


Clearing • groove • pseudoinclusion

Schematic cell nuclei — not histology

Psammoma bodies show concentric calcification

- Round, laminated calcifications are characteristic of PTC.
- They often lie within papillary cores or adjacent stroma.
- Their microscopic organization differs from coarse nonspecific calcification.



Concentric lamellated calcification

Schematic psammoma body

Psammoma bodies have diagnostic utility in FNA

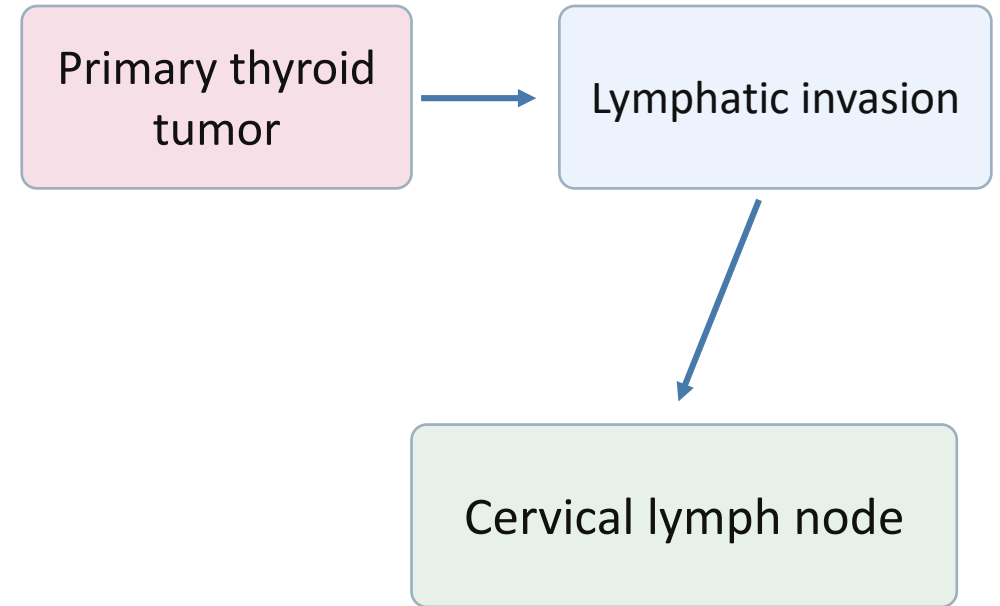
- Their identification supports PTC in thyroid aspirates.
- Their rarity in follicular and medullary thyroid carcinomas.
- They supplement rather than replace the full cytologic assessment.

Microscopic hallmarks: Structure and nuclei

Architectural clues	Nuclear clues	Stromal / invasive clues
Complex branching papillae	Fine chromatin clearing	Psammoma bodies
Fibrovascular papillary cores	Nuclear grooves / wrinkling	Lymphatic involvement
Cuboidal epithelial covering	Cytoplasmic pseudoinclusions	Variable stromal fibrosis

Lymphatic invasion is common in PTC

- Tumor cells may enter intrathyroidal lymphatics.
- Regional lymphatic dissemination explains frequent cervical nodes.
- The pattern differs from the blood-borne spread of follicular carcinoma.



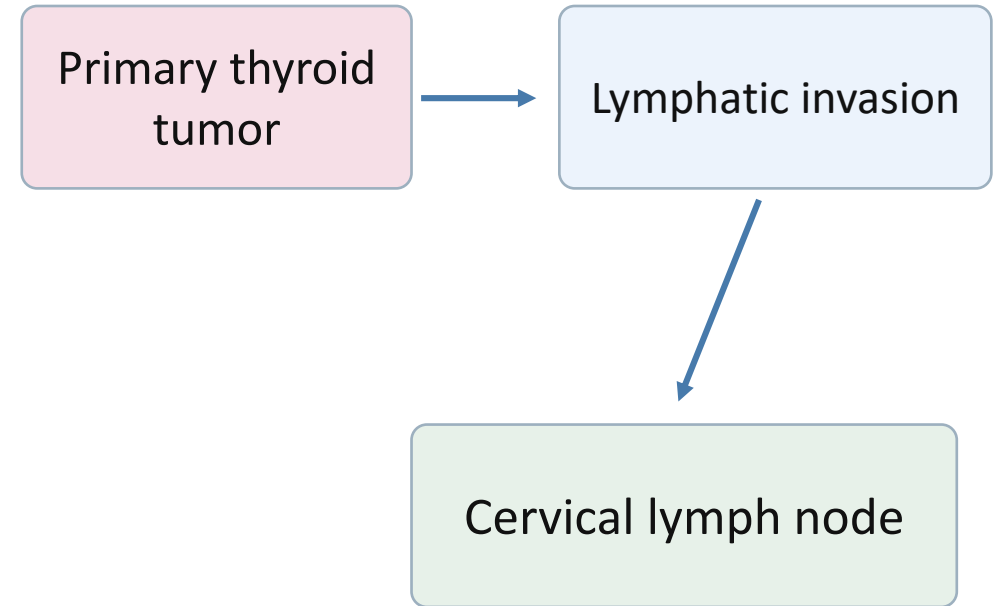
Common route in conventional PTC

Blood-vessel invasion is less frequent

- Conventional PTC preferentially involves lymphatic channels.
- Blood-vessel invasion is uncommon, particularly in smaller tumors.
- The route of invasion predicts the usual pattern of dissemination.

Regional cervical nodal metastasis is common

- Adjacent cervical nodes may harbor metastatic tumor.
- Nodal involvement in up to one-half of cases.
- A palpable node may be the first sign of the primary carcinoma.



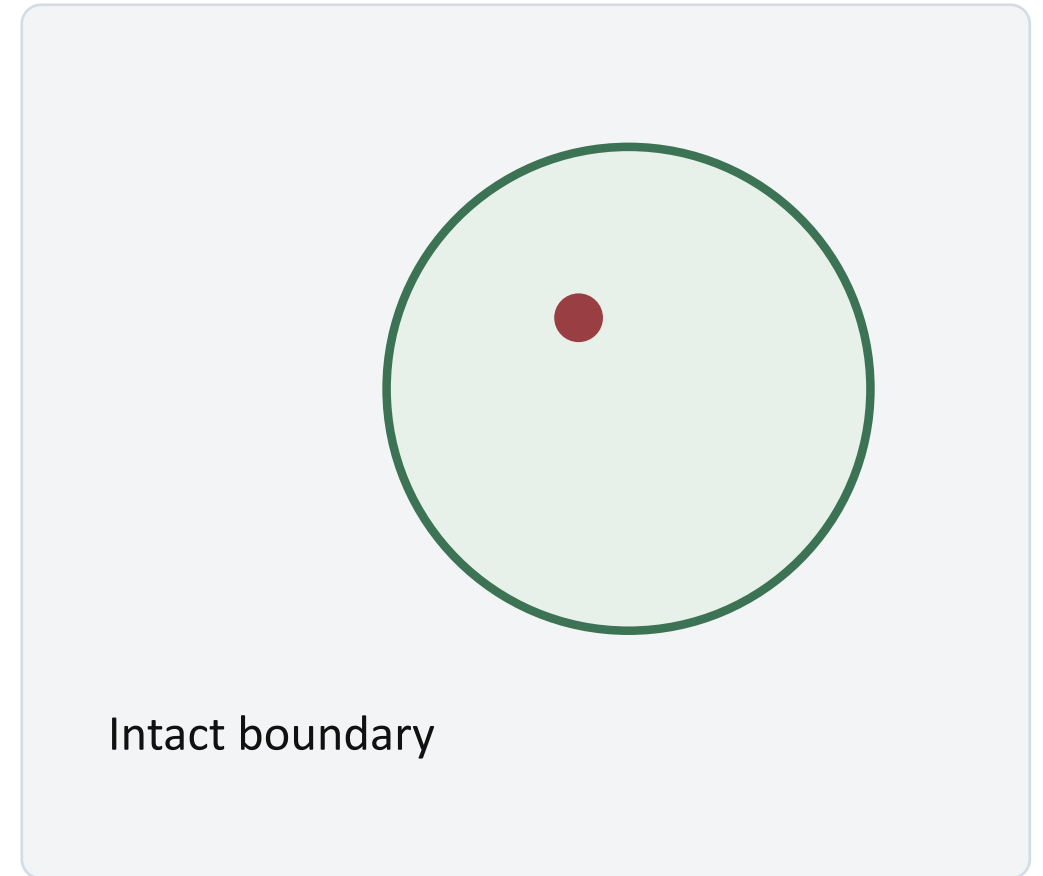
Common route in conventional PTC

PTC versus follicular carcinoma: Spread

Feature	Papillary carcinoma	Follicular carcinoma
Preferred route	Lymphatic	Hematogenous
Regional nodes	Often involved	Uncommon
Blood vessels	Less common in small PTC	Important diagnostic feature
Distant spread	May occur	Characteristic when invasive

Follicular growth does not exclude papillary-type nuclei

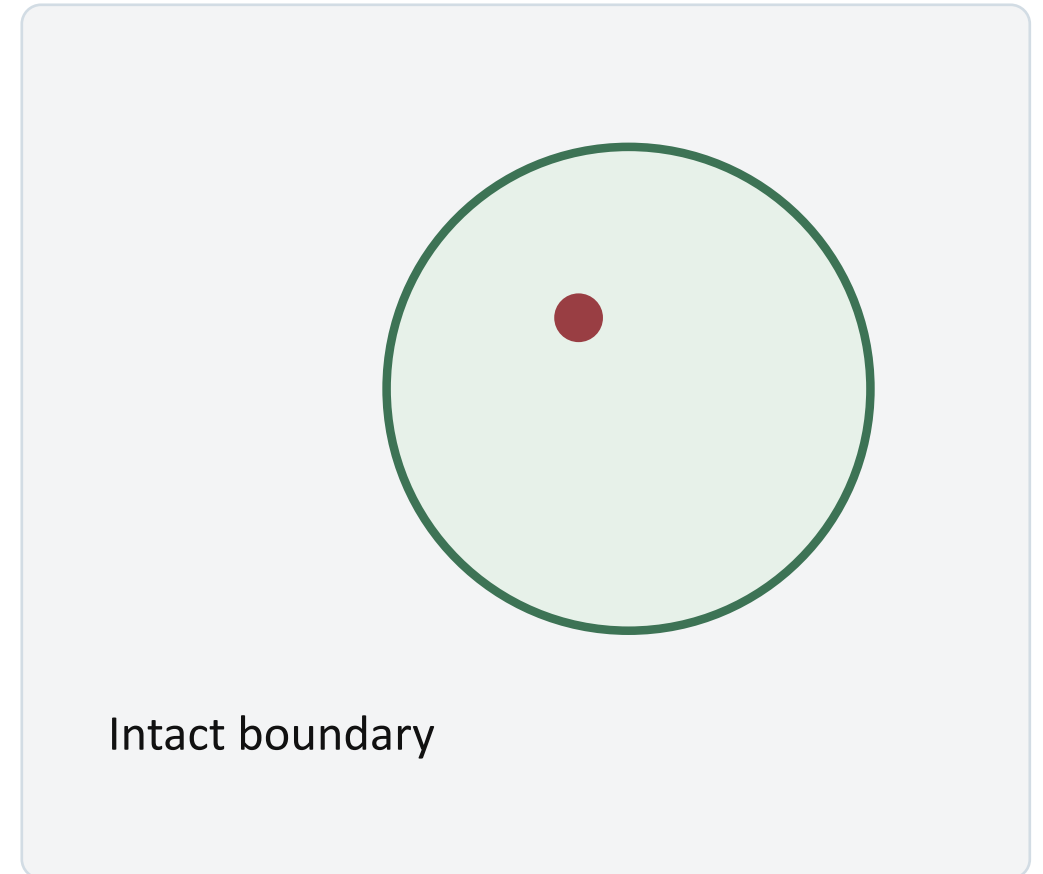
- Some encapsulated lesions show an entirely follicular pattern.
- Their nuclei nevertheless resemble those of PTC.
- Invasion determines whether some lesions belong to an invasive category.



Encapsulated noninvasive pattern — schematic

NIFTP is noninvasive by definition

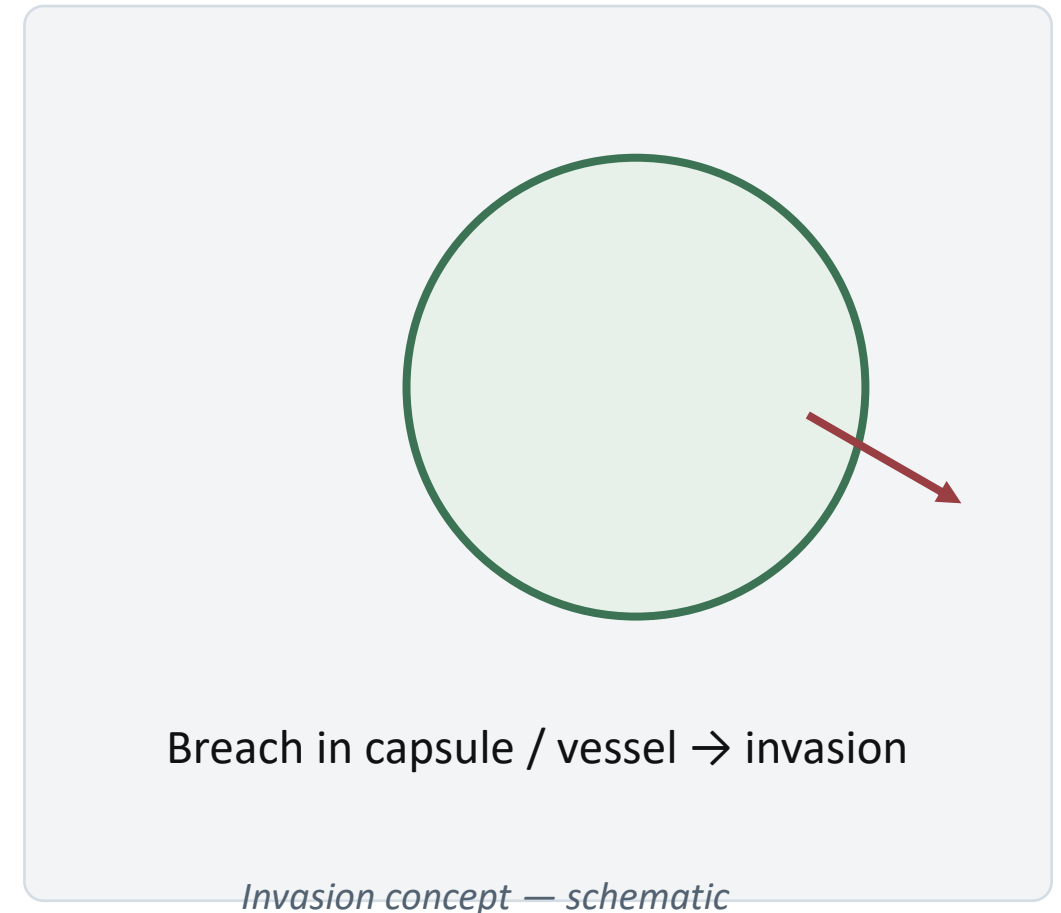
- Noninvasive follicular thyroid neoplasm with papillary-like nuclear features.
- Strict criteria are required for this designation.
- The source describes essentially absent recurrence or metastatic risk in correctly defined lesions.



Encapsulated noninvasive pattern — schematic

Invasive encapsulated FV-PTC breaches boundaries

- Capsular, vascular or intrathyroidal invasion indicates invasive disease.
- This category differs from NIFTP despite similar papillary-type nuclei.
- Invasive follicular-patterned tumors may disseminate hematogenously.



Follicular-patterned tumors: Boundary assessment

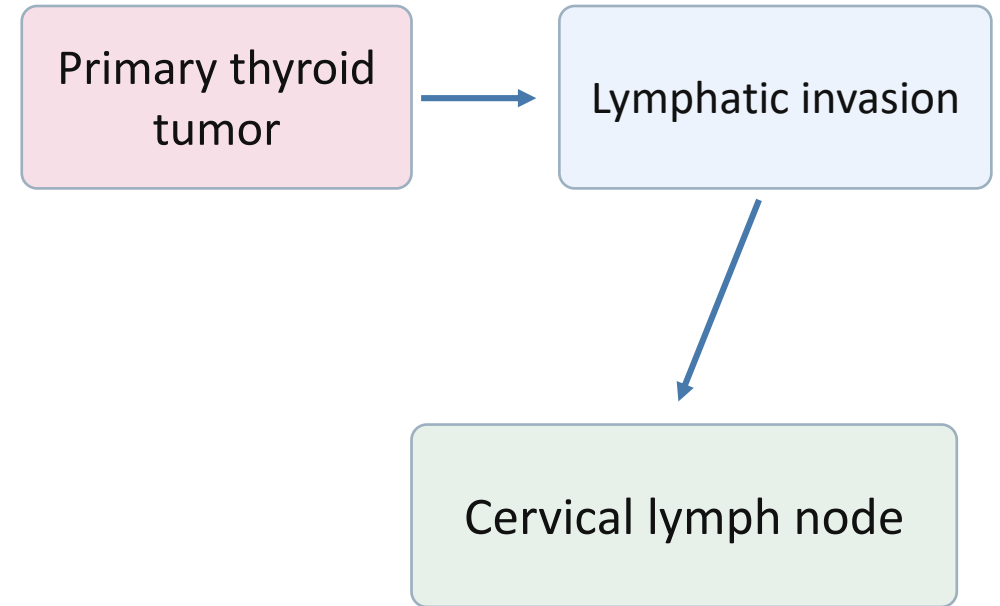
Entity	Nuclear appearance	Invasion
Follicular adenoma	Lacks PTC-type nuclei	Absent
NIFTP	PTC-like nuclear changes	Absent; strict criteria apply
Invasive encapsulated FV-PTC	PTC-like nuclear changes	Capsular / vascular / intrathyroidal
Follicular carcinoma	Lacks classic PTC-type nuclei	Capsular and/or vascular

Most patients present with a thyroid nodule

- Conventional PTC is often asymptomatic at discovery.
- The lesion may be found during examination or neck imaging.
- Clinical palpation alone cannot reliably label the nodule benign or malignant.

A cervical lymph node can be the first clue

- PTC sometimes declares itself through regional lymph node enlargement.
- The thyroid primary may be clinically inconspicuous.
- Node pathology must be interpreted alongside thyroid examination.



Common route in conventional PTC

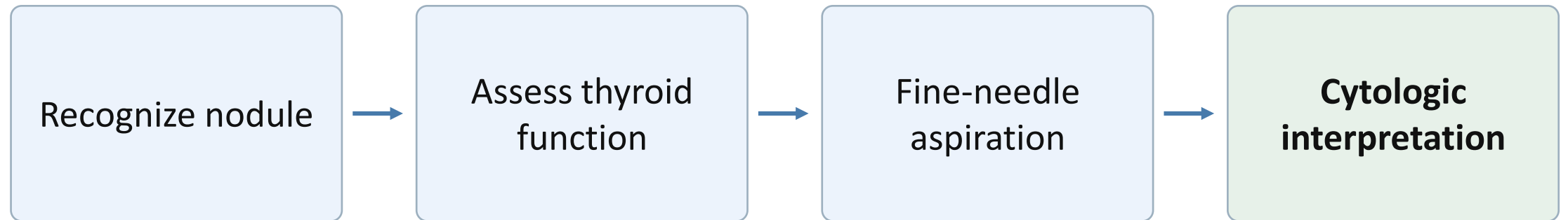
Movement with swallowing is not a benign sign

- Many PTC nodules move with the thyroid during deglutition.
- This finding establishes thyroid attachment rather than histologic behavior.
- Benign and malignant nodules may be indistinguishable clinically.

Compressive symptoms raise concern for advanced disease

- Hoarseness may signal involvement of nearby vocal structures.
- Dysphagia suggests disturbance of swallowing structures.
- Cough or dyspnea can occur in locally advanced neck disease.

Nodule assessment combines function and morphology

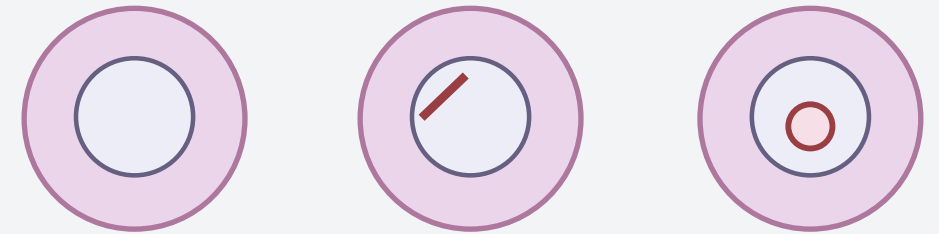


Scintigraphy is generally reserved for low TSH; Structural and cytologic findings carry the malignant/benign assessment.

Conceptual mechanism — editable schematic

Fine-needle aspiration evaluates cell morphology

- FNA is a major tool to separate benign from malignant thyroid nodules.
- Papillary cellular arrangements can appear in aspirates.
- Nuclear clearing, grooves and pseudoinclusions guide interpretation.



Clearing • groove • pseudoinclusion

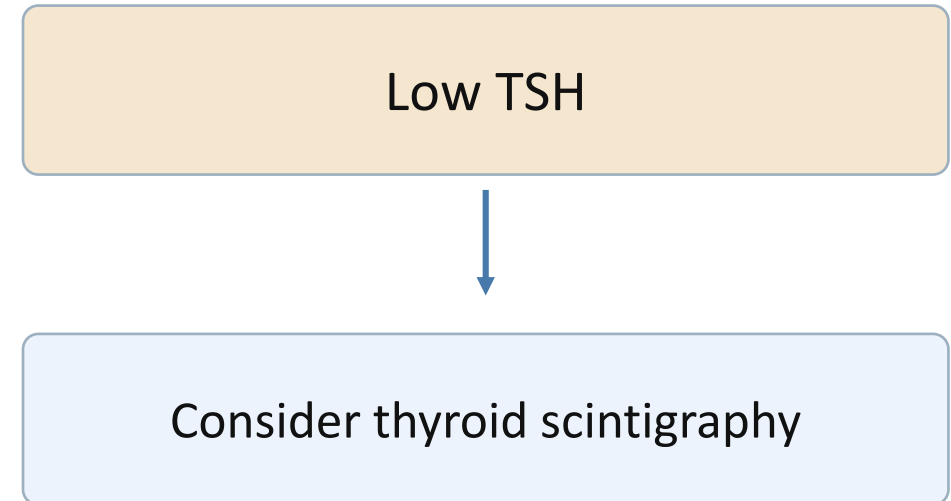
Schematic cell nuclei — not histology

Fine-needle aspirates can reveal stromal clues

- Psammoma bodies support the diagnosis of PTC.
- Papillary fragments may accompany the nuclear features.
- Sampling variation makes pattern recognition more reliable than a single clue.

TSH determines whether scintigraphy is informative

- The source generally reserves scintigraphy for a low TSH concentration.
- Functioning “hot” nodules produce excess thyroid hormone.
- PTCs are usually nonfunctioning (“cold”) lesions.



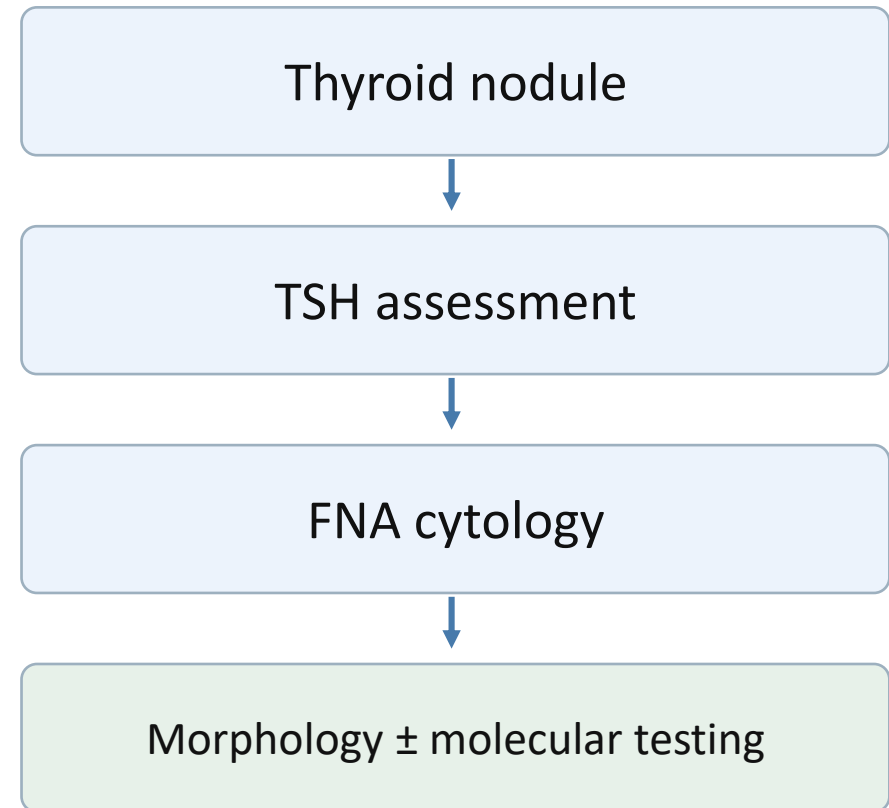
Source-based diagnostic principle, not full algorithm

Cold versus hot nodules

Scintigraphic finding	Interpretation	Malignancy implication
Cold	Reduced tracer uptake	PTC usually appears cold
Hot	Excess thyroid hormone production	Hot nodules are almost never malignant

Molecular testing complements indeterminate cytology

- Not every aspiration is unequivocally benign or malignant.
- Ancillary molecular diagnostics can help resolve indeterminate cases.
- Results must be integrated with cytology, not viewed in isolation.



Simplified diagnostic elements, not a complete guideline

Clinical decisions should integrate multiple domains

- Clinical symptoms and examination define immediate concerns.
- TSH/scintigraphy provide functional context when relevant.
- FNA supplies morphologic evidence; Molecular assays may clarify ambiguity.
- Extent and recurrence risk inform treatment selection.

The overall prognosis of PTC is excellent

- 10-year survival exceeding 95%.
- Excellent disease-specific outcomes coexist with frequent nodal spread.
- Prognosis is heterogeneous and depends on stage and other risk factors.

Recurrence is distinct from disease-specific survival

- Local or regional recurrence occurs in approximately 5%–20% in the source.
- A patient may experience recurrence despite an excellent long-term survival outlook.
- Risk-based follow-up is therefore clinically meaningful.

Distant metastases are less frequent but important

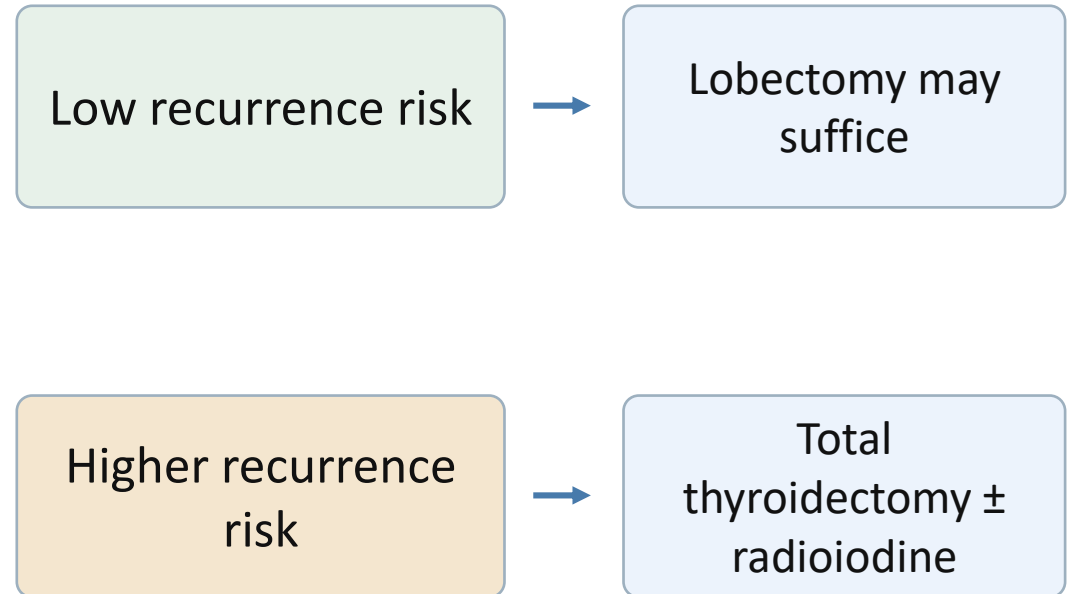
- Distant metastatic disease in 10%–15% of patients.
- Distant spread contributes importantly to stage and prognosis.
- The lungs are a recognized distant metastatic site in thyroid carcinoma.

Prognostic variables emphasized by Robbins

Factor	Direction of concern	Reason for importance
Age older than 55 years	Less favorable prognosis	Patient-level risk context
Extrathyroidal extension	Adverse	Local anatomical spread
Distant metastases	Adverse	Advanced stage / systemic disease
Recurrence-risk profile	Guides management intensity	Selection of surgery ± radioiodine

Recurrence risk drives treatment intensity

- Some favorable-risk tumors have excellent outcomes after lobectomy alone.
- Higher-risk cases may require total thyroidectomy followed by radioiodine.
- Surgery must balance oncologic control against endocrine and nerve injury.



Conceptual risk-adapted strategy; Not a guideline algorithm

Thyroid-sparing surgery has functional benefits

- Preserving thyroid tissue may preserve endogenous hormone production.
- Less extensive surgery may lower some treatment-associated harms.
- Recurrent laryngeal nerve injury can produce vocal cord palsy.

Radioiodine is selected according to recurrence risk

- Radioiodine ablation following total thyroidectomy in higher-risk PTC.
- It is not presented as mandatory for all PTCs.
- Treatment choices require individual risk assessment beyond morphology alone.

Papillary versus medullary thyroid carcinoma

Feature	Papillary carcinoma	Medullary carcinoma
Cell of origin	Follicular epithelium	Parafollicular C cell
Microscopic hallmark	PTC-type nuclei $\pm$ papillae	Neuroendocrine cells; stromal amyloid
Typical molecular change	BRAF V600E; kinase fusions	RET activating point mutations
Serum marker	Thyroglobulin in post-thyroidectomy context	Calcitonin; CEA

Conventional PTC versus aggressive thyroid cancers

Dimension	Conventional PTC	High-grade / anaplastic
Differentiation	Usually well differentiated	High-grade or undifferentiated
Architecture	Papillae; defining nuclei	Necrosis / mitoses; solid or pleomorphic
Molecular setting	BRAF and kinase fusions	Additional TP53 / TERT promoter hits
Clinical course	Frequently favorable	Greater aggressiveness

Clinical reasoning exercise: A cervical node

A hypothetical 37-year-old has a painless thyroid nodule and an enlarged ipsilateral cervical lymph node. Cytology from the thyroid shows crowded pale nuclei with grooves and pseudoinclusions.

Interpretation task

- Which thyroid neoplasm is most likely?
- Which dissemination route best explains the cervical node?

Interpretation: Nuclear phenotype plus lymphatic spread

- Papillary thyroid carcinoma is favored by the combined nuclear features.
- Lymphatic dissemination provides a coherent explanation for cervical nodal disease.
- Neither the nodule's mobility nor nodal involvement alone establishes prognosis.

Clinical reasoning exercise: Follicular pattern

A hypothetical encapsulated follicular-patterned thyroid lesion has enlarged pale nuclei with grooves. Extensive histologic sampling shows no capsular, vascular or intrathyroidal invasion.

Interpretation task

- Why does conventional papillary architecture not apply?
- Which noninvasive category should be considered if strict criteria are satisfied?

Interpretation: Distinguish noninvasive follicular tumors

- PTC-type nuclei can occur in an entirely follicular growth pattern.
- If strict requirements are met, the noninvasive lesion is designated NIFTP.
- Capsular, vascular or intrathyroidal invasion instead supports invasive encapsulated FV-PTC.

Integrative pathology summary

- Conventional PTC is defined by papillary architecture and a distinctive nuclear phenotype.
- BRAF V600E and kinase fusions converge on oncogenic growth signaling.
- Lymphatic dissemination and cervical nodal disease are common.
- Excellent overall prognosis requires stage- and risk-aware interpretation.

Primary reading and source scope

Core textbook

Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026).

Chapter 24, The Endocrine System — Thyroid carcinomas and Papillary carcinoma.

Main lesion: printed pages 989–990. Molecular parent context and adjacent differential material: pages 988–992.

Illustrations throughout this lecture are native-editable conceptual schematics, not diagnostic photomicrographs.