

High Grade Differentiated, Poorly Differentiated, and Anaplastic (Undifferentiated) Carcinoma

Aggressive follicular-cell–derived thyroid malignancies

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Distinguish high grade differentiated, poorly differentiated, and anaplastic thyroid carcinoma.
- Explain progression from papillary or follicular carcinoma and the additional genetic alterations.
- Connect architecture and cellular morphology with the degree of differentiation.
- Relate the distinct clinical presentations to invasion, dissemination, and prognosis.

A small group with disproportionate lethality

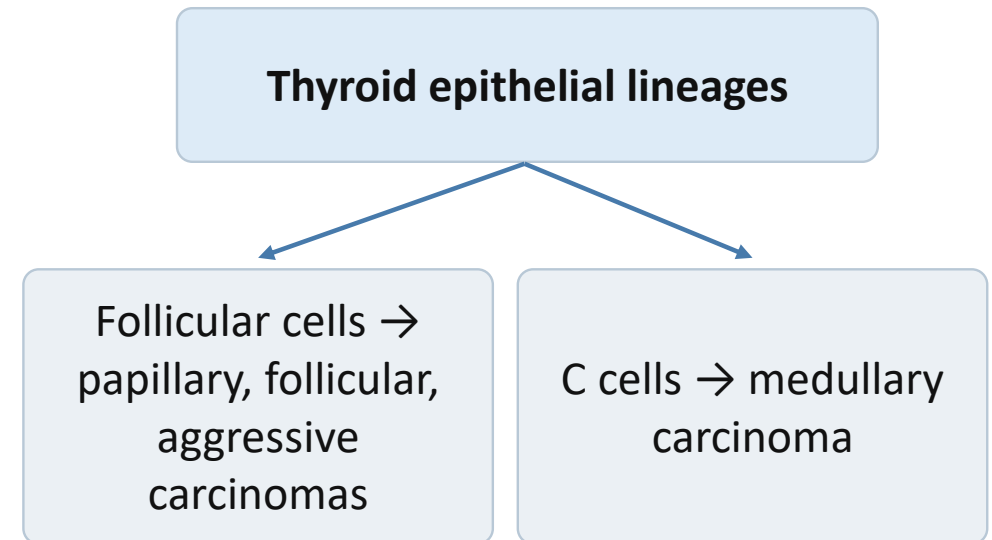
- These aggressive cancers arise from the follicular epithelium of the thyroid.
- High grade differentiated, poorly differentiated, and anaplastic lesions together account for fewer than 5% of thyroid tumors.
- The anaplastic subset has an exceptionally high mortality burden despite its rarity.

<5% of thyroid tumors: Combined aggressive group

Anaplastic carcinoma: Mortality approaching 100%

Follicular-cell origin defines the disease family

- The cell of origin links these tumors to papillary and follicular thyroid carcinomas.
- Loss of recognizable follicular differentiation is most profound in anaplastic carcinoma.
- Medullary carcinoma arises instead from parafollicular C cells and belongs to a separate lineage.



Three entities: Do not collapse them into one

- High grade differentiated carcinoma retains thyroid tumor differentiation but develops aggressive histologic features.
- Poorly differentiated carcinoma has characteristic solid, insular, or trabecular architecture.
- Anaplastic carcinoma no longer resembles thyroid follicular epithelium.

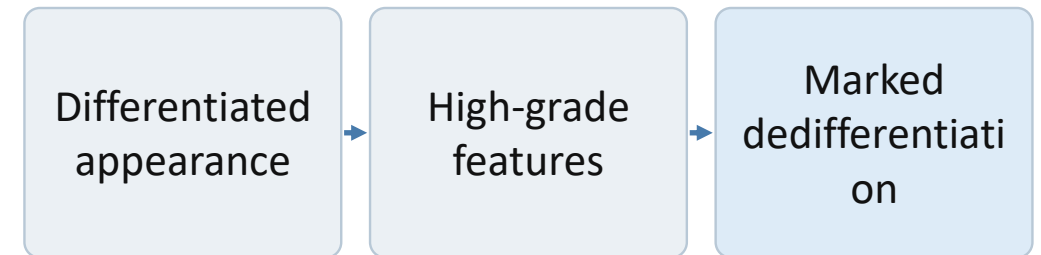
High grade differentiated

Poorly differentiated

Anaplastic / undifferentiated

Differentiation and aggressiveness are different axes

- Mitotic activity and tumor necrosis identify high-grade behavior in the first two categories.
- Architectural growth pattern helps recognize poorly differentiated carcinoma.
- Complete loss of follicular-cell resemblance characterizes anaplastic carcinoma.



Conceptual relationship; Not a mandatory linear sequence

Clinical age distribution

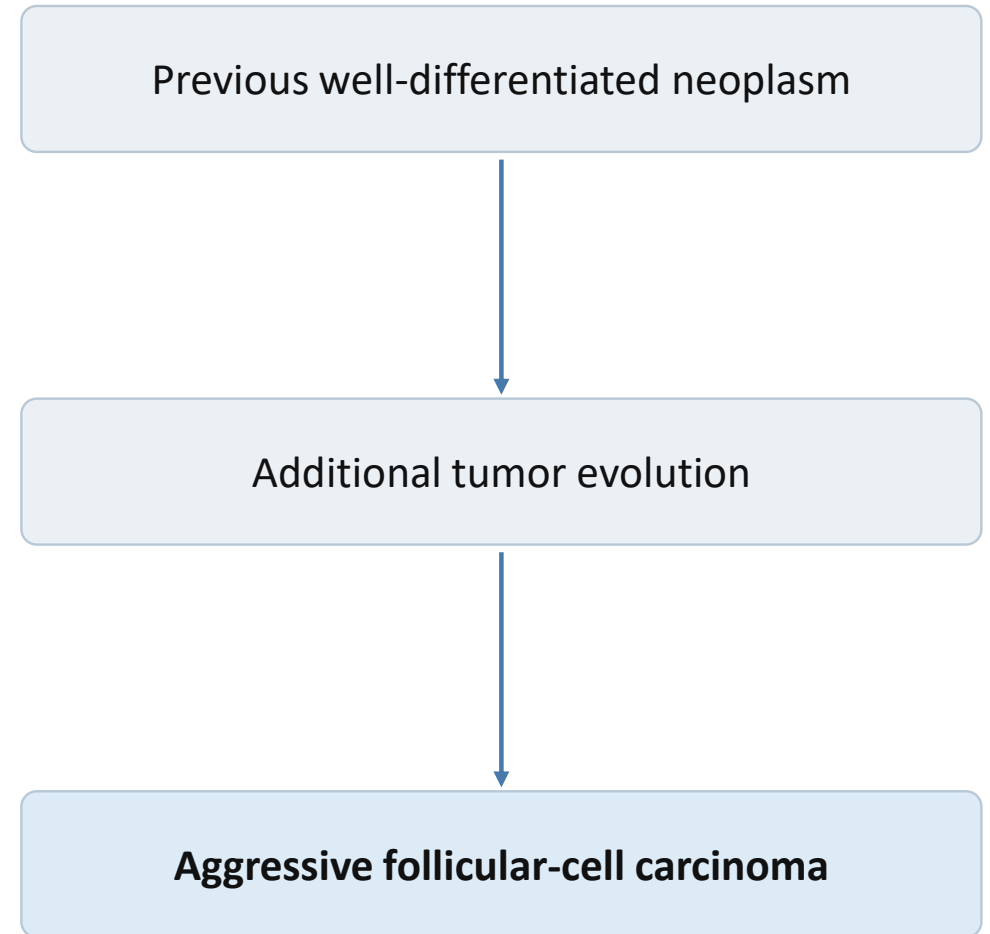
- Patients are generally older than those with other forms of thyroid cancer.
- The cited Robbins mean age for the aggressive group is approximately 65 years.
- Older age provides context but is not sufficient for histologic classification.

Mean age ≈65 years

Diagnosis remains morphology-dependent

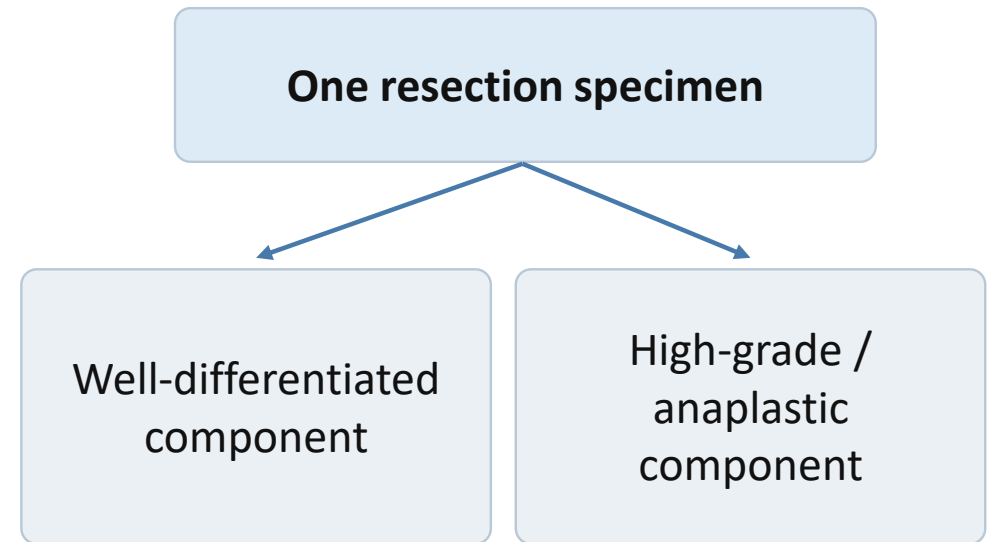
Pre-existing differentiated thyroid tumors

- Approximately one-quarter have a history of a well-differentiated follicular neoplasm.
- This historical association supports progression in a subset of patients.
- Absence of a documented earlier tumor does not establish de novo origin.



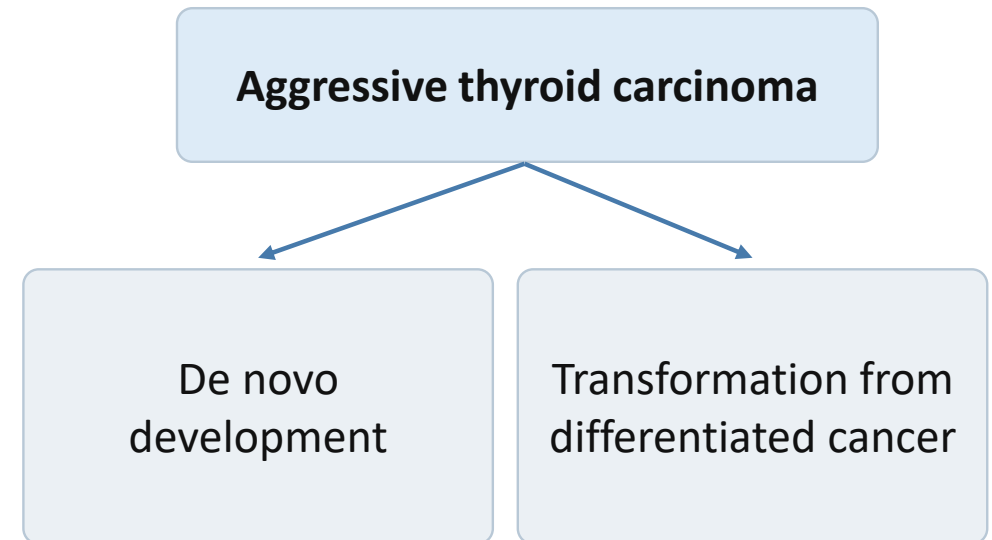
A concurrent differentiated component is a clue

- About one-quarter have a concurrent well-differentiated tumor in the resection specimen.
- Papillary or follicular carcinoma foci can coexist with anaplastic morphology.
- Such coexistence supports a possible shared neoplastic origin.



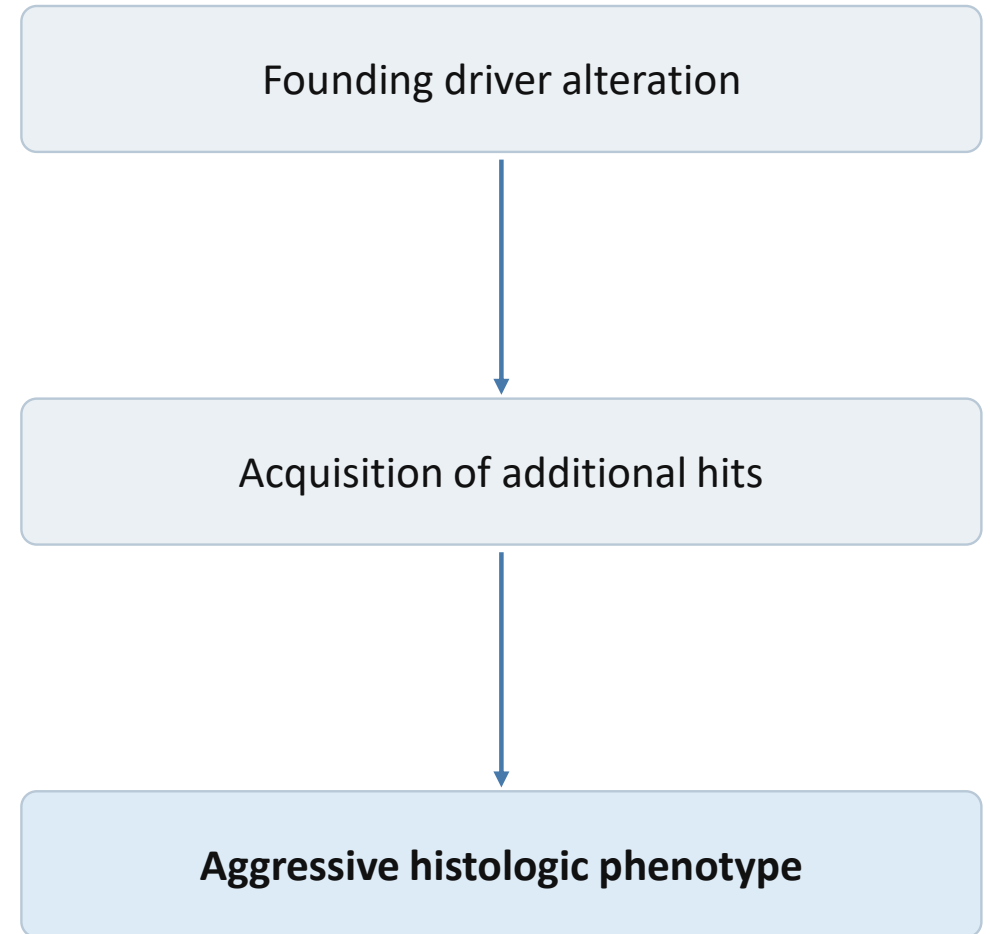
De novo and progression pathways

- Aggressive carcinomas may arise de novo.
- Transformation of pre-existing papillary or follicular carcinoma as the more common pathway.
- Different routes can converge on morphologically aggressive tumors.



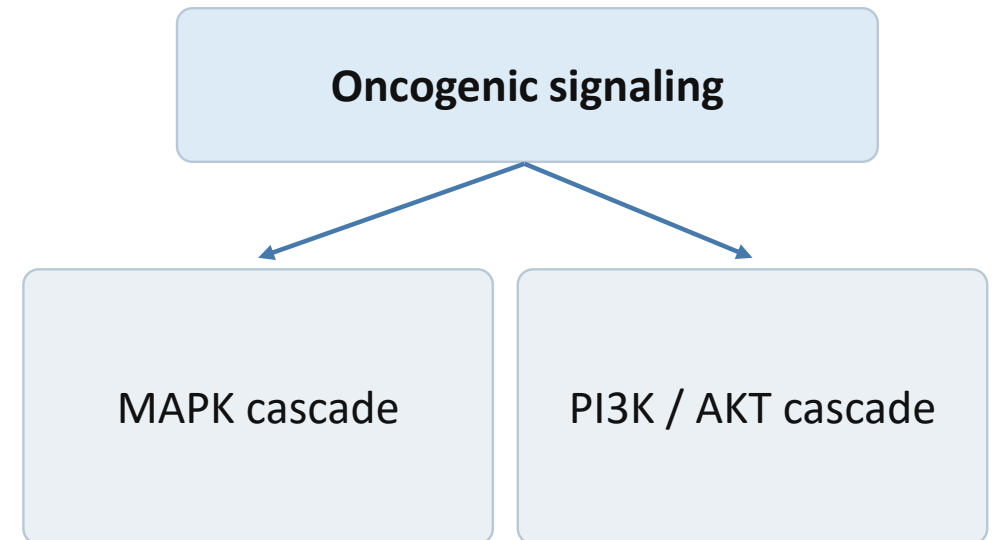
Genetic progression: A two-layer model

- Underlying papillary or follicular carcinoma drivers may persist during progression.
- Additional molecular alterations are associated with aggressive evolution.
- Histologic dedifferentiation does not necessarily remove the original oncogenic driver.



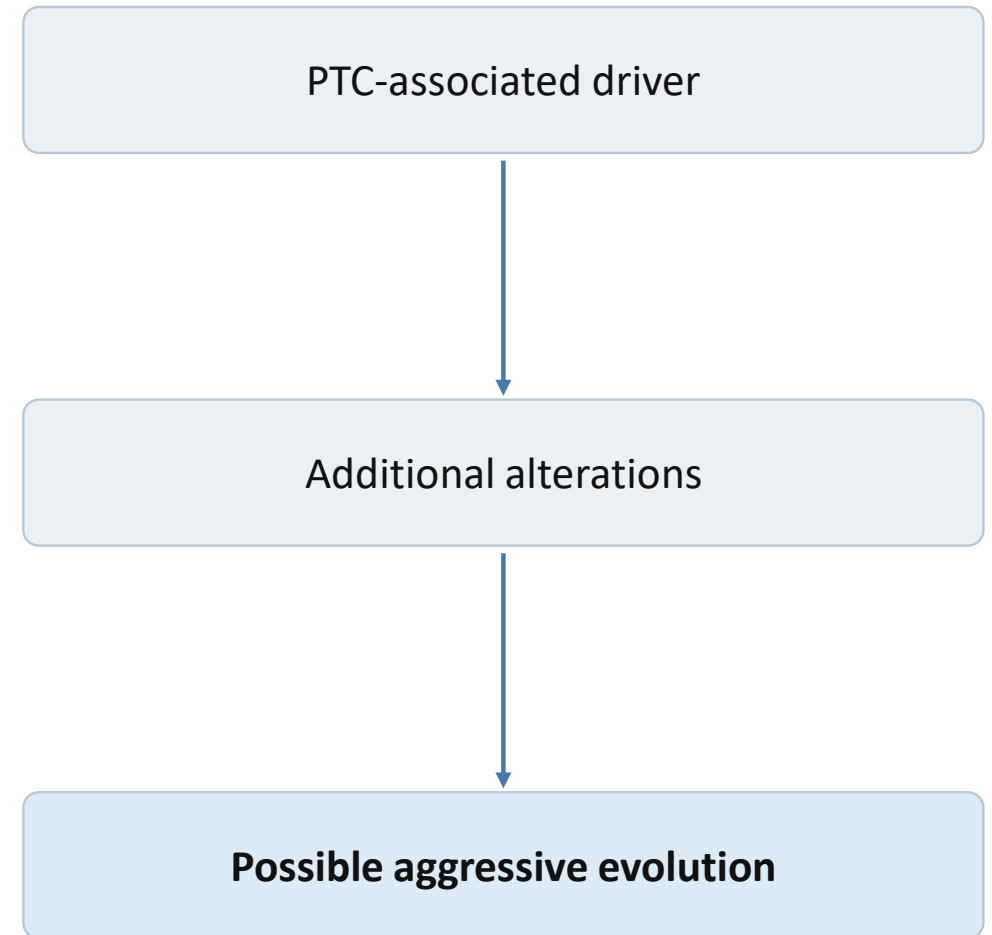
Follicular-cell neoplasms share signaling networks

- Receptor tyrosine kinase–linked signaling in thyroid follicular-cell cancers.
- MAP kinase and PI3K/AKT pathways are prominent molecular systems.
- Different upstream events can converge on increased cell growth and proliferation.



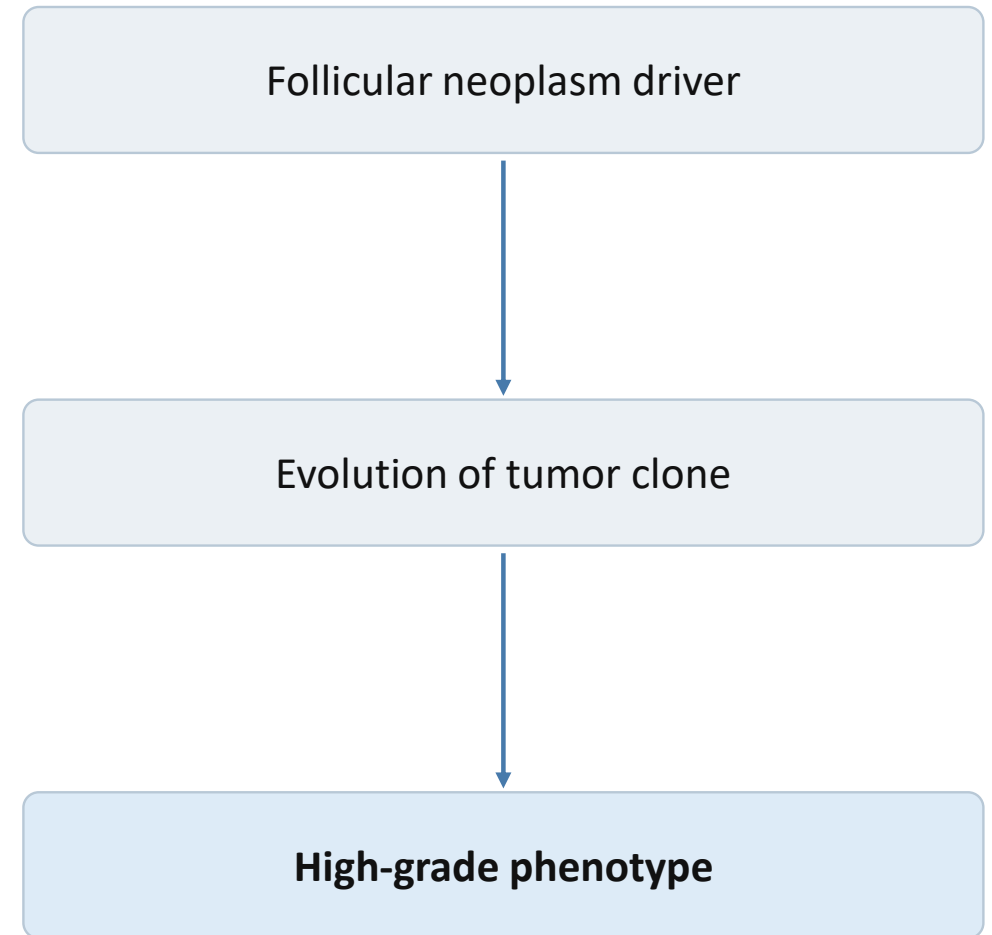
Papillary carcinoma provides a molecular background

- Conventional papillary carcinoma commonly harbors activating BRAF alterations or kinase gene fusions.
- The source names RET, NTRK, and BRAF fusions among PTC-associated alterations.
- Aggressive tumors arising from PTC may retain an earlier driver event.



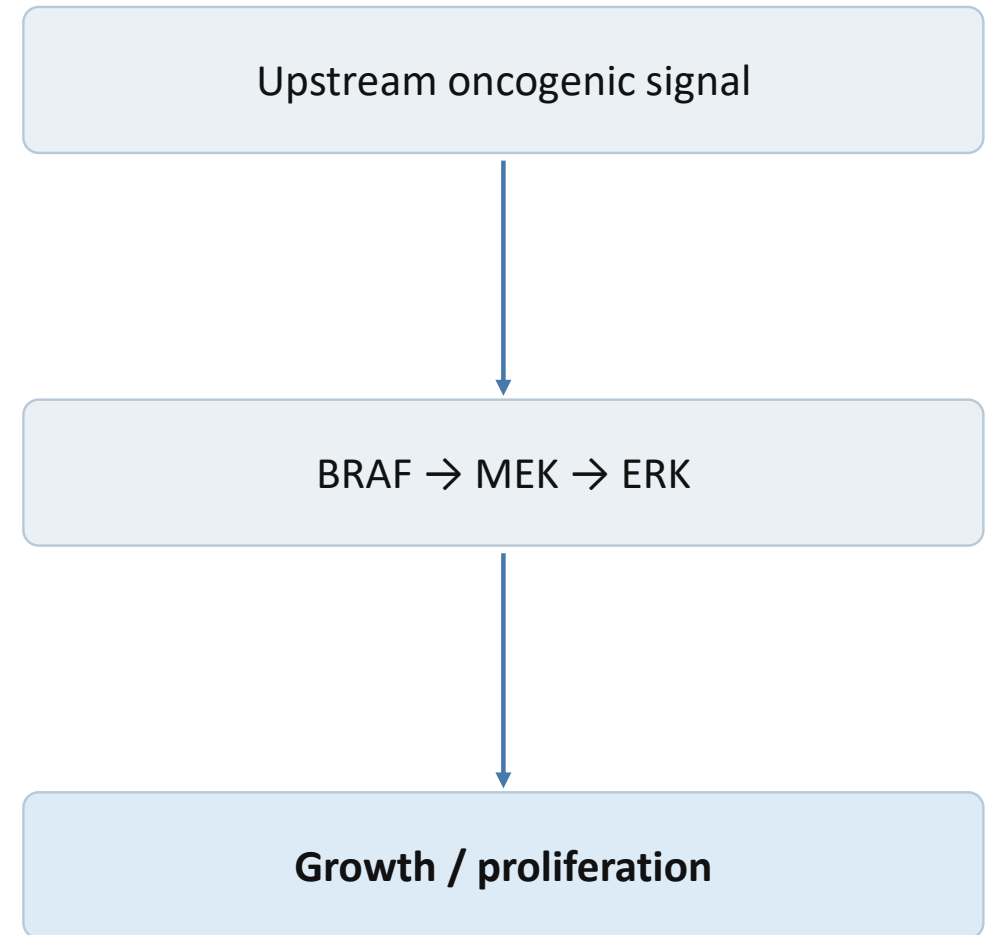
Follicular carcinoma provides another background

- Follicular neoplasms are often associated with activating RAS mutations.
- Robbins also describes PAX8::PPARG fusion and PI3K pathway abnormalities in subsets.
- A progression-associated carcinoma may retain genetic features of its follicular precursor.



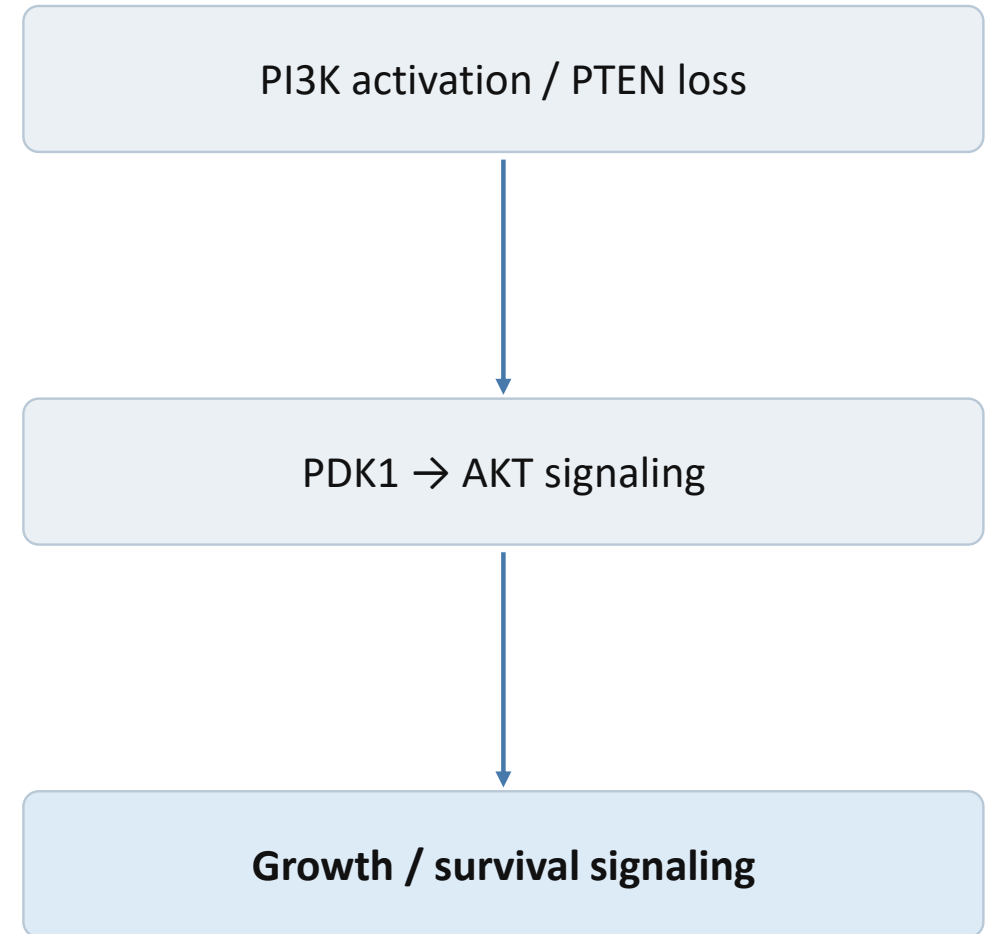
MAPK signaling: Conceptual sequence

- Receptor and RAS-related signals can activate downstream BRAF, MEK, and ERK.
- Activation of the pathway promotes growth-related cellular programs.
- This is a general follicular-cell cancer context—not a subtype-specific diagnostic test.



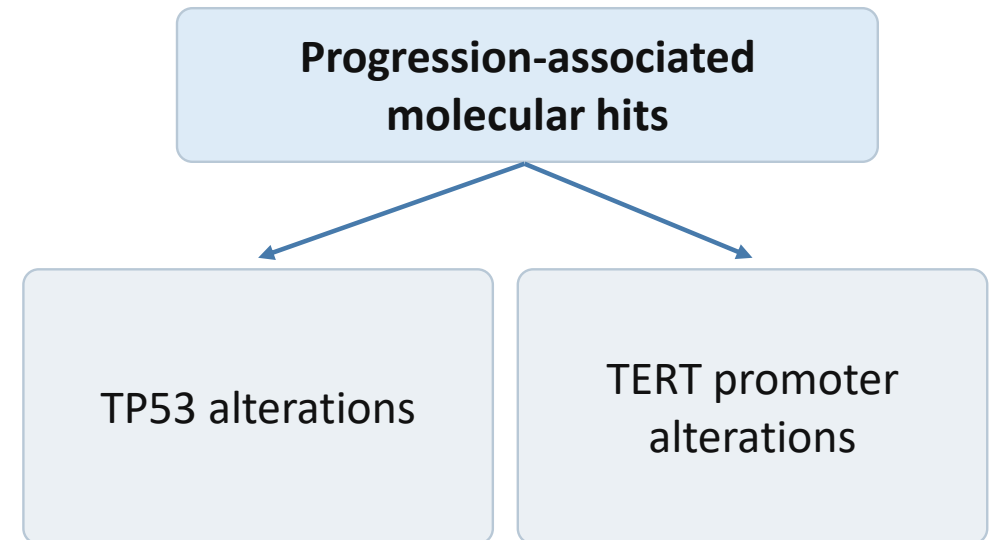
PI3K/AKT signaling in the parent context

- Robbins maps PI3K, PDK1, and AKT within a growth-signaling pathway.
- PIK3CA activation or PTEN loss is described in subsets of follicular carcinomas.
- These alterations are relevant to precursor biology rather than a unique hallmark of anaplastic carcinoma.



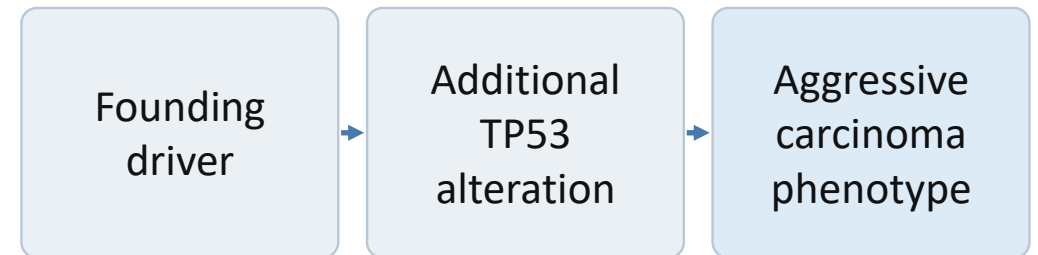
Additional hits distinguish aggressive tumors

- Robbins particularly highlights TP53 mutation and TERT promoter mutation.
- These are strongly associated with the aggressive follicular-cell carcinoma group.
- The text proposes important roles in pathogenesis and biologic behavior; It does not make either alteration obligatory.



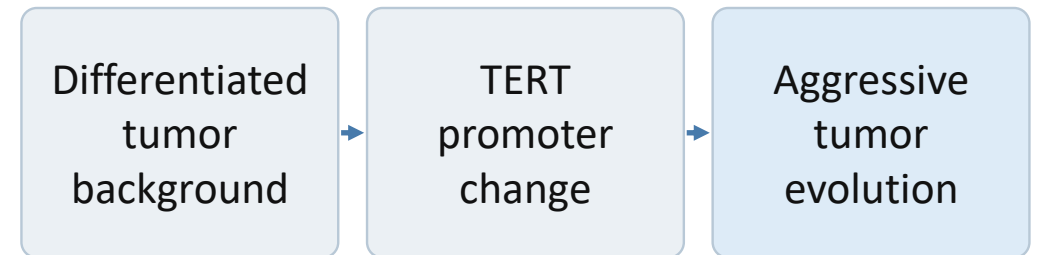
TP53 alteration in tumor progression

- TP53 mutations are emphasized as common additional events in aggressive lesions.
- Their association supports a multistep model of thyroid carcinoma progression.
- A TP53 mutation alone should not replace morphological diagnosis.



TERT promoter alteration in aggressive disease

- TERT encodes the catalytic component of telomerase.
- Promoter-region mutations are emphasized in high-grade, poorly differentiated, and anaplastic carcinomas.
- The source frames this as a progression-associated genetic event, not a standalone classifier.



Genotype can persist as phenotype is lost

- Anaplastic cells often lose thyroid follicular differentiation markers.
- The same tumor may retain driver mutations acquired before dedifferentiation.
- Driver persistence and phenotypic loss are complementary observations, not contradictory findings.

What molecular findings do not establish

- Neither BRAF/RAS background nor progression-associated TP53/TERT status substitutes for histology.
- The supplied Robbins excerpt does not specify a molecular-only diagnostic algorithm.
- Do not infer an exact progression chronology for every individual tumor.

Separate evidence types

Molecular context $\neq$ morphology

Association $\neq$ required event

Histologic assessment begins with two questions

- Does the tumor still retain recognizable thyroid follicular differentiation?
- Is tumor necrosis or increased mitotic activity present?
- What architecture or cytologic appearance supports a specific category?

Degree of differentiation



Necrosis / mitotic activity



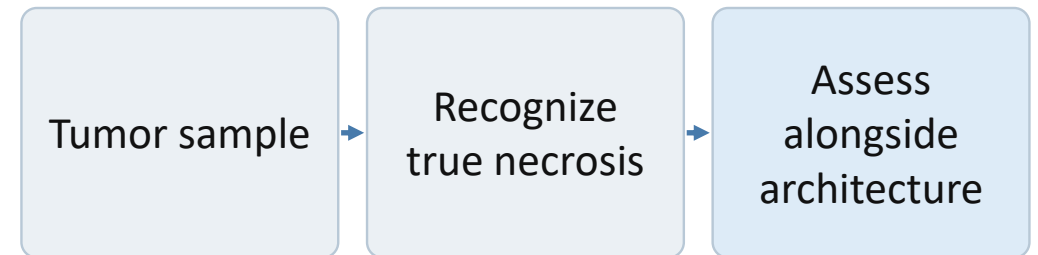
Architectural and cytologic pattern

High grade differentiated carcinoma

- This category retains recognizable differentiated carcinoma morphology.
- Its aggressive histology is linked to tumor necrosis or increased mitotic activity.
- The label “high grade” should not be mistaken for complete loss of differentiation.

Tumor necrosis as an adverse histologic signal

- Necrosis as a feature of high grade differentiated and poorly differentiated carcinomas.
- Necrosis must be interpreted in an actual tissue context rather than inferred from a clinical mass.
- The source excerpt does not provide a quantitative necrosis cutoff.



Increased mitotic activity

- Elevated mitotic activity is the other high-grade feature highlighted.
- Its interpretation requires examination of tumor cells in histologic sections.
- No numerical mitotic-count threshold is given in the supplied section; Do not insert one.

Histologic tumor evaluation



Increased mitotic activity



Aggressive morphologic category

Poorly differentiated carcinoma: Architectural signature

- Robbins specifies solid, insular (nested), and trabecular growth patterns.
- These architectural patterns help separate poorly differentiated tumors from retained differentiated forms.
- Necrosis or increased mitoses also contributes to their aggressive histology.

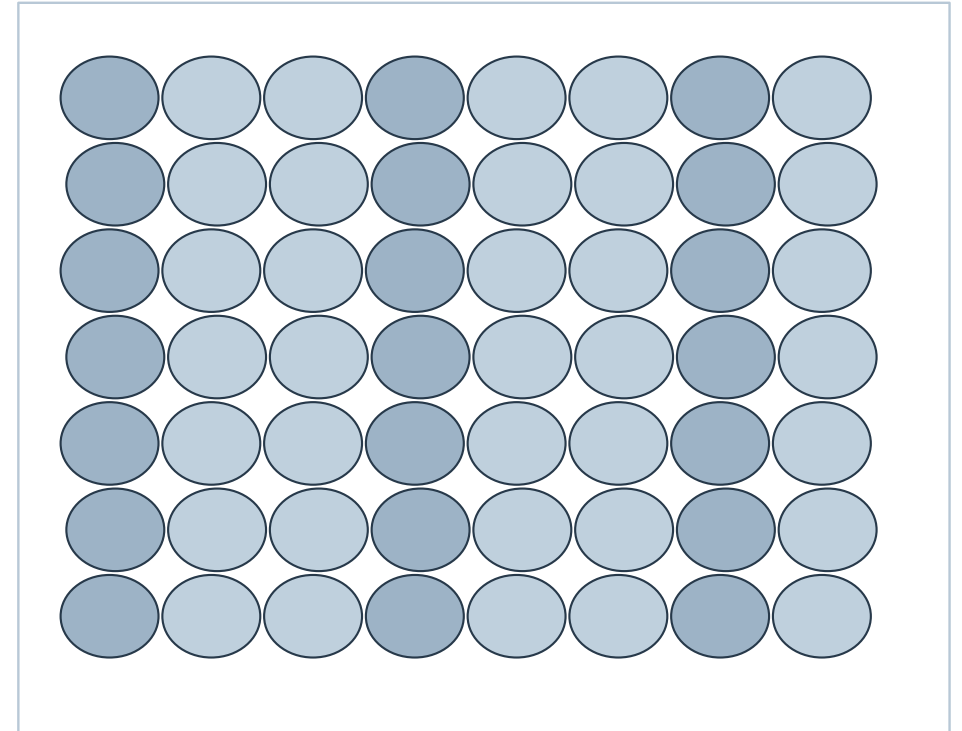
Solid sheets

Insular / nested groups

Trabecular cords

Solid growth pattern — schematic

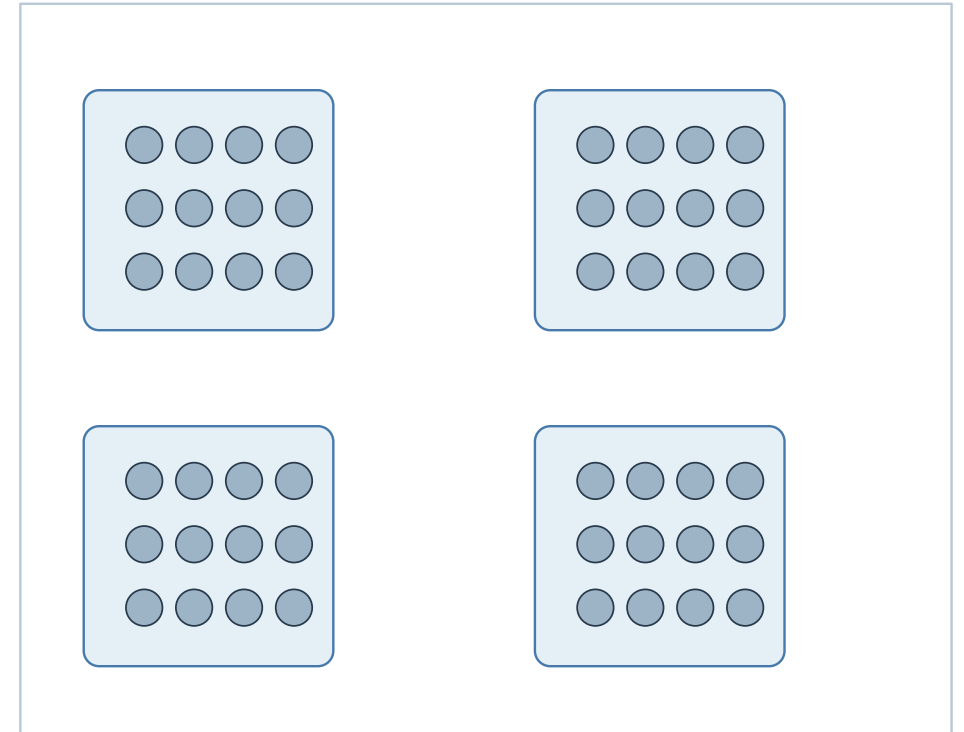
- Solid architecture consists of broadly confluent groups without a conspicuous follicular arrangement.
- Poorly differentiated carcinoma can show this pattern among its recognized architectures.
- This original drawing conveys arrangement only; It is not diagnostic microscopy.



Original schematic — not a histologic specimen

Insular growth pattern — schematic

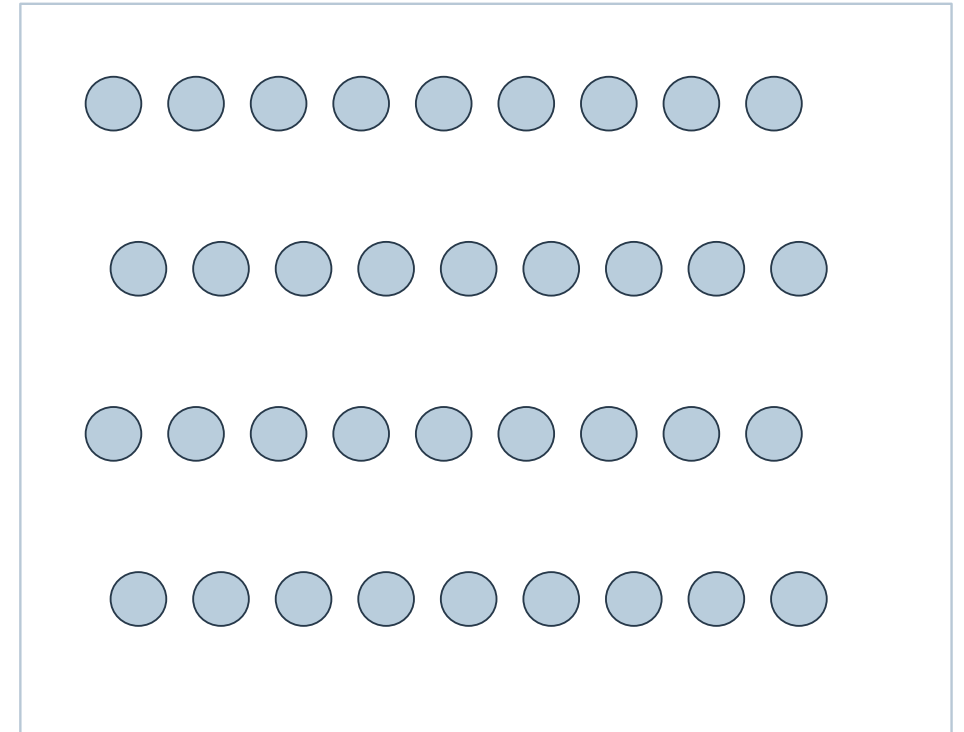
- An insular pattern organizes cells into nests or islands.
- Insular architecture is one of the growth patterns described for poorly differentiated carcinoma.
- A pattern alone is not presented here as a complete diagnostic criterion.



Original schematic — not a histologic specimen

Trabecular growth pattern — schematic

- Trabecular architecture produces elongated cords or bands of tumor cells.
- Robbins recognizes this as a pattern within poorly differentiated carcinoma.
- The actual tumor must be assessed for mitotic activity, necrosis, and overall differentiation.



Original schematic — not a histologic specimen

Integrating architecture and high-grade features

- Solid, insular, or trabecular architecture focuses attention on poorly differentiated carcinoma.
- Necrosis or increased mitotic activity establishes the high-grade component.
- This combination is more informative than using either architecture or cellular activity in isolation.

Recognize growth architecture



Assess necrosis / mitoses



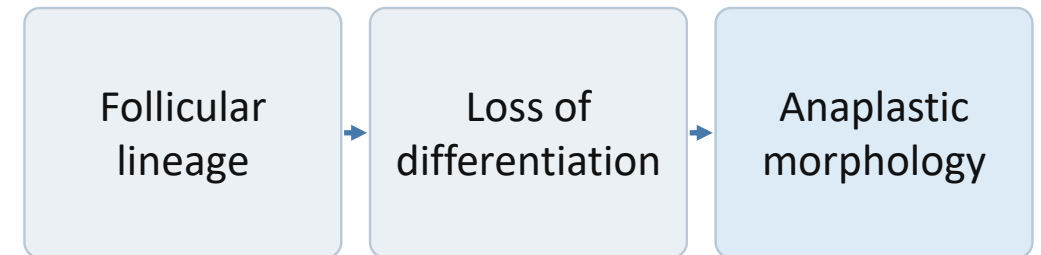
Integrate tumor category

High grade differentiated versus poorly differentiated

- High grade differentiated tumors retain a differentiated architectural identity.
- Poorly differentiated tumors are characterized by solid, insular, or trabecular arrangements.
- Both may show necrosis or increased mitotic activity.

Anaplastic carcinoma: Defining loss of resemblance

- Anaplastic carcinoma no longer resembles thyroid follicular epithelial cells.
- The microscopic appearance can vary markedly from one tumor to another.
- The absence of recognizable follicular architecture is fundamental to the textbook description.



Anaplastic carcinoma is morphologically heterogeneous

- Epithelioid, spindled, pleomorphic, and giant-cell-rich forms are described.
- Some epithelioid tumors resemble squamous cell carcinoma.
- Some spindled tumors resemble mesenchymal sarcoma.

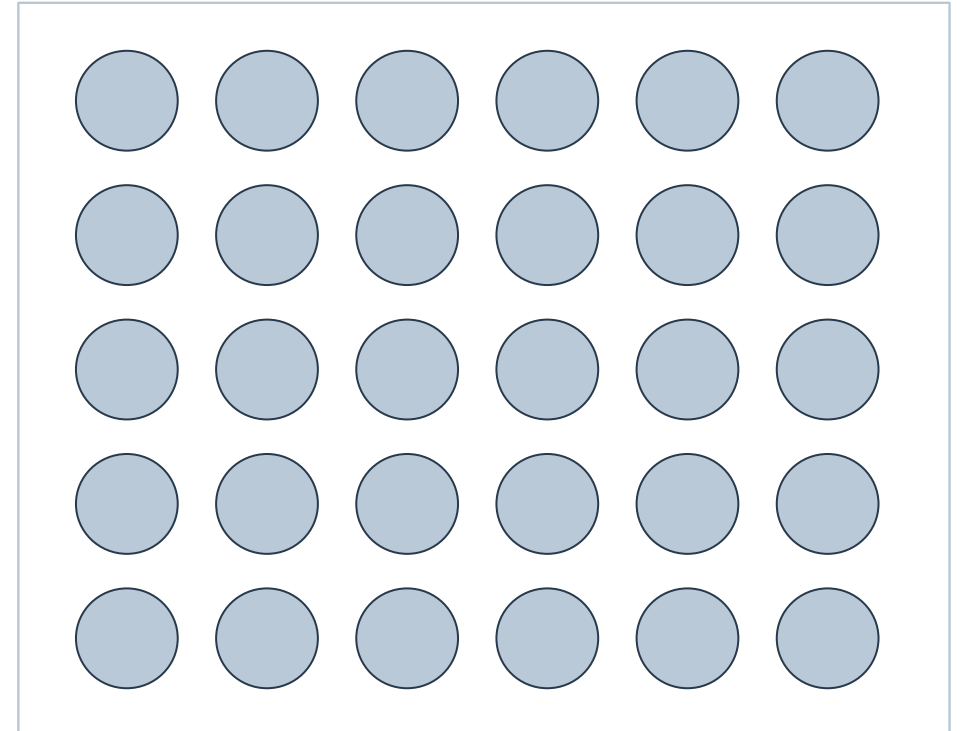
Epithelioid / squamoid

Spindled / sarcomatoid

Pleomorphic / giant cell-rich

Epithelioid anaplastic carcinoma — schematic

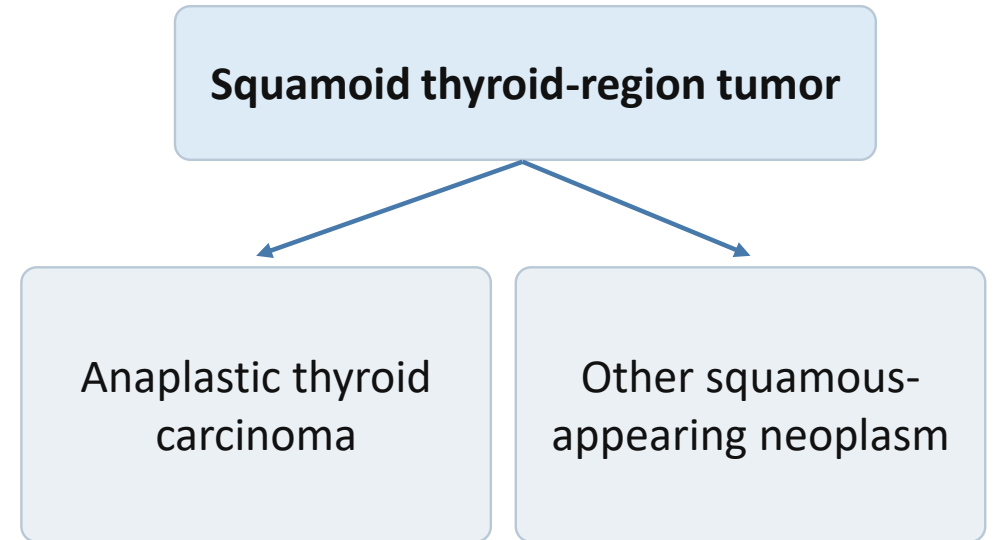
- Anaplastic tumors may show a prominent epithelioid cellular appearance.
- Histologic resemblance to other epithelial cancers can complicate recognition of thyroid origin.
- Clinical and specimen context remain essential when morphology is not thyroid-like.



Original schematic — not a histologic specimen

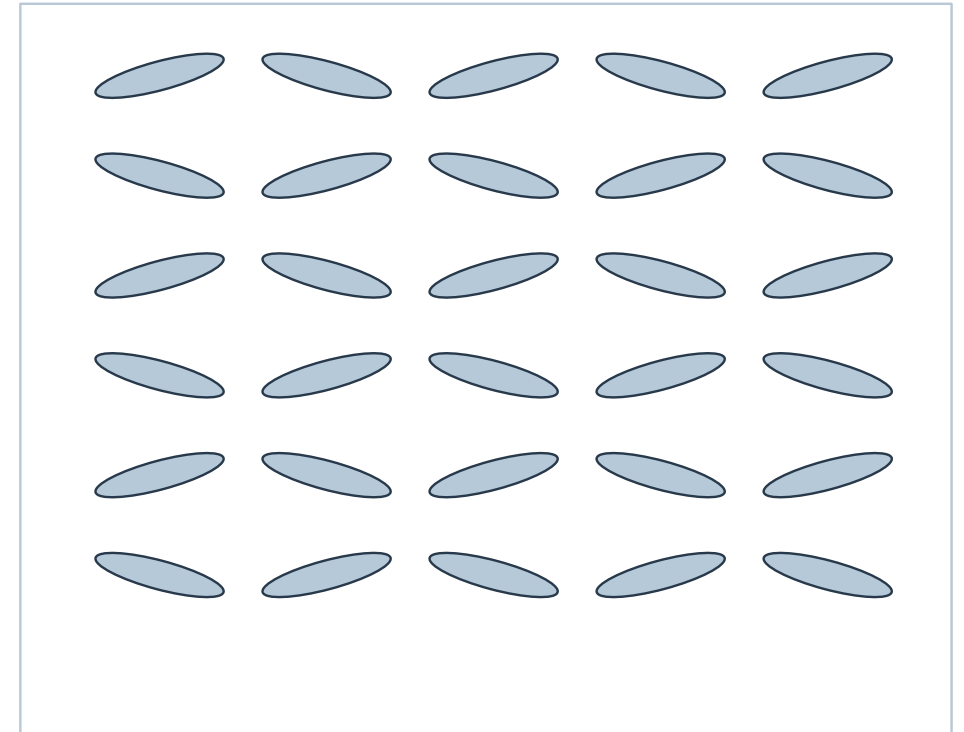
Squamous resemblance is a diagnostic trap

- Some epithelioid anaplastic carcinomas resemble squamous cell carcinoma.
- Resemblance on a section does not itself establish a separate squamous primary.
- Consider the anatomic setting and any accompanying differentiated thyroid carcinoma.



Spindled anaplastic carcinoma — schematic

- Spindled cells are included in the morphologic spectrum of anaplastic carcinoma.
- The arrangement may resemble sarcoma rather than a conventional thyroid carcinoma.
- Loss of familiar thyroid morphology does not imply non-epithelial origin.



Original schematic — not a histologic specimen

Sarcoma-like morphology: Why origin is difficult

- The spindle-cell pattern can mimic a sarcomatous malignancy.
- A coexisting thyroid-type carcinoma focus is useful evidence of tumor context.
- The excerpt emphasizes retained drivers despite loss of follicular differentiation markers.

Sarcoma-like cellular form



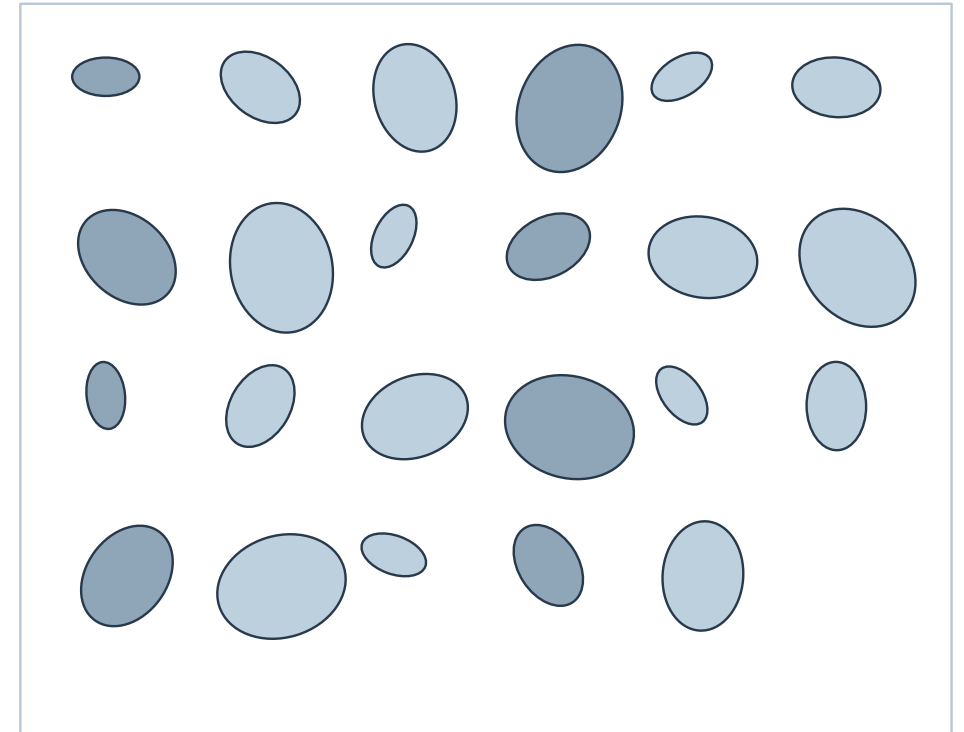
Seek thyroid tumor context



Integrate lineage evidence

Pleomorphic anaplastic carcinoma — schematic

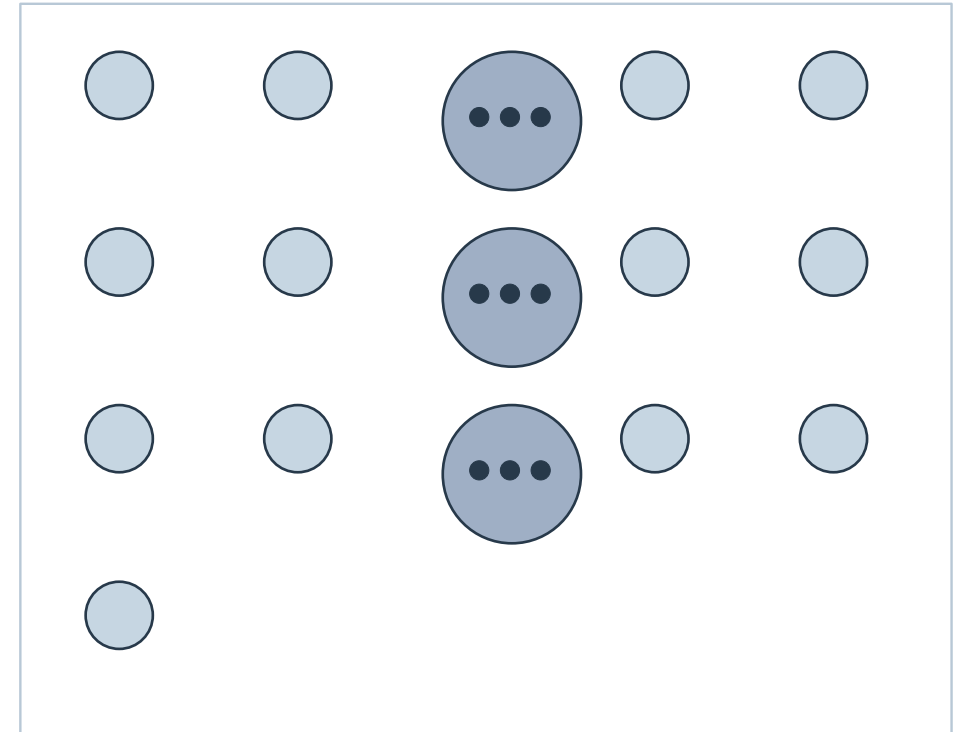
- Pleomorphism is explicitly described among the appearances of anaplastic carcinoma.
- Cells may vary conspicuously in size and shape.
- This pattern emphasizes dedifferentiation rather than a specific differentiated thyroid architecture.



Original schematic — not a histologic specimen

Giant-cell–rich anaplastic carcinoma — schematic

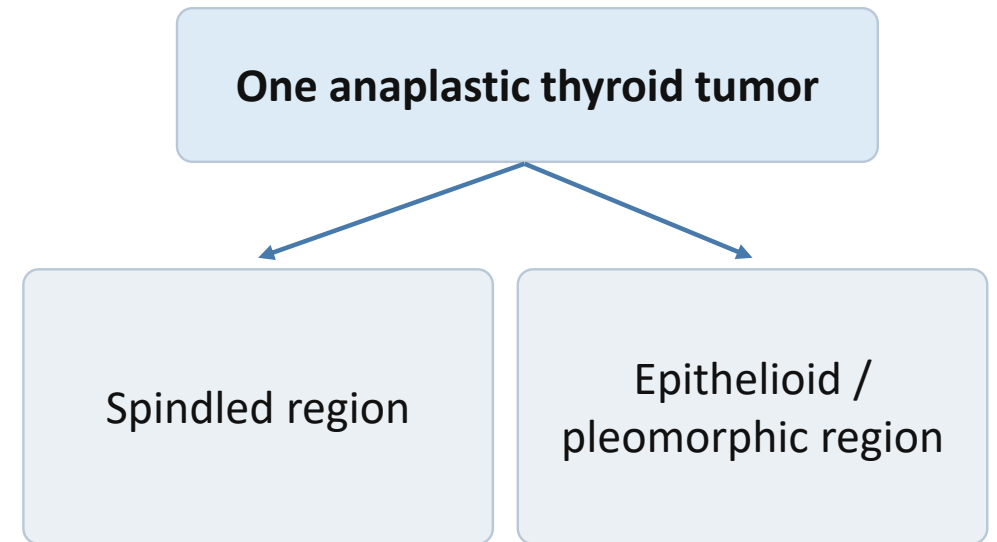
- Giant-cell–rich morphology is another form named in the Robbins section.
- This is one component of the variable anaplastic morphologic spectrum.
- Do not identify a neoplasm solely from illustrated large cells without full tissue context.



Original schematic — not a histologic specimen

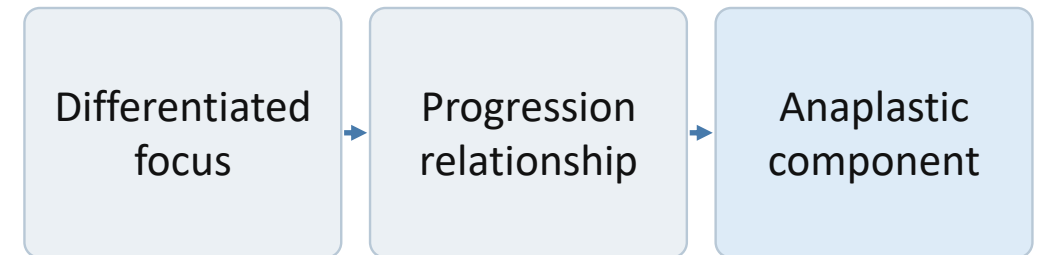
One tumor can carry several morphologies

- Variable anaplastic cytology rather than one uniform cellular form.
- Sampling a single region may not capture the full neoplastic appearance.
- Concurrent differentiated foci can reveal a relationship that anaplastic areas obscure.



Coexisting papillary or follicular foci

- Papillary or follicular carcinoma foci in some anaplastic tumors.
- This coexistence is consistent with origin from a well-differentiated carcinoma.
- Interpret the differentiated and undifferentiated areas as potential parts of a shared neoplasm.

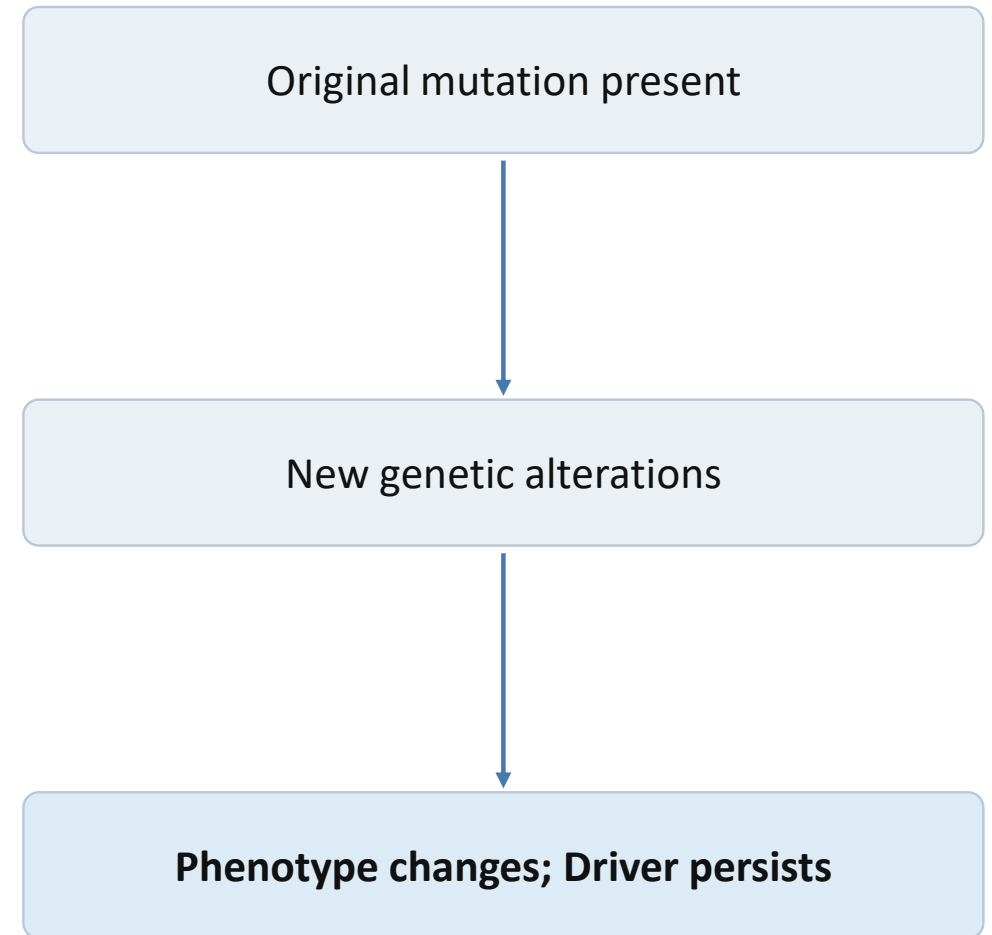


Loss of differentiation markers

- Anaplastic neoplastic cells often lose markers of follicular cell differentiation.
- The parent carcinoma discussion gives thyroglobulin and thyroid peroxidase as examples of differentiation markers.
- The primary excerpt does not provide marker-specific diagnostic sensitivity or required immunohistochemical panels.

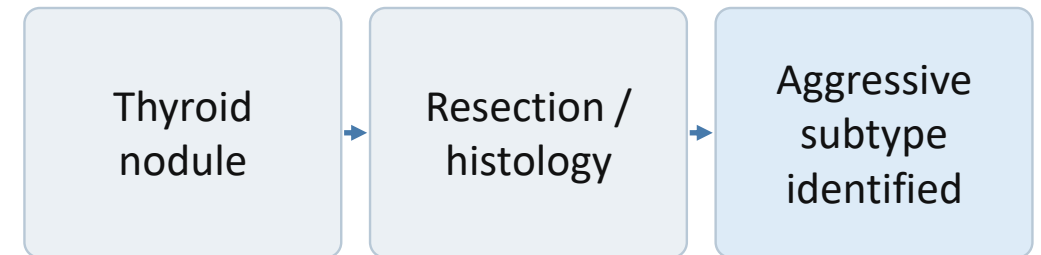
A retained molecular driver may provide continuity

- Tumor cells can retain the mutations of their differentiated precursor.
- Driver retention is consistent with clonal continuity even when morphology changes.
- This is supportive reasoning, not proof of identical origin in every individual case.



Clinical onset: High-grade and poorly differentiated

- High grade differentiated and poorly differentiated tumors may initially resemble ordinary papillary or follicular carcinoma.
- The aggressive category may become apparent only after resection and histologic review.
- Clinical appearance alone may underestimate tumor grade.



Anaplastic carcinoma: A rapidly enlarging neck mass

- Anaplastic carcinoma usually produces a bulky neck mass with rapid enlargement.
- At presentation, the disease commonly extends beyond thyroid boundaries.
- Such a presentation sharply contrasts with many indolent differentiated thyroid nodules.

Rapid local tumor growth



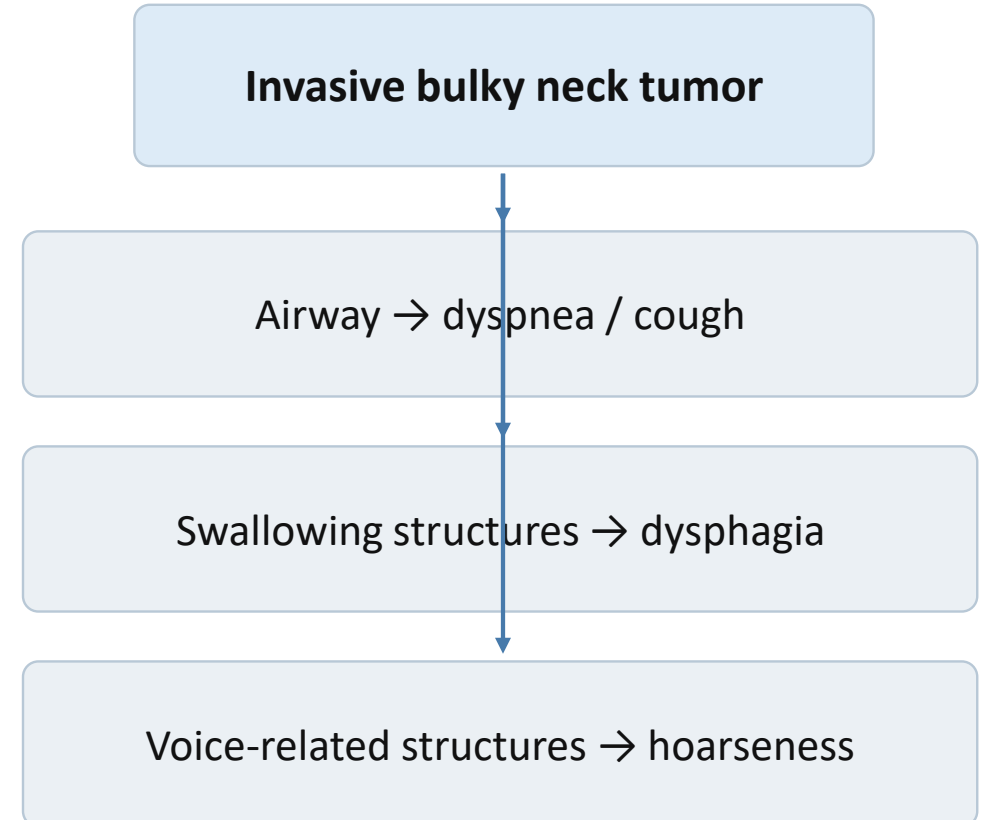
Bulky cervical mass



Compression / invasion

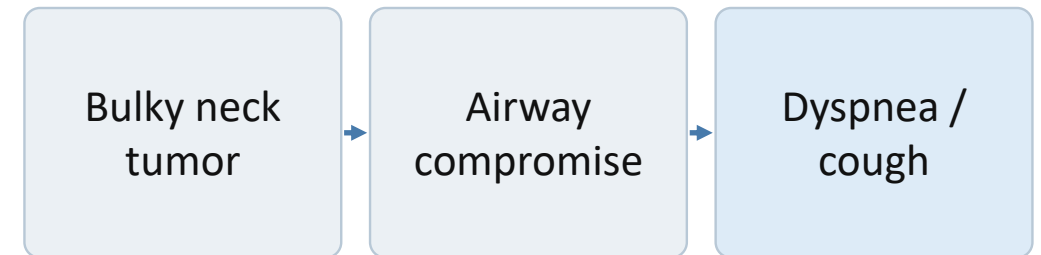
Local spread explains compressive symptoms

- Invasion or compression of neighboring structures causes clinically important symptoms.
- Dyspnea, dysphagia, hoarseness, and cough.
- Symptoms follow anatomic compromise, not simply the microscopic label “anaplastic.”



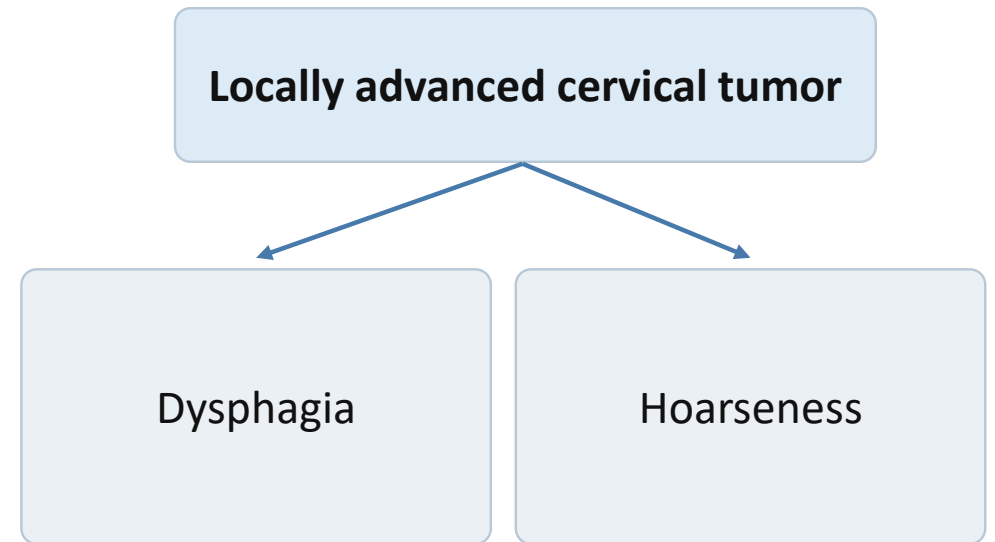
Dyspnea and cough: Airway-related consequences

- Rapidly enlarging thyroid-region disease can affect adjacent respiratory structures.
- Dyspnea and cough are among the common symptoms listed.
- The mechanism relates to local mass effect and invasion, not necessarily distant metastasis.



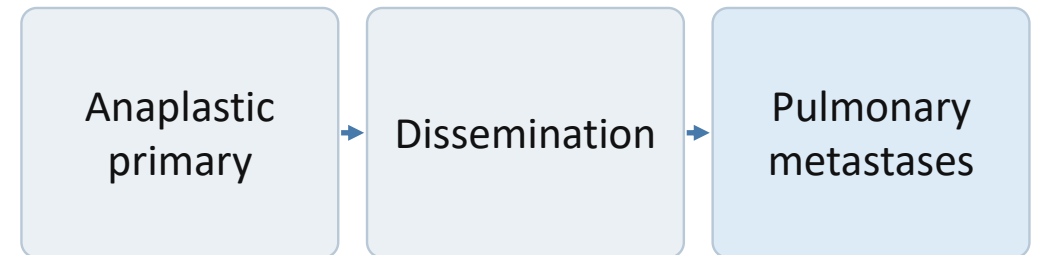
Dysphagia and hoarseness: Local invasion clues

- Dysphagia reflects interference with swallowing structures.
- Hoarseness points to involvement of voice-related anatomy in the local disease process.
- These symptoms can signal advanced local extension in the clinical setting described.



Distant spread: The lungs are emphasized

- Anaplastic carcinoma is often metastatic by the time it presents.
- The lungs are specifically described as a common distant metastatic site.
- Local invasion and distant metastasis can coexist at diagnosis.



Extent at presentation drives urgency

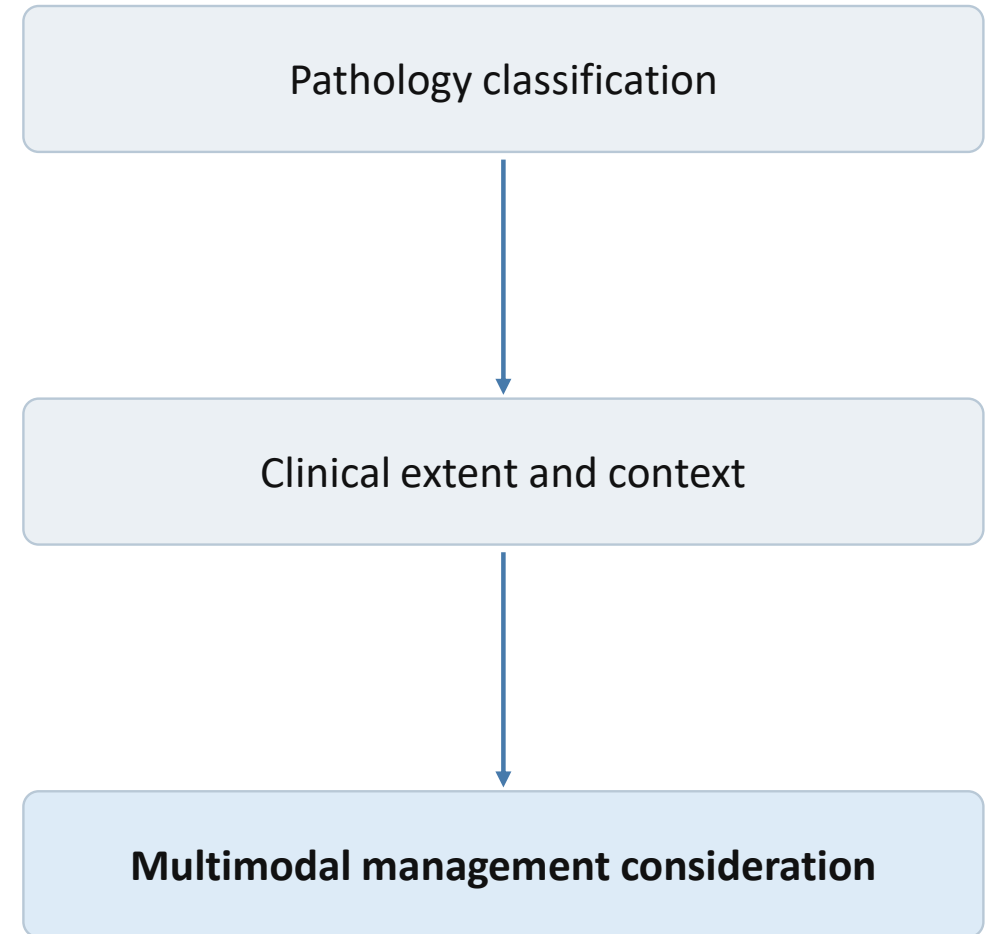
- Most anaplastic carcinomas have already spread beyond the thyroid or metastasized to the lungs at presentation.
- This high disease burden helps explain the severe clinical course.
- The source does not provide a formal stage table or an individual survival prediction.

Clinicopathologic contrast across the spectrum

- High grade differentiated and poorly differentiated tumors may be recognized histologically after surgery.
- Anaplastic carcinomas usually present with dramatically rapid local growth.
- The degree of dedifferentiation relates to a major difference in clinical behavior.

Management description: Preserve the source boundary

- High grade differentiated and poorly differentiated cancers fare somewhat better with surgery, external beam radiotherapy, and radioactive iodine.
- This is a textbook-level treatment overview, not a detailed therapeutic protocol.
- Treatment is not described as uniformly effective across individual tumors.



Radioactive iodine: Do not assume uniform response

- Radioactive iodine is among the modalities listed for high grade differentiated and poorly differentiated lesions.
- Anaplastic cells often lose features of follicular differentiation.
- The excerpt does not provide uptake rates or support universal iodine sensitivity for aggressive tumors.

Anaplastic carcinoma prognosis

- Anaplastic thyroid carcinoma as among the most aggressive cancers.
- Death occurs within less than one year in most cases in the cited textbook description.
- The near-universal mortality statement is a broad description, not a patient-specific forecast.

Mortality approaches 100% (textbook statement)

Most deaths within <1 year (textbook statement)

Relative outcome: High-grade versus anaplastic

- High grade differentiated and poorly differentiated carcinomas have somewhat better outcomes than anaplastic carcinoma.
- This relative difference is compatible with their retained degree of differentiation.
- The excerpt does not give separate survival curves or rates for the two higher-grade categories.

Morphology–clinic correlation: One comparison

- Retained differentiated appearance is compatible with a clinically less explosive presentation.
- Solid, insular, or trabecular growth signals poorly differentiated architecture.
- Severe dedifferentiation corresponds to highly invasive, bulky, and rapidly progressive disease.

High grade: Retained morphology

**Poorly differentiated: Altered
architecture**

Anaplastic: Marked dedifferentiation

A practical pathology assessment sequence

- Identify the follicular-cell carcinoma context and inspect for a differentiated component.
- Assess tumor differentiation, necrosis, and mitotic activity.
- Identify solid/insular/trabecular growth or anaplastic cytologic patterns.
- Integrate clinical evolution and available molecular history without substituting them for histology.

Architecture and cell phenotype



Necrosis / mitotic activity



Clinical–molecular integration

Case exercise: A deceptively ordinary thyroid mass

- A resected thyroid nodule is clinically similar to a common papillary or follicular carcinoma.
- Histology shows an aggressive carcinoma with insular and trabecular architecture.
- Tumor necrosis is noted in the tissue sample.
- Which category in this lecture is most strongly suggested?

Interpretation exercise

Clue: Insular / trabecular architecture

Clue: Histologic necrosis

Question: Which morphology anchors classification?

Case reasoning: The architectural clue

- The solid, insular, or trabecular arrangement is specifically linked to poorly differentiated carcinoma.
- Necrosis adds high-grade evidence, but does not alone name the architectural subtype.
- Clinical resemblance to a differentiated nodule does not exclude aggressive histology.

Architecture → PDTC clue



Necrosis → aggressiveness



Integrate both features

Case exercise: Rapidly enlarging cervical mass

- An older patient develops a rapidly enlarging bulky neck mass with hoarseness and dysphagia.
- Sectioned tumor is pleomorphic and lacks recognizable thyroid follicular morphology.
- A well-differentiated thyroid carcinoma focus is also present.
- Which pathologic process best integrates the findings?

Interpretation exercise

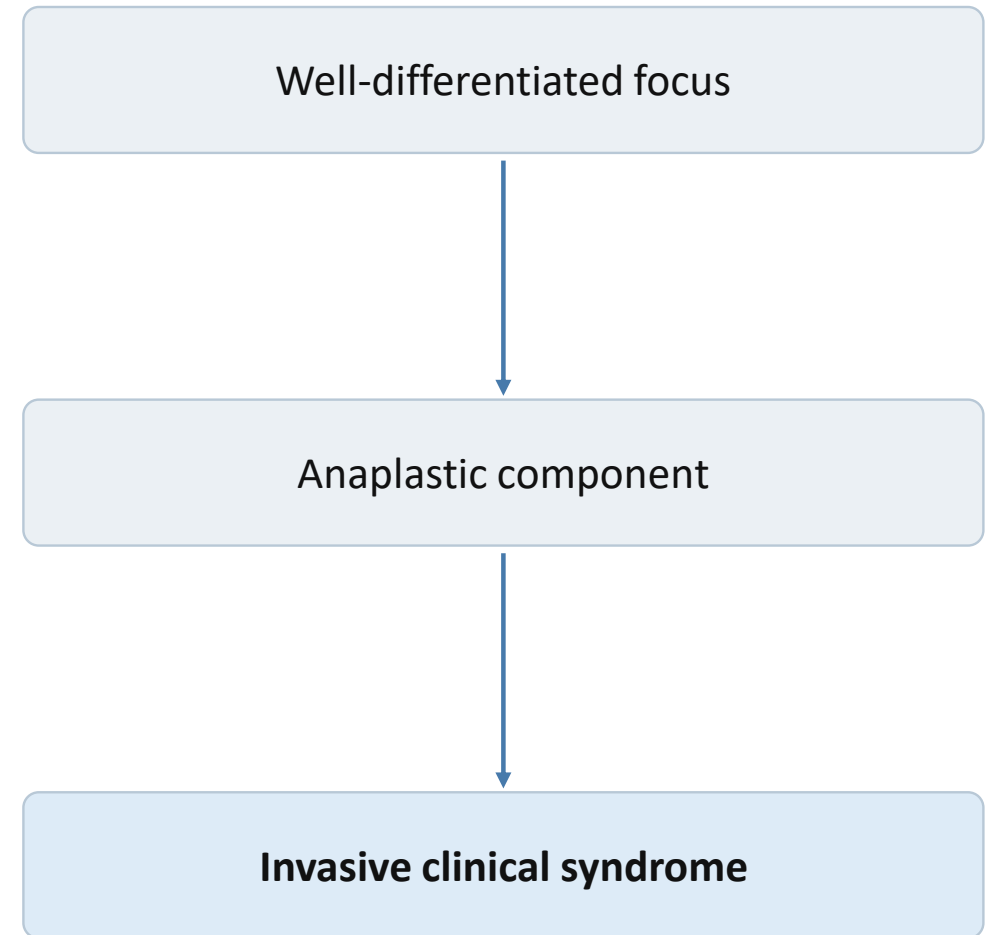
Clinical: Rapid invasive neck growth

Histology: Loss of differentiation

Question: Which tumor evolution is plausible?

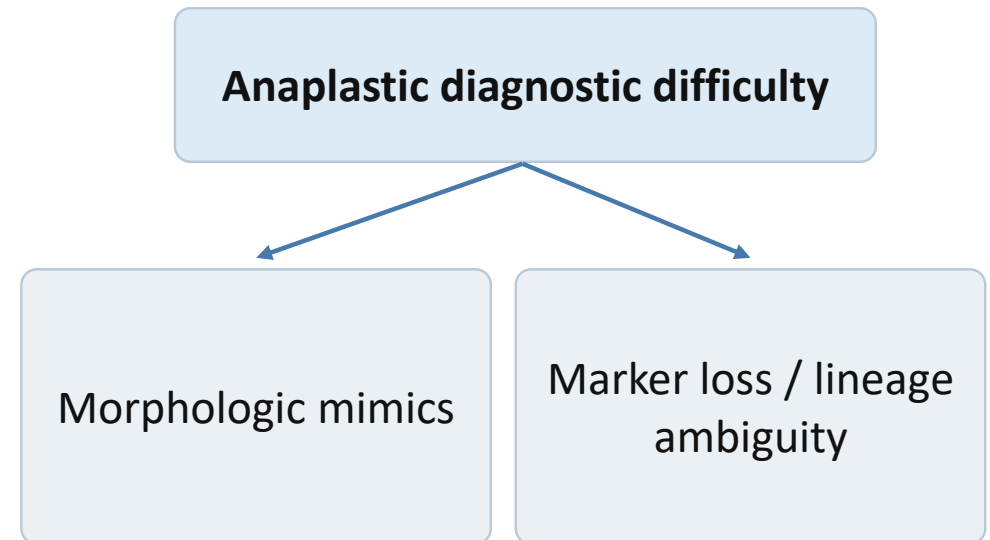
Case reasoning: Phenotype plus tumor history

- The anaplastic cytology accounts for the undifferentiated microscopic appearance.
- The coexisting differentiated component is consistent with progression from earlier thyroid carcinoma.
- The local symptoms follow invasion of adjacent neck structures.



Diagnostic pitfalls worth remembering

- Anaplastic epithelial patterns can resemble squamous cell carcinoma.
- Anaplastic spindle-cell patterns can resemble sarcoma.
- Loss of thyroid differentiation markers can obscure tissue lineage.
- No isolated morphologic or molecular feature should be used beyond the limits described by the source.



High-yield comparative matrix

- High grade differentiated: Thyroid-type differentiation with necrosis or increased mitoses.
- Poorly differentiated: Solid, insular, or trabecular architecture plus aggressive histologic features.
- Anaplastic: Extreme morphologic variation and loss of follicular-cell resemblance.

What the supplied source does not establish

- No subtype-specific mitotic numerical cutoff or complete modern diagnostic criteria are provided.
- No marker-panel sensitivity, treatment-response percentage, or contemporary stage-based algorithm is supplied.
- These omissions should not be filled with invented thresholds or extrapolated practice recommendations.

Explicit evidence limits

No numerical histologic cutoffs

No validated treatment algorithm

No invented molecular tests

Five points to retain

- These rare aggressive tumors derive from thyroid follicular epithelium.
- Tumor necrosis and increased mitotic activity signal high-grade histology.
- Solid, insular, and trabecular growth characterizes poorly differentiated carcinoma.
- Anaplastic tumors lose follicular resemblance and often spread rapidly.
- Anaplastic prognosis is markedly worse than the higher-grade differentiated categories.

Primary reference and evidence boundary

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition, thyroid carcinoma section.
- The lecture integrates the aggressive carcinoma passage with adjacent follicular-cell carcinoma background.
- Morphologic cell-pattern drawings are original explanatory schematics; they are not photomicrographs.
- No contemporary classification cutoffs or external clinical recommendations were added.