

Differentiation and Anaplasia

Neoplastic resemblance, cytologic atypia and tumor function

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Learning objectives

Define tumor differentiation using both morphology and function.

Recognize cellular, nuclear, mitotic and architectural features of anaplasia.

Interpret differentiation without equating it with benign or malignant status.

Explain why some tumors retain normal products while others secrete unexpected proteins.

Classification of a tumor requires more than a single microscopic feature.

Differentiation: The reference is normal tissue

Differentiation asks how closely neoplastic parenchymal cells resemble their normal counterpart.

Resemblance may involve cell shape, tissue organization and specialized activity.

The appropriate comparison depends on the cell or tissue of origin.

Compare tumor cells with the correct normal lineage.

Tumor parenchyma and stroma have different roles

Neoplastic parenchyma

Constitutes the tumor cell population

Principal basis for tumor classification

The component evaluated for differentiation

Reactive stroma

Provides connective tissue and blood vessels

Includes immune and other supporting cells

Supports growth but is not the
differentiation reference

Morphologic and functional resemblance are distinct

Morphology

Cell and nuclear form

Preservation of glandular or squamous patterns

Architecture and orientation

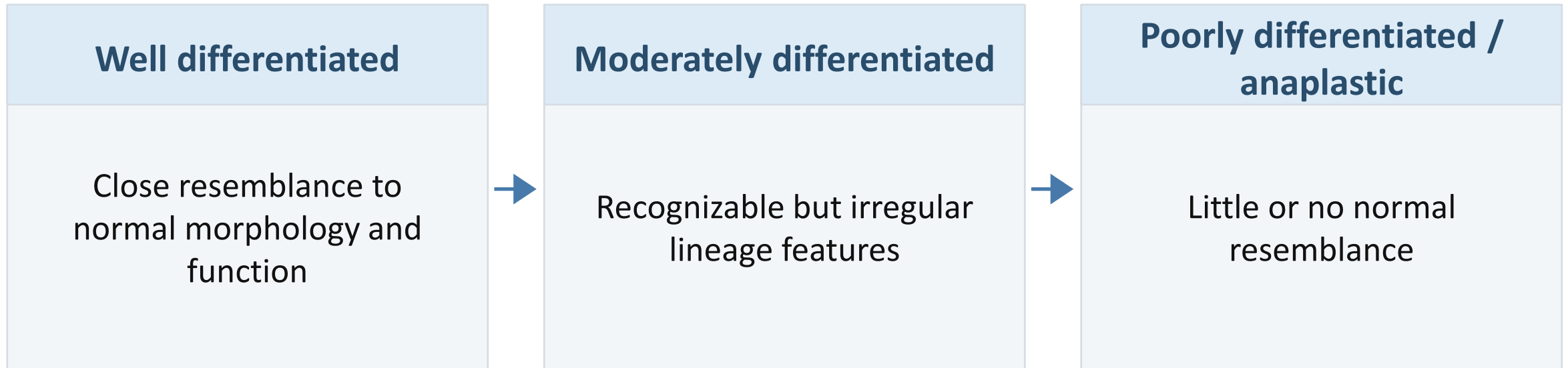
Function

Production of normal tissue products

Hormonal or secretory specialization

Loss or alteration in anaplastic tumors

Differentiation is a spectrum, not a switch



Descriptive continuum: No universal numeric boundaries are asserted here

Benign tumors generally resemble their tissue of origin

Benign neoplasms are almost always well differentiated.

Their constituent cells may be nearly indistinguishable from normal counterparts.

The abnormality may be recognized primarily by formation of a localized mass.

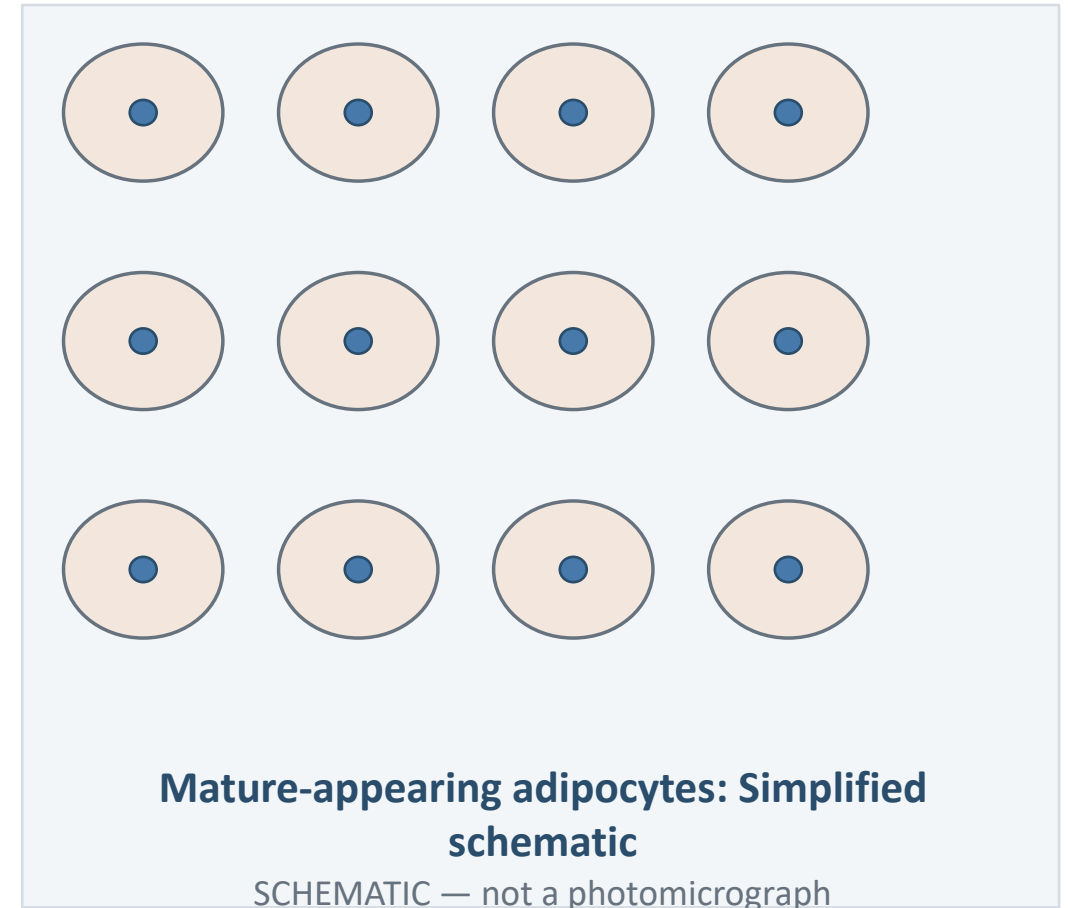
Benignity does not require bizarre cytology.

A lipoma can look like normal adipose tissue

Lipoma consists of benign adipocytes that resemble mature fat cells.

Individual cells may be difficult to recognize as neoplastic.

The discrete aggregate of cells establishes the lesion as a tumor.



Neoplastic identity is not always a cytologic diagnosis

Individual adipocyte

Mature appearing

Little or no atypia

May look entirely normal

Mass of adipocytes

A discrete growth

Localized proliferation

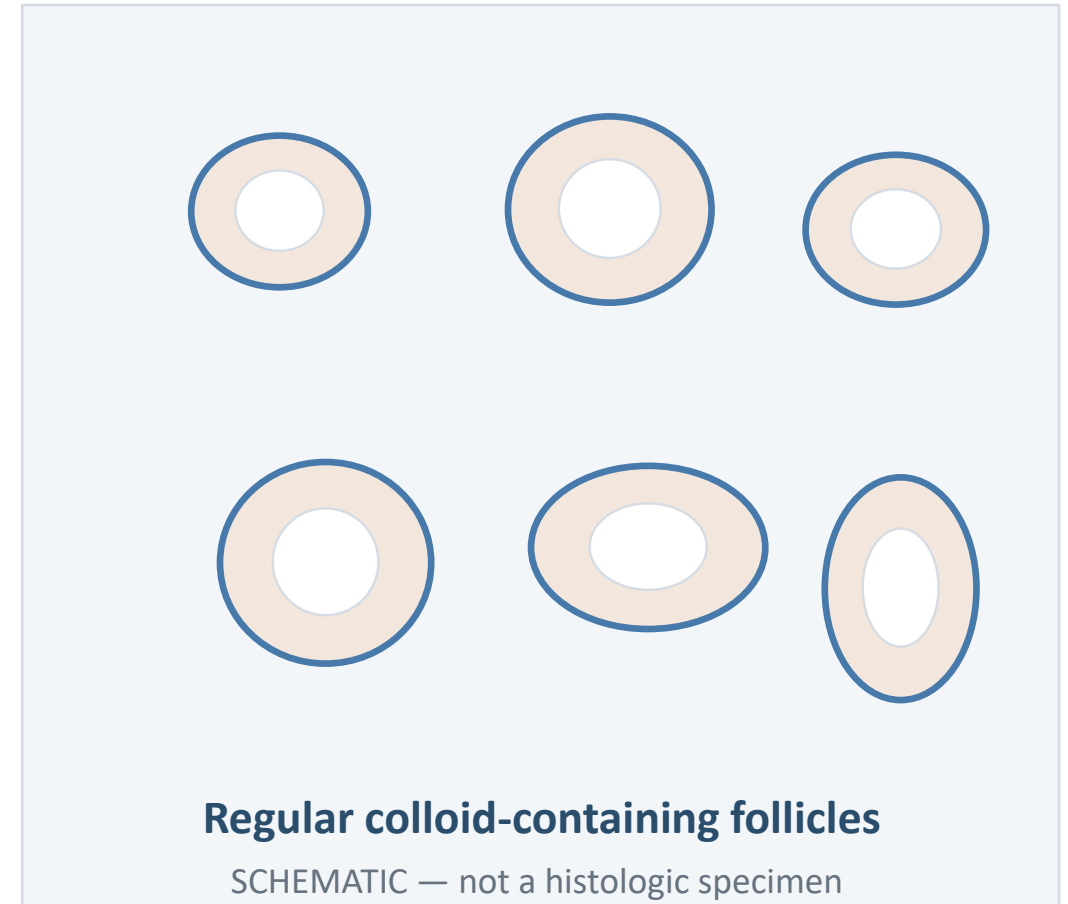
Neoplastic nature evident at tissue level

Thyroid follicular adenoma retains follicular architecture

Benign thyroid follicular adenoma exhibits well-formed follicles.

The follicles may contain colloid and resemble normal thyroid tissue.

This illustrates substantial tissue-specific differentiation.



Mitotic figures in well-differentiated benign tumors

Mitoses are usually infrequent in well-differentiated benign tumors.

When observed, they usually have a normal configuration.

This tendency is helpful context, not a universal diagnostic rule.

Mitotic count alone never substitutes for full tumor assessment.

Malignancy can coexist with substantial differentiation

High differentiation

Normal-like cellular features

May preserve tissue architecture

Specialized products may be retained

Malignant behavior

Tumor invades surrounding structures

Tumor may metastasize

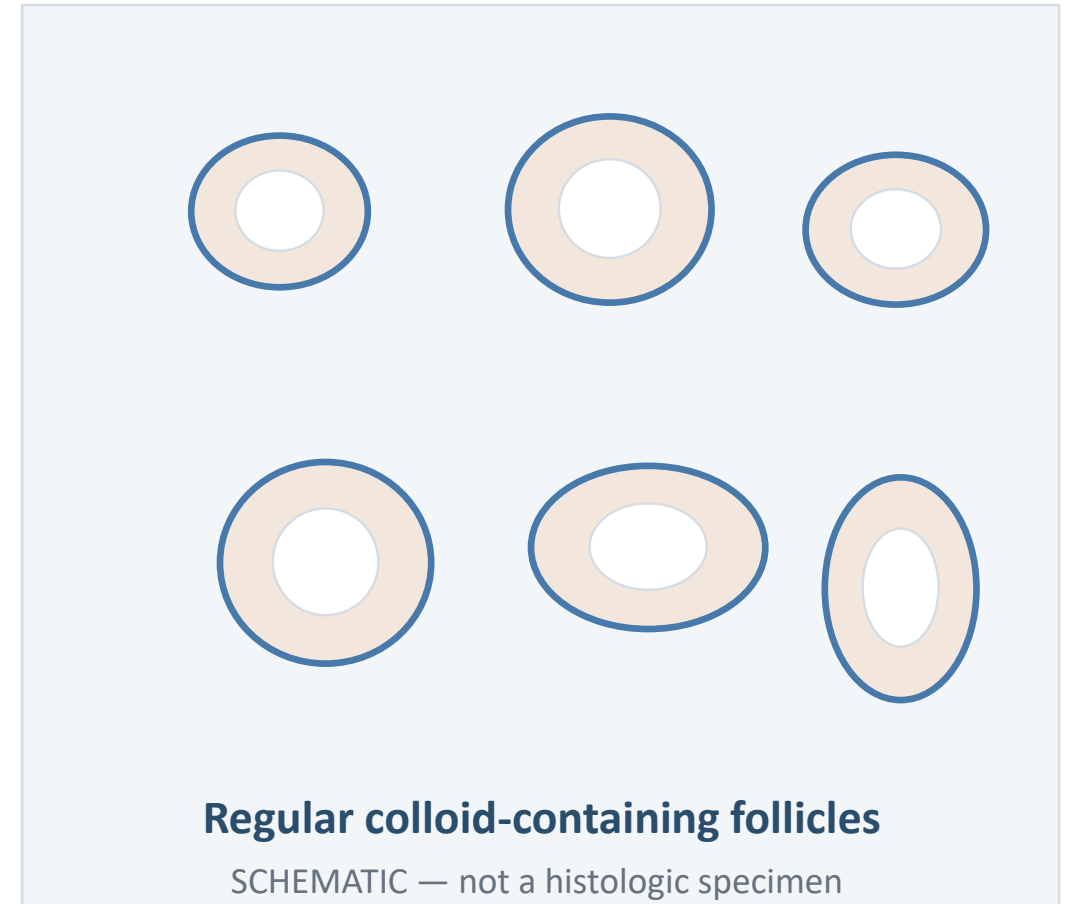
Bland cytology does not establish benignity

A differentiated thyroid carcinoma can form follicles

Some thyroid adenocarcinomas form follicles resembling those of normal thyroid.

Preserved follicles demonstrate differentiation, not necessarily benignity.

Invasion and metastatic capability establish malignant behavior.



Squamous differentiation may produce keratin pearls

Well-differentiated squamous cell carcinomas may form keratin pearls.

Keratin production recapitulates the function of mature squamous cells.

Keratinization can coexist with malignant invasive growth.



Concentric keratinization: Conceptual pearl

SCHEMATIC — not a histologic specimen

Tissue resemblance and invasion answer different questions

Differentiation	Benign behavior	Malignant behavior
Well differentiated	Common (e.g., lipoma)	Possible despite bland cells
Poorly differentiated / anaplastic	Not a characteristic benign pattern	Strongly suggests malignancy
Key distinction	Localized, usually noninvasive	Invasion and metastatic potential

The two dimensions are related but not interchangeable.

Moderate differentiation retains recognizable lineage features

Moderately differentiated tumors lie between the well-differentiated and anaplastic extremes.

Some characteristic structures remain, but are distorted or incomplete.

This descriptive category does not replace evaluation of invasion.

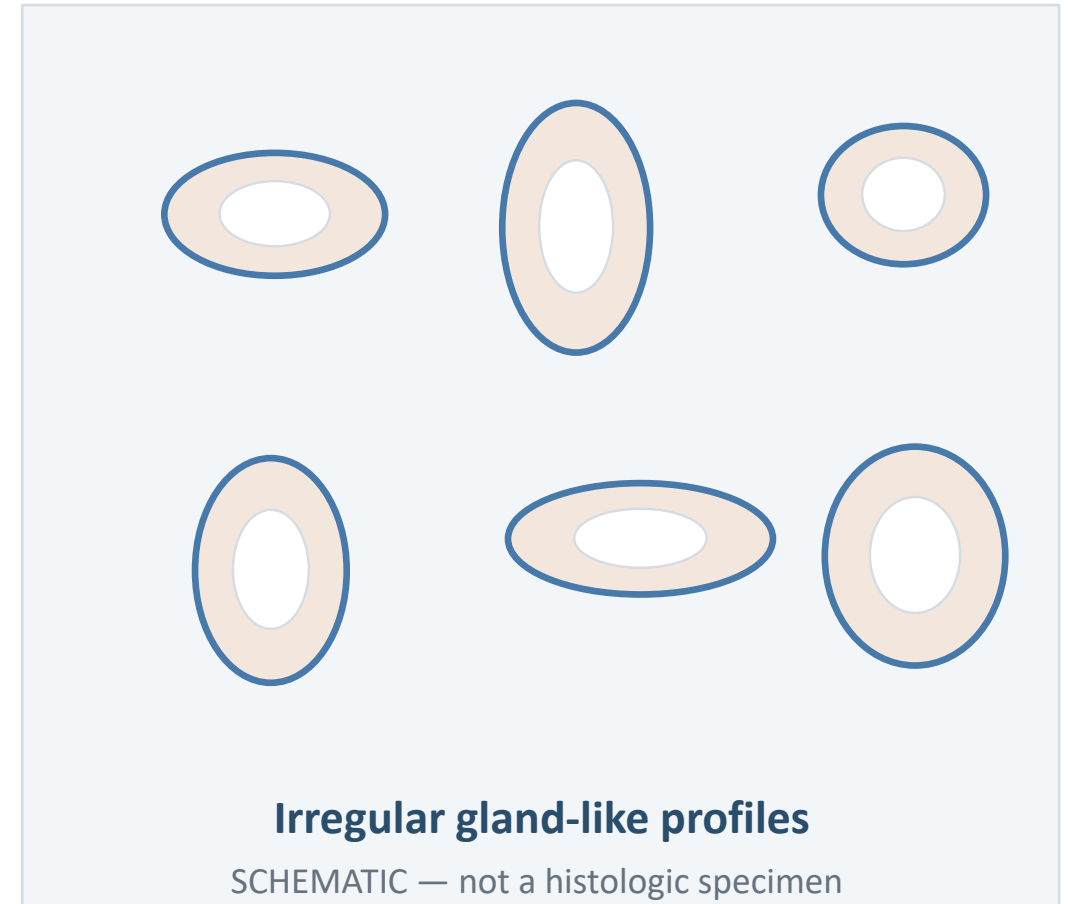
“Moderate” describes resemblance—not a standalone behavior test.

Colon adenocarcinoma may form irregular glands

Moderately differentiated colon adenocarcinoma may retain gland formation.

Malignant glands vary in size and shape and depart from normal colonic architecture.

The Robbins example invades the colonic muscular layer.



Recognizing residual glandular differentiation

Normal-like glands

Relatively uniform size and shape
Ordered relationship to surrounding tissue
Architecture resembles site of origin

Malignant differentiated glands

Glands are distorted and irregular
Tissue arrangement is abnormal
The lesion may invade deeper layers

Differentiation should not be used as a binary label

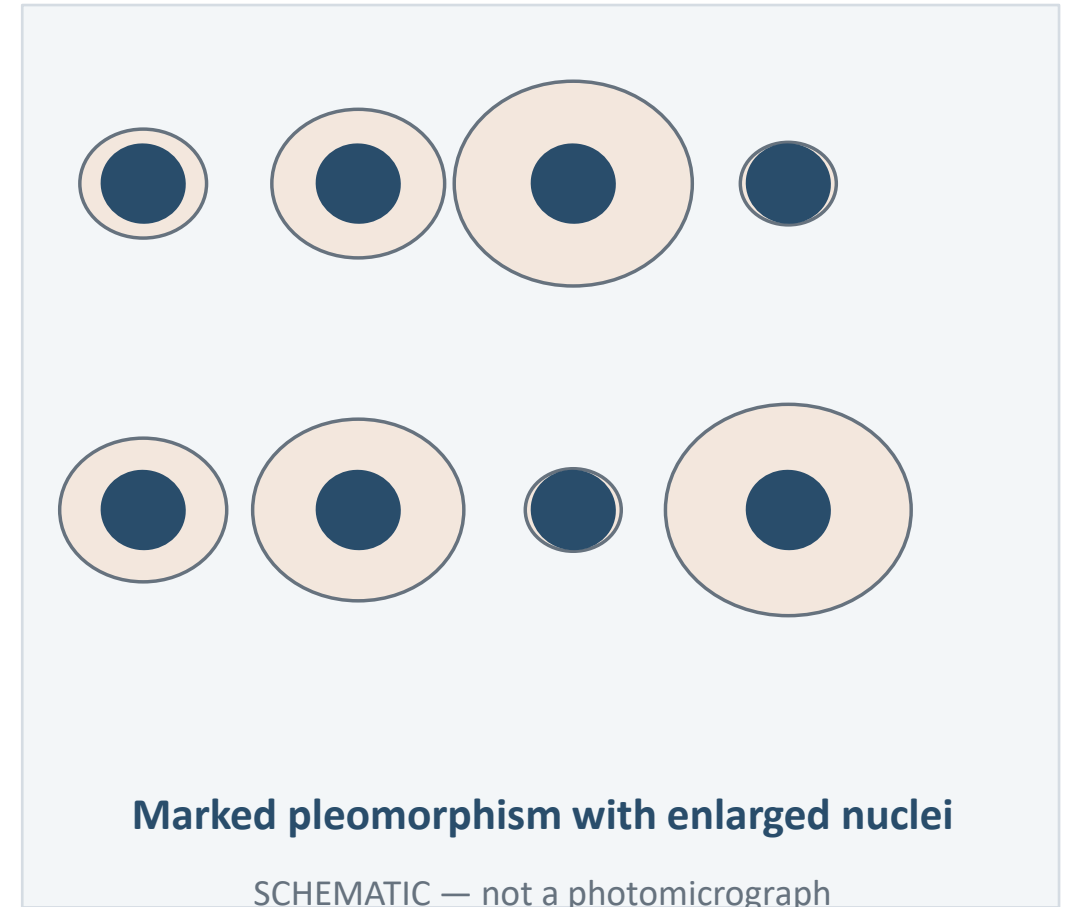
Descriptive position	Typical morphologic idea	Diagnostic limitation
Well differentiated	Close resemblance to normal tissue	Can still be malignant
Moderately differentiated	Some characteristic structures remain	Cannot infer extent of spread
Anaplastic / undifferentiated	Little resemblance to normal tissue	Suggests malignancy; site may be unclear

The most anaplastic tumors lose normal resemblance

Poorly differentiated tumors show only limited lineage-specific morphology.

Highly anaplastic tumors may appear undifferentiated.

Anaplasia is strongly associated with malignant behavior.



Anaplasia is a cellular phenotype, not a tumor name

Anaplasia refers to lack of differentiation.

It is recognized through characteristic cytologic and architectural abnormalities.

Its prominence varies; Not every malignant tumor is markedly anaplastic.

Anaplasia predicts malignancy, but its absence does not exclude cancer.

A morphologic survey has several independent axes

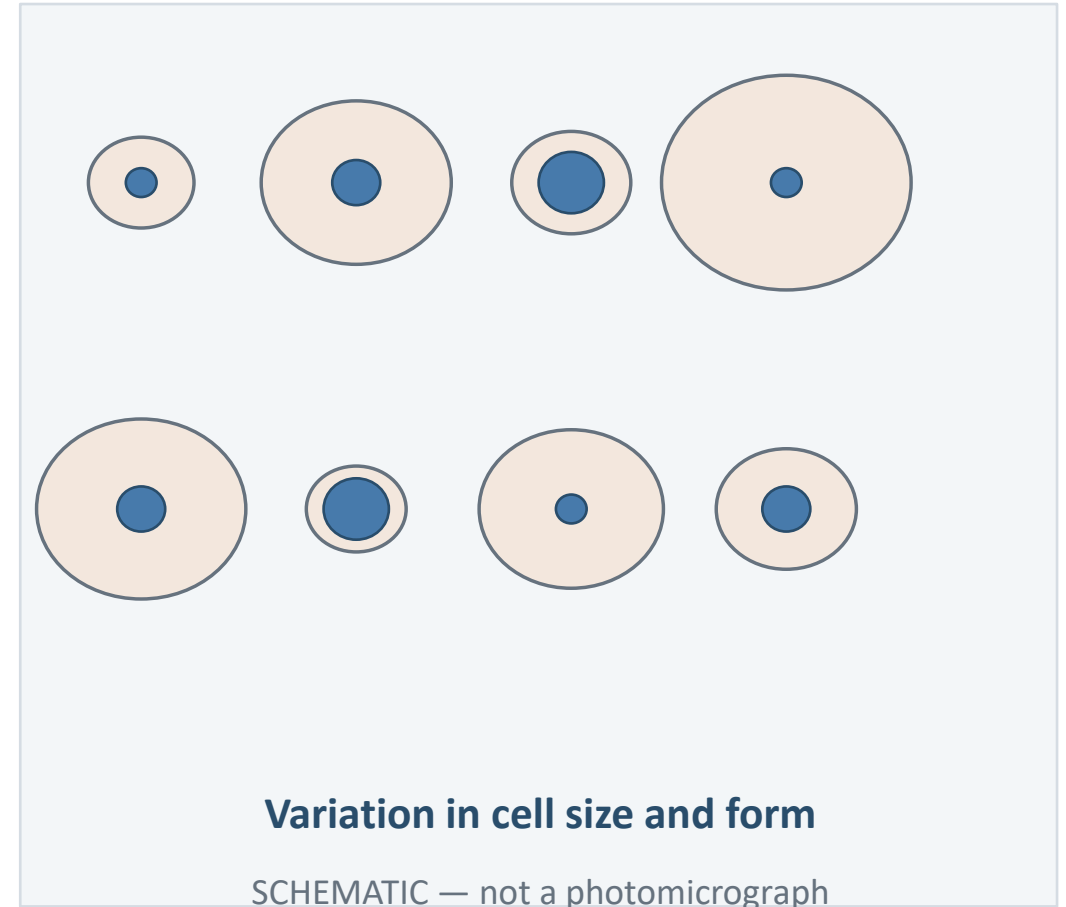
Domain	Morphologic finding	Meaning
Cell population	Pleomorphism	Marked variation among tumor cells
Nucleus	Enlargement, hyperchromasia, nucleoli	Nuclear atypia
Cell division	Atypical mitotic forms	Abnormal mitotic configuration
Architecture	Loss of polarity	Disordered orientation and growth
Tumor environment	Ischemic necrosis	Vascular support may lag behind growth

Pleomorphism means variable cell size and shape

Pleomorphism describes nonuniform tumor cells within a single lesion.

Cells may range from small, relatively primitive-appearing forms to very large cells.

Variation in form is more conspicuous in many anaplastic tumors.

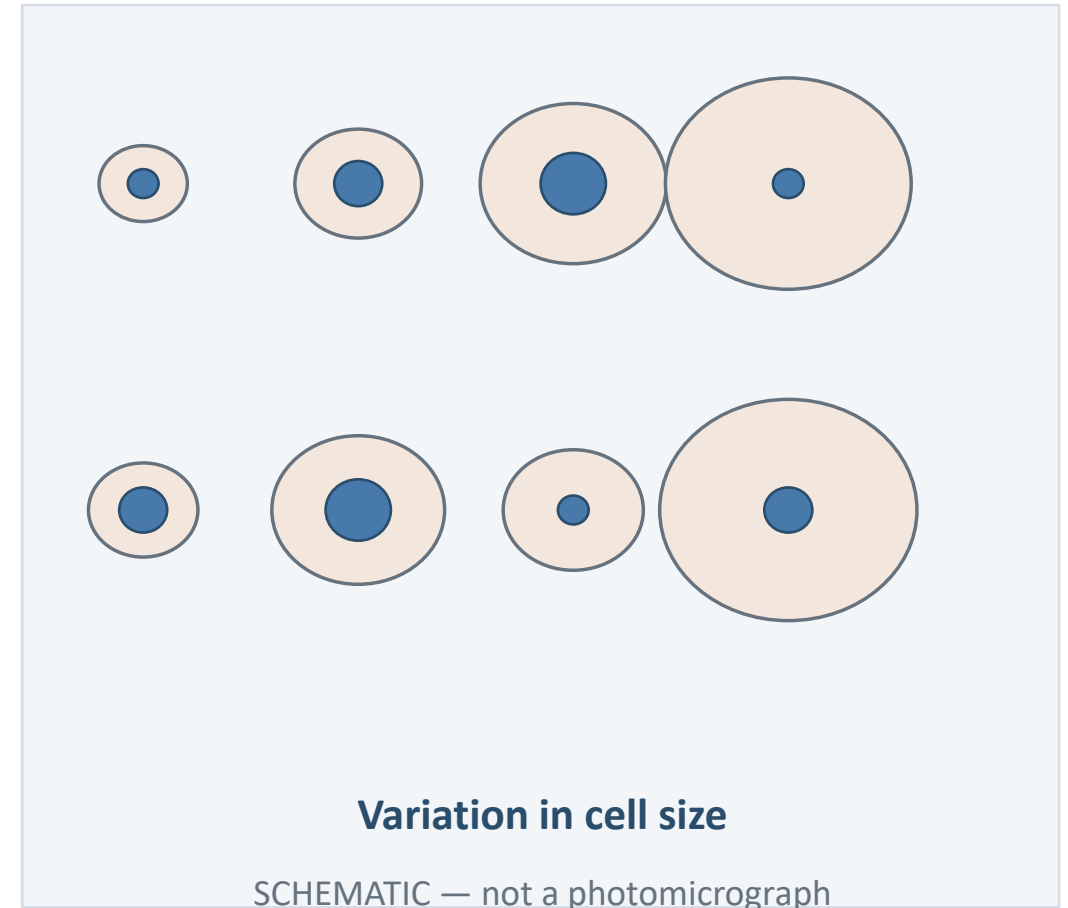


Cell-size variation is a direct visual clue

A uniform cell population has a relatively narrow range of forms.

Pleomorphic tumors contain visibly different cell sizes and contours.

Morphologic variation is assessed across the field, not from one isolated cell.

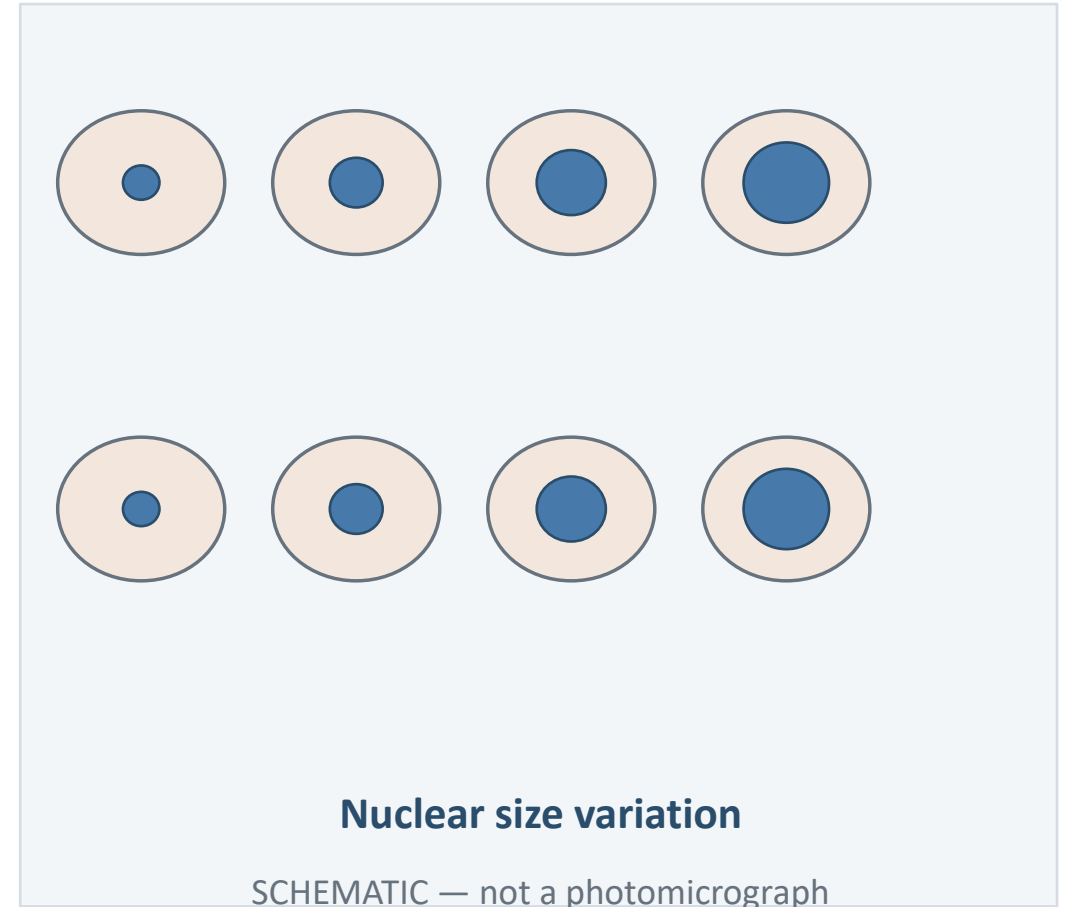


Nuclear pleomorphism can exceed cellular variation

Tumor nuclei may differ markedly in size and shape.

Some cells contain extraordinarily large or distorted nuclei.

Nuclear atypia is assessed together with cytoplasm and architecture.

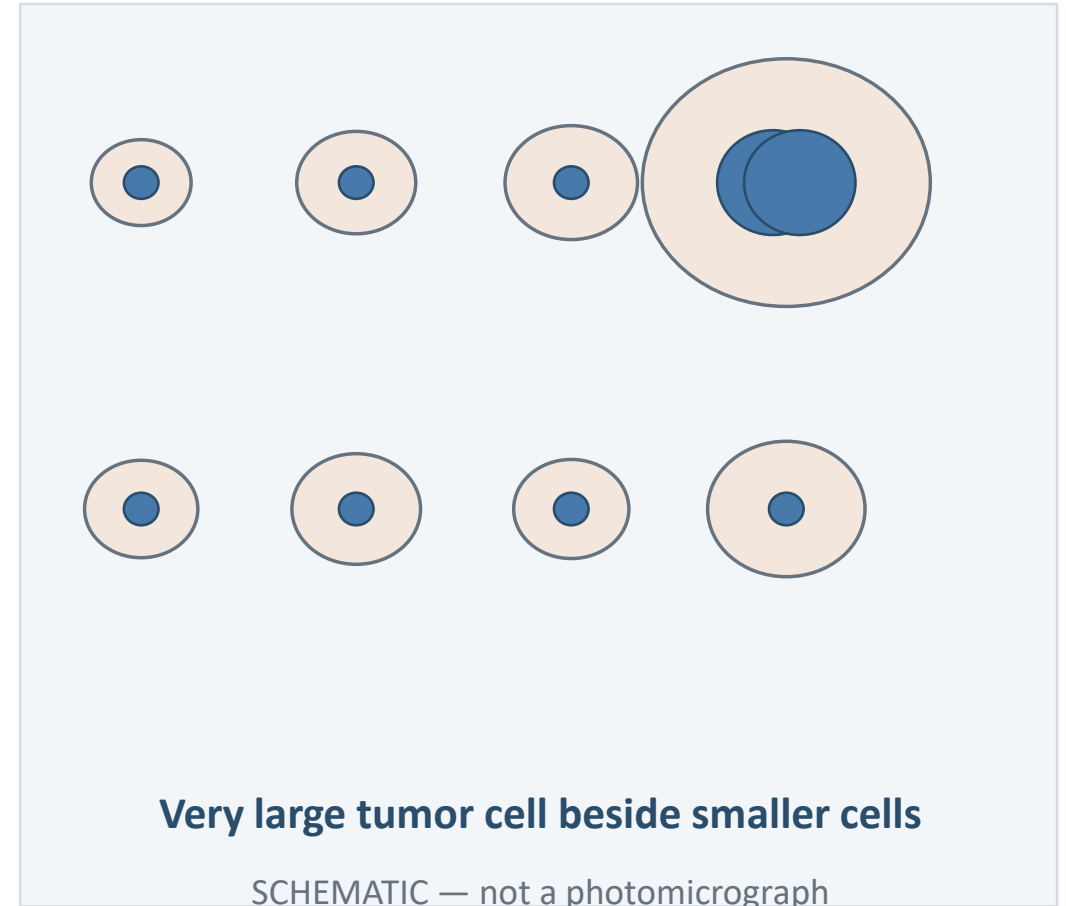


Tumor giant cells are extreme examples of pleomorphism

Anaplastic tumors may contain cells far larger than their neighbors.

One tumor giant cell may have a single huge, bizarre nucleus.

Others contain two or more large, hyperchromatic nuclei.



Do not mistake tumor giant cells for macrophage giant cells

Tumor giant cell

Often has bizarre giant nuclei

May have one huge polymorphic nucleus

May contain multiple large atypical nuclei

Inflammatory giant cell

Macrophage-derived

Langhans or foreign body type

Contains numerous small, relatively normal nuclei

Nuclear-to-cytoplasmic ratio often increases

Anaplastic nuclei can occupy a disproportionate fraction of the cell.

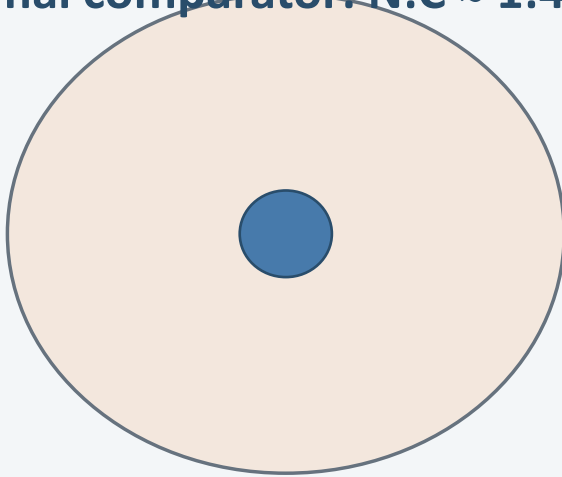
Ratios approaching 1:1 in cancer cells.

The cited normal comparison is approximately 1:4 to 1:6.

Ratio is a morphologic clue—not a universal numerical threshold.

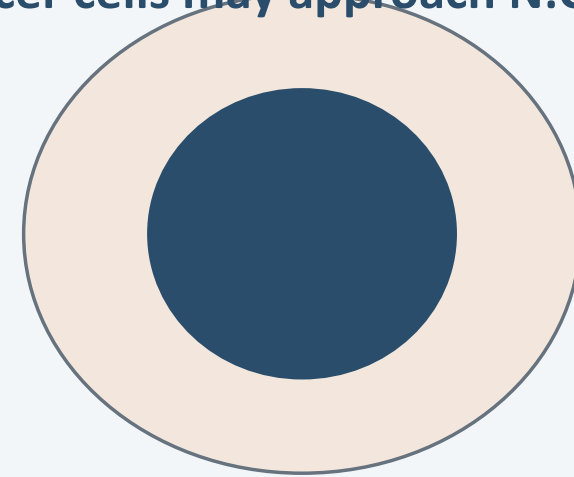
Large nuclei change the balance of the cell

Normal comparator: N:C $\approx$ 1:4 to 1:6



Relatively small nucleus

Cancer cells may approach N:C $\approx$ 1:1



Disproportionately large nucleus

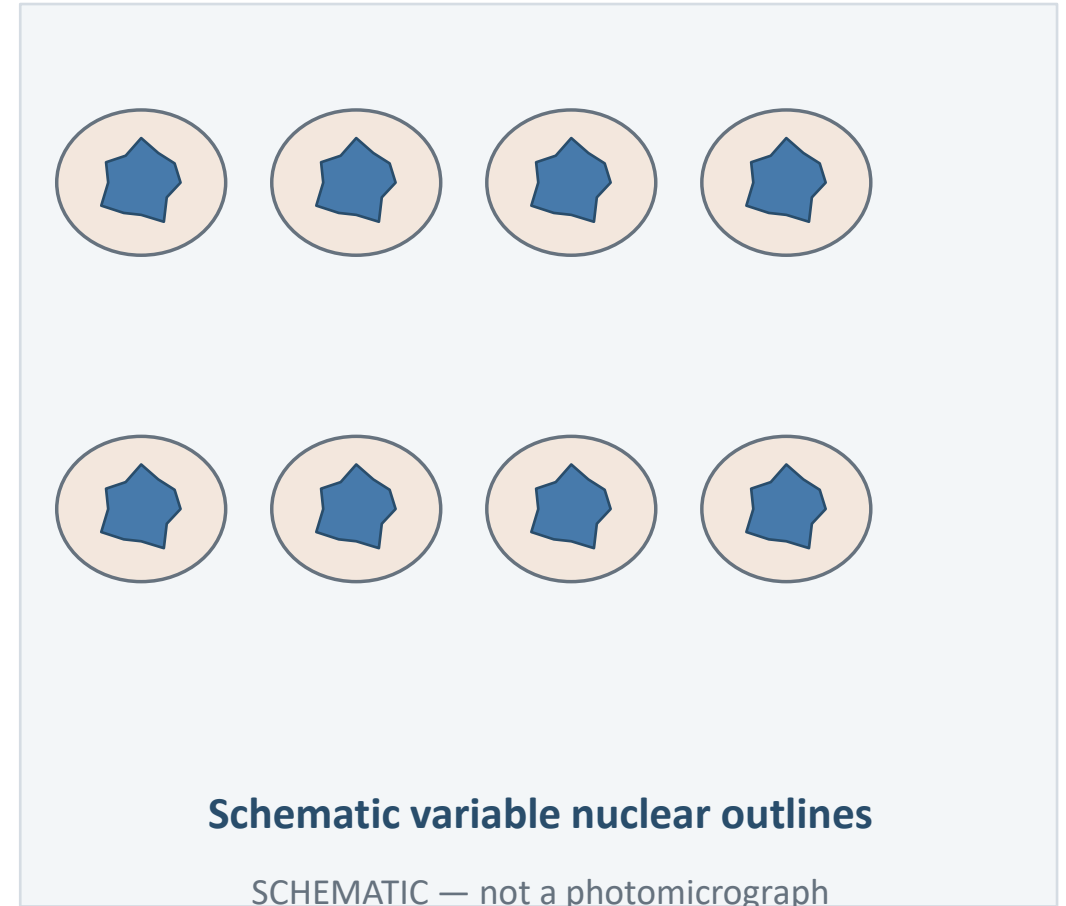
SCHEMATIC — ratios are textual examples, not drawn to scale

Irregular nuclear contours suggest atypia

Cancer cell nuclei may have variable, irregular shapes.

Compare the nuclear outline across multiple cells.

Irregularity gains diagnostic weight alongside other abnormal findings.



Hyperchromasia reflects darker nuclear staining

Hyperchromatic nuclei stain more darkly than expected.

Coarse chromatin and increased nuclear darkness.

Color intensity is considered with nuclear size and shape.

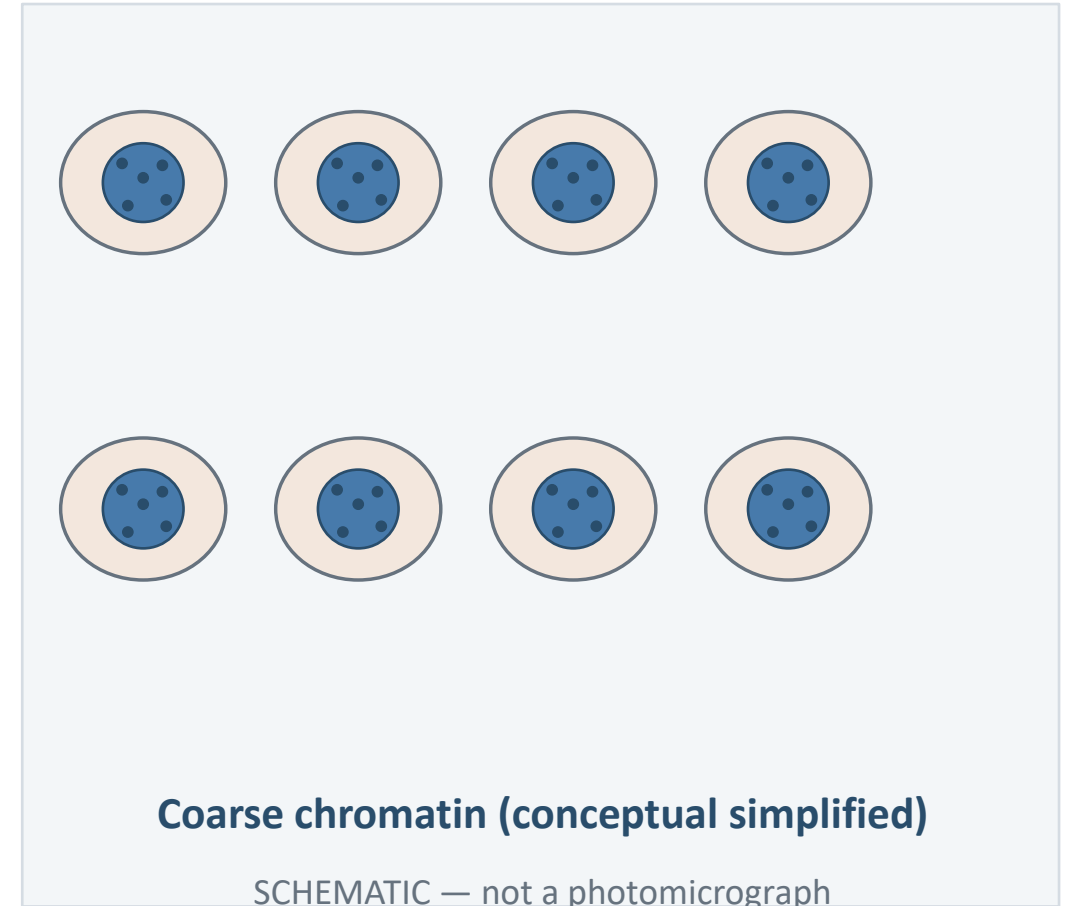


Chromatin may be coarsely clumped

Anaplastic nuclei may have coarse, irregularly distributed chromatin.

Chromatin often appears concentrated near the nuclear membrane.

This differs from a fine, relatively even chromatin pattern.

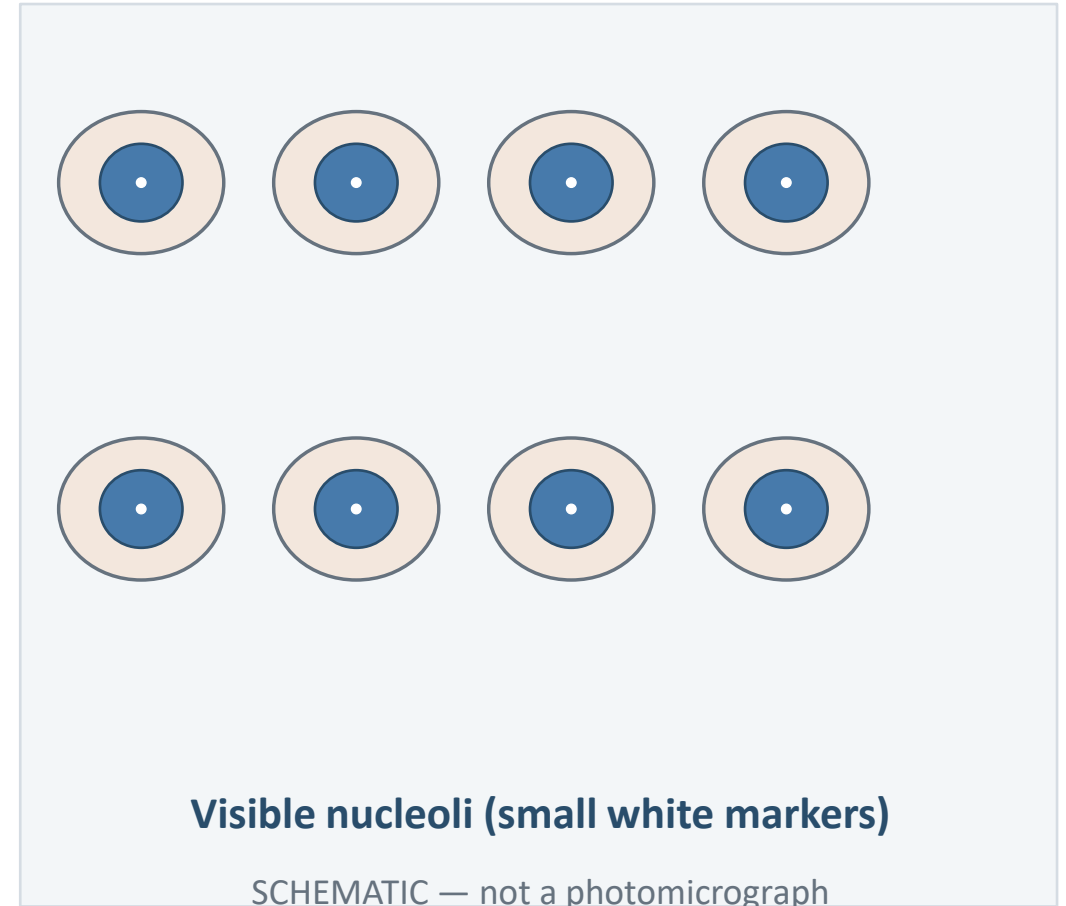


Prominent nucleoli are another nuclear abnormality

Abnormally large nucleoli are common in many cancer cells.

Nucleolar prominence should be interpreted in overall nuclear context.

No single nucleolar appearance independently establishes malignancy.



Read nuclear atypia as a constellation

Feature	What to look for	Interpret with
High N:C ratio	Nucleus dominates cytoplasm	Cell type and context
Irregular contour	Variable or angulated outline	Pleomorphism
Hyperchromasia	Darkly staining nuclei	Chromatin pattern
Coarse chromatin	Clumping, peripheral accentuation	Nucleoli and contours
Large nucleoli	Conspicuous nuclear structures	Other malignant features

Mitoses may be numerous in undifferentiated cancer

Undifferentiated malignancies frequently have abundant mitotic figures.

This finding reflects active tumor cell proliferation.

The number of mitoses must be assessed with the wider histologic picture.

High mitotic activity is common in some cancers, but not synonymous with cancer.

Mitosis itself is not evidence of malignancy

Nonmalignant proliferating tissues

Intestinal epithelium normally renews rapidly

Hyperplasia may contain many mitoses

Mitoses may have normal configuration

Malignant lesions

Some cancers show numerous mitoses

Others are well differentiated with fewer

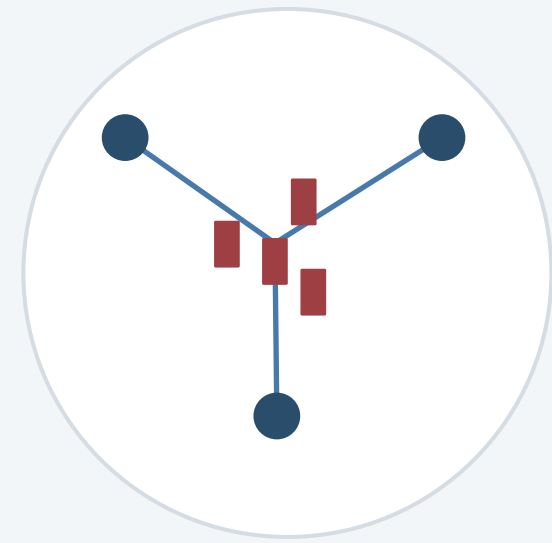
Atypical configurations are more concerning

Atypical mitotic figures are more informative

Anaplastic malignancies may contain bizarre mitotic configurations.

A multipolar or tripolar spindle is an example illustrated by Robbins.

Atypical shape is more concerning than mitotic presence alone.



Three spindle poles (tripolar)

SCHEMATIC — not a mitotic micrograph

Mitotic quantity and mitotic quality differ

Observation	What it indicates	What it does not establish
Many ordinary mitoses	Active cell turnover	Malignancy by itself
Few ordinary mitoses	Low observed mitotic activity	Definite benignity
Bizarre multipolar mitosis	Abnormal cell division pattern	Tumor type without context

Loss of polarity is architectural, not merely nuclear

Normal epithelial cells have an ordered orientation to each other and to basement membranes.

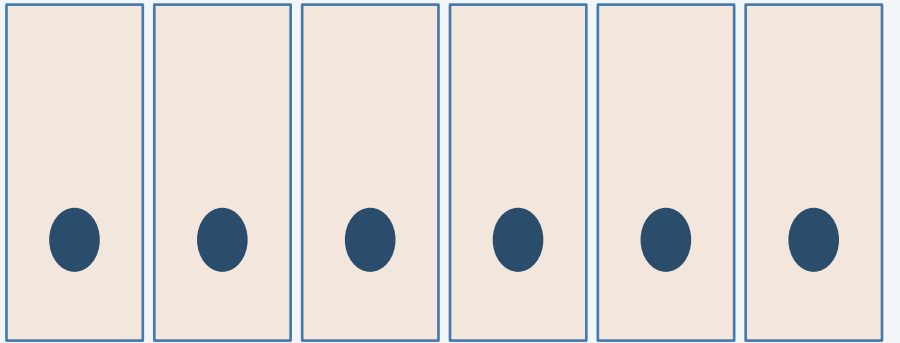
Anaplastic tumors may lose this spatial organization.

Tumor cells then grow as disorganized sheets or masses.

Loss of polarity is a tissue-level feature of anaplasia.

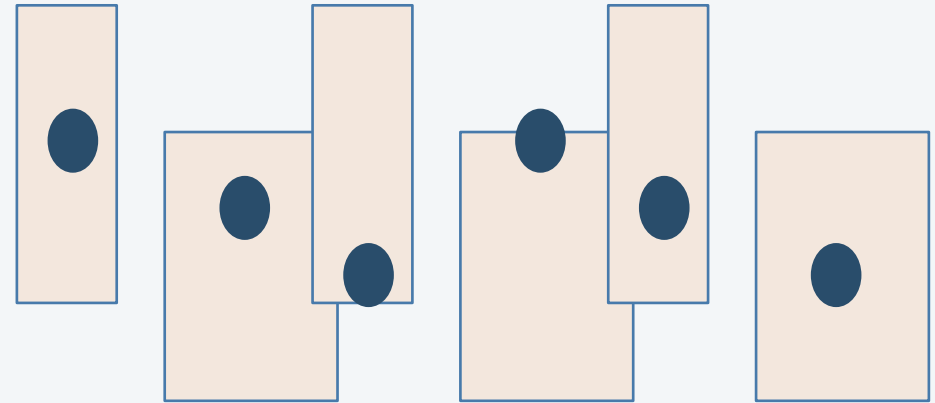
Ordered epithelium versus disrupted polarity

Orderly epithelial orientation



Basement membrane

Disordered tumor cell orientation



Basement membrane

SCHEMATIC — simplified cell orientation, not a tissue section

Architectural disorder complements cytologic atypia

Cytologic examination

Nuclear shape and size

Chromatin and nucleoli

Cellular pleomorphism

Architectural examination

Cell orientation and polarity

Gland or sheet organization

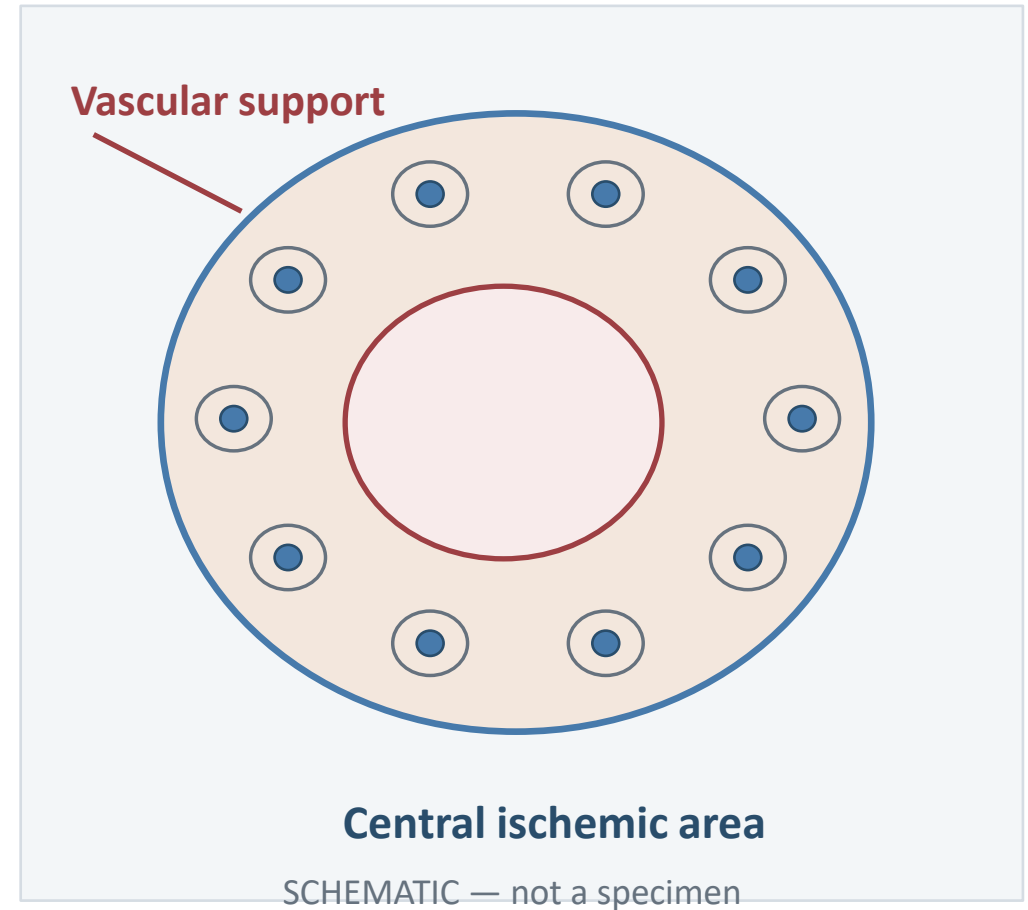
Relationship to basement membrane

Ischemic necrosis may appear within rapidly growing tumors

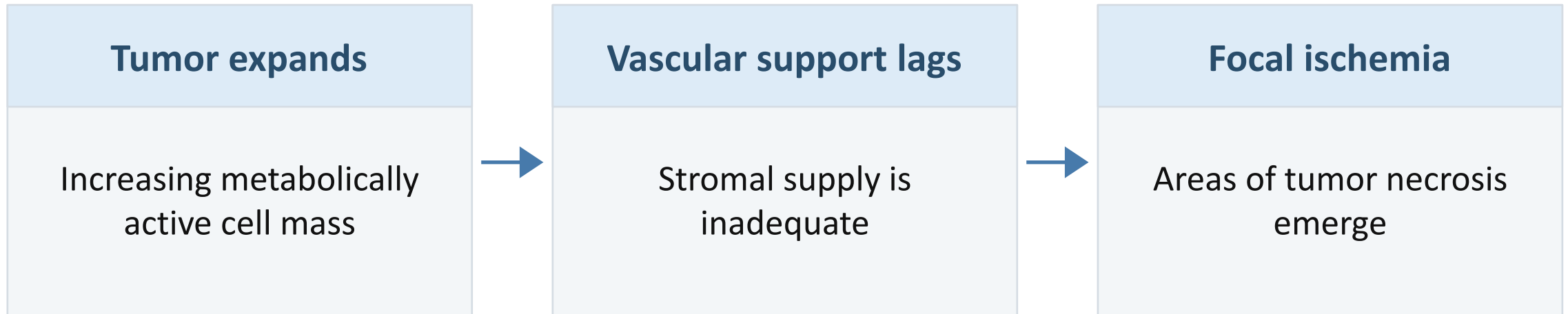
Growing tumor cells require an adequate blood supply.

Vascular stroma may not keep pace with rapid cancer growth.

Insufficient perfusion can produce ischemic necrosis.



Tumor growth and vascular support can become mismatched



Necrosis is contextual—not a stand-alone cancer test

Ischemic necrosis among changes found in rapidly growing cancers.

Its presence should be integrated with cytonuclear and architectural findings.

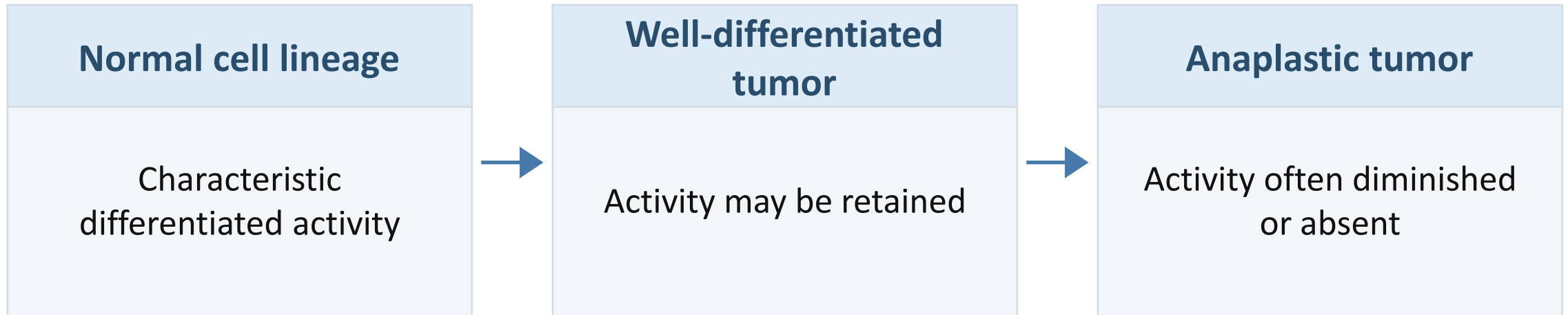
The broader diagnostic question remains tumor identity and invasive behavior.

Do not infer a histologic grade from necrosis alone.

Use a structured assessment of anaplastic morphology

Start with	Ask	Then inspect
Cellular variation	Are cells uniform or pleomorphic?	Giant tumor cells
Nuclear detail	Are contours, chromatin and nucleoli atypical?	N:C ratio
Division	Are mitoses atypical?	Multipolar figures
Architecture	Is polarity retained?	Ordered tissue organization
Stroma	Is perfusion visibly insufficient?	Ischemic necrosis

Differentiation has a functional dimension



Well-differentiated endocrine tumors may secrete hormones

Endocrine neoplasms may retain the specialized secretory function of their tissue.

The secreted hormone may be measurable in the circulation.

Such measurements can help identify tumors and follow therapeutic response.

Function can be diagnostically informative when it is retained.

Keratin production reflects squamous differentiation

Cellular identity

Squamous lineage

Terminal maturation may be recognizable

Keratin is a specialized product

Tumor interpretation

Keratinization signals differentiation

Keratin pearls may occur in carcinoma

Invasion still determines malignancy

Bile production reflects hepatocellular differentiation

Well-differentiated hepatocellular carcinomas may elaborate bile.

The product reflects a retained function of hepatocytes.

Functional resemblance may persist despite malignant behavior.

A retained normal product is not proof of benignity.

Loss of specialization accompanies marked anaplasia

Well-differentiated neoplasm

Often resembles original cells

May retain normal products

Lineage may be recognizable

Highly anaplastic neoplasm

Typically loses specialized activity

May lack obvious mature architecture

May express unexpected proteins

Cancer cells may express unusual proteins

Highly anaplastic cells can acquire features absent from the normal adult lineage.

Some tumors express fetal proteins not made by corresponding mature cells.

Others express proteins associated with a different cell type.

Abnormal functional expression broadens the tumor phenotype.

Bronchogenic carcinomas can secrete ectopic hormones

Unexpected product mentioned by Robbins

Interpretive concept

Corticotropin

Hormone production outside normal source

Parathyroid-like hormone

Ectopic hormone-related activity

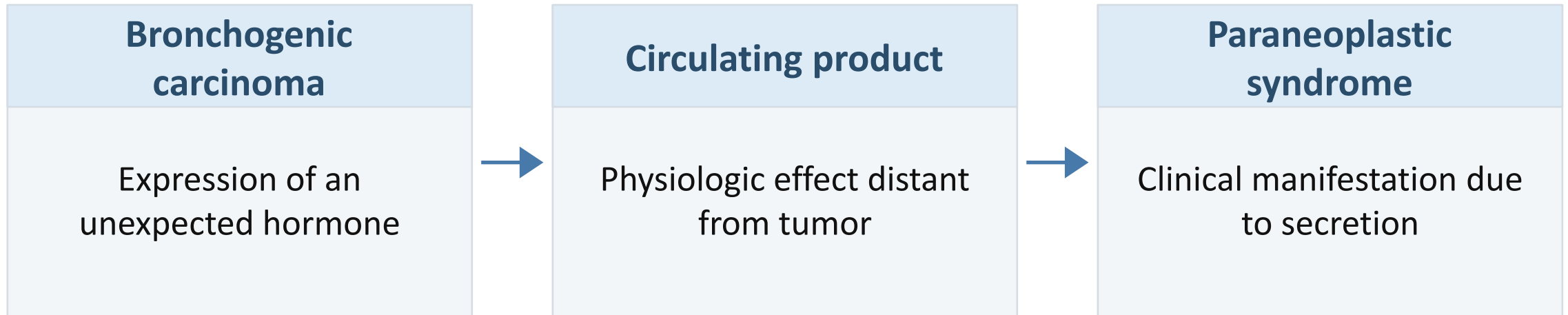
Insulin

Unexpected endocrine phenotype

Glucagon

Unexpected endocrine phenotype

Ectopic secretion can cause paraneoplastic syndromes



Morphology and function need not move together

Morphologic context	Illustrative product	Interpretive implication
Well-differentiated squamous carcinoma	Keratin	Retained lineage-specific function
Well-differentiated hepatocellular carcinoma	Bile	Retained lineage-specific function
Well-differentiated endocrine tumor	Native hormone	May aid diagnosis and follow-up
Highly anaplastic neoplasm	Absent or unexpected secretion	Specialization may be lost or redirected

Growth rate alone cannot reliably separate benign from malignant

Malignant tumors tend, on average, to grow faster than benign tumors.

There are important exceptions across both groups.

Growth rate as an unreliable sole discriminator.

Growth kinetics cannot replace pathologic assessment.

A differentiated appearance does not exclude invasion

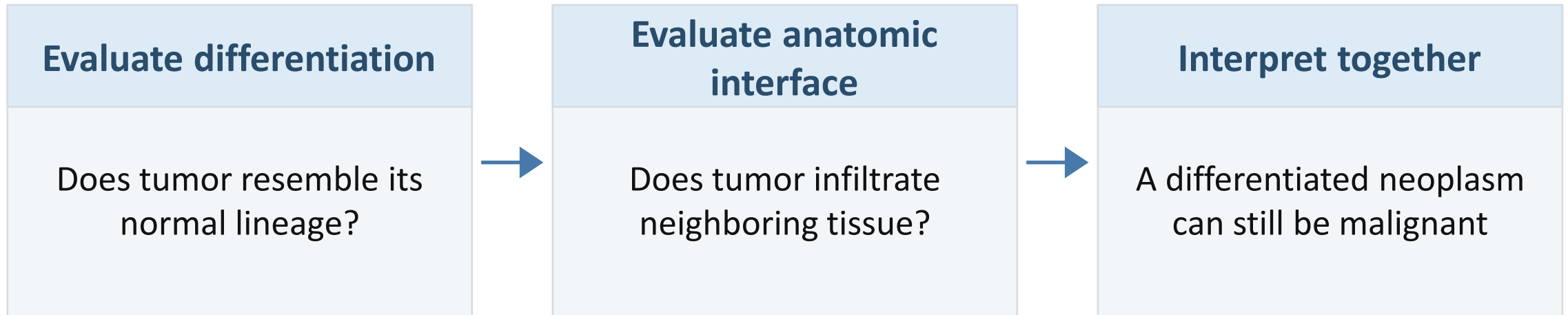
Well-differentiated malignant cells can resemble normal mature cells.

Their malignant nature may be established by invasion of adjacent tissues.

The capacity to metastasize further distinguishes malignant behavior.

Do not diagnose benignity solely from bland cytology.

Distinguishing differentiation from malignant behavior



Clinical interpretation: Bland adipocytes in a mass

Apply the morphologic principles

A discrete soft-tissue lesion is composed of mature, uniform adipocytes. Individual cells resemble normal adipose tissue. What establishes that it is a neoplastic lesion?

Reason from the findings; No additional case data are assumed.

Application: Identify the lesion at tissue level

**The discrete mass of otherwise mature-appearing adipocytes supports a lipoma.
Individual bland cell appearance alone need not reveal neoplasia.**

The tissue-level growth pattern matters.

Differentiation is high; Pleomorphism is not required.

This does not imply all fatty masses are automatically benign.

Clinical interpretation: Distorted colon glands

Apply the morphologic principles

A colonic tumor contains gland-forming epithelium, but the glands are irregular and infiltrate the muscular layer. How is differentiation described, and why is this malignant?

Reason from the findings; No additional case data are assumed.

Application: Gland formation and invasion are compatible

Residual gland formation supports moderate differentiation; Invasive growth into the muscular layer demonstrates malignant behavior.

Glandular architecture is preserved only in part.

Irregular gland shape signals morphologic departure from normal.

Differentiation and invasion answer different questions.

Clinical interpretation: Many mitoses in the intestine

Apply the morphologic principles

A sample of rapidly renewing intestinal epithelium has numerous mitoses. Can the presence of mitoses alone establish malignancy?

Reason from the findings; No additional case data are assumed.

Application: Proliferation is not the same as anaplasia

**No. Normal intestinal epithelium and hyperplastic tissues may have many mitoses.
Bizarre atypical figures and other abnormalities are more concerning.**

Confirm the cell population and tissue context.

Inspect mitotic configuration, not just frequency.

Evaluate architecture and accompanying nuclear features.

Case integration: Pleomorphic cells with tripolar mitoses

Apply the morphologic principles

A tumor shows extreme nuclear size variation, hyperchromatic nuclei, loss of polarity and a tripolar mitotic figure. Which morphologic concept unifies these findings?

Reason from the findings; No additional case data are assumed.

Application: The defining pattern is anaplasia

The combined pattern indicates marked anaplasia: Lack of differentiation with nuclear atypia, pleomorphism and disordered cell division and architecture.

Atypical mitosis is particularly informative.

Multiple concordant findings strengthen interpretation.

Additional evidence still establishes exact tumor lineage and extent.

Interpretation checklist for tumor differentiation

Question	Finding supporting differentiation	Finding supporting anaplasia
Does it resemble origin?	Recognizable tissue-specific structures	Little resemblance
Are cells uniform?	Bland, similar-looking cells	Marked pleomorphism
Are nuclei mature appearing?	Relatively normal morphology	High N:C ratio, irregular contours
Are divisions ordinary?	Infrequent, typical figures	Bizarre atypical mitoses
Is orientation retained?	Ordered polarity	Disorganized growth
Is function retained?	Characteristic secretions/products	Lost or unexpected products

Central conclusions

Differentiation measures morphologic and functional resemblance to normal lineage.

Anaplasia describes loss of differentiation and a constellation of cytologic and architectural abnormalities.

Well-differentiated tumors can be malignant; Invasion and metastasis remain decisive behavioral features.

Functional retention or ectopic secretion can be diagnostically and clinically significant.

Interpret phenotype, architecture and behavior together.

Reference and source limitations

Primary source

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

Chapter 7, Neoplasia: “Differentiation and Anaplasia,” printed pages 239–241.

Parent context: “Characteristics of Benign and Malignant Neoplasms,” page 239.

Schematic figures in this lecture are not diagnostic specimens.