

Ovarian Clear Cell Carcinoma

Pathogenesis • morphology • diagnosis • clinicopathologic
significance

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Learning outcomes

- Recognize clear cell carcinoma as a distinct ovarian epithelial histotype.
- Relate endometriosis and molecular alterations to pathogenesis.
- Identify the major gross and microscopic architectural patterns.
- Select and interpret a focused immunohistochemical panel.
- Explain how stage modifies prognosis and diagnostic priorities.

Five principal ovarian carcinoma histotypes

High-grade serous

Frequently linked to fallopian tube precursor lesions.

Low-grade serous

A different molecular and clinical pathway from high-grade serous.

Endometrioid

Endometrial-type glands; May be associated with endometriosis.

Clear cell

Distinct WHO histotype; Characteristically complex architecture and clear/hobnail cells.

Mucinous

Intestinal/gastric-type mucinous differentiation; Exclude metastasis.

Defining ovarian clear cell carcinoma

A malignant epithelial neoplasm with characteristic architecture and cytology.

- Large epithelial cells often have abundant optically clear cytoplasm.
- Recognition requires integration of architecture, cytology, and context.
- Clear cytoplasm alone is neither necessary nor sufficient for diagnosis.

Textbook terminology versus current classification

Robbins: descriptive relationship	WHO 2020: diagnostic classification
Notes overlap with ovarian endometrioid carcinoma.	Lists clear cell carcinoma as a separate principal histotype.
Shared mutations help explain biological relationships.	Histotype assignment remains morphologically informed.
Do not interpret “variant” as a current synonym.	Report the distinctive clear cell carcinoma diagnosis.

A relatively uncommon ovarian carcinoma

Clear cell carcinoma as approximately 6% of malignant ovarian tumors.

- It is substantially less frequent than serous carcinoma.
- Benign and borderline clear cell tumors are exceedingly rare.
- Relative rarity makes histotype-specific recognition important.

Benign, borderline, and malignant clear cell lesions

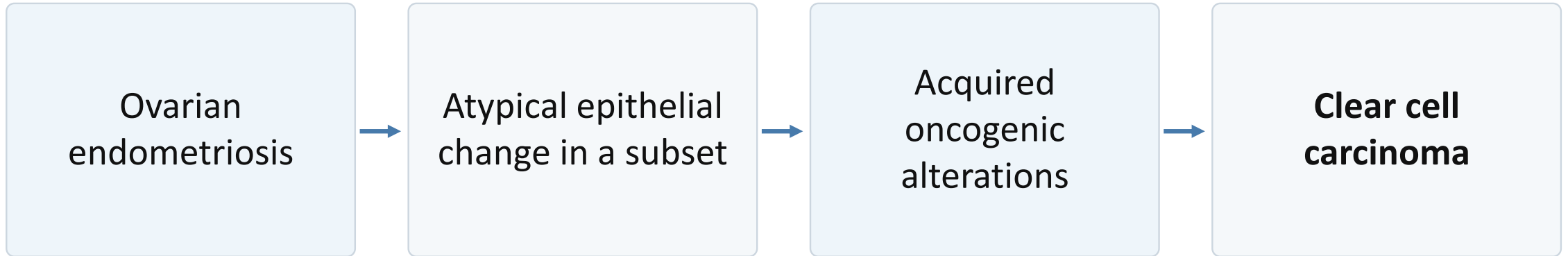
Category	Meaning in this context
Benign	Exceedingly rare according to Robbins.
Borderline	Exceedingly rare; not a common pathway.
Clear cell carcinoma	The clinically important malignant epithelial category.

Association with ovarian endometriosis

Endometriosis is a recognized setting for ovarian clear cell carcinoma.

- A carcinoma may coexist with an endometriotic cyst.
- Endometriosis-associated tumors share biological themes with endometrioid carcinoma.
- An association is not proof that every tumor arose from endometriosis.

Endometriosis-associated carcinogenesis

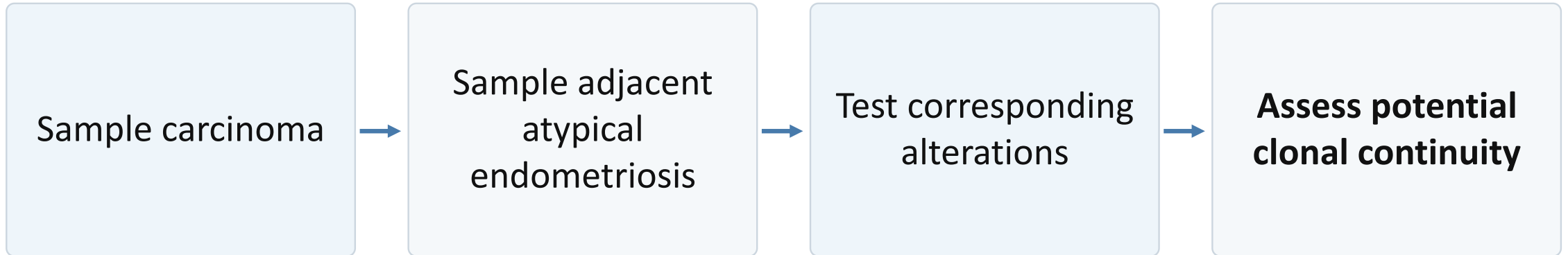


A conceptual pathway in a subset of tumors; Not all endometriosis progresses to malignancy.

Association, precursor evidence, and causation

Observation	Interpretive strength
Endometriosis near a carcinoma	Association; not automatically direct precursor evidence.
Contiguous atypical endometriosis	Supports a precursor–carcinoma relationship.
Shared somatic molecular alteration	Supports clonal relationship in the studied lesion.

What molecular study adds



Concordant alterations can strengthen, but not replace, morphologic assessment.

Clear cell and endometrioid carcinomas

Feature	Clear cell carcinoma	Endometrioid carcinoma
Classification	Distinct ovarian histotype	Distinct ovarian histotype
Endometriosis association	Recognized	Recognized
Typical morphology	Clear/hobnail cells; varied architecture	Endometrial-type tubular glands
Molecular overlap	ARID1A, PIK3CA and others	ARID1A, PI3K-pathway and other changes

Genes cited for clear cell carcinoma

ARID1A

Chromatin remodeling; Shared with endometrioid tumors.

PIK3CA

A component of PI3K signaling.

PTEN

Negative regulator of the PI3K signaling pathway.

KRAS

Oncogenic signaling alteration in a subset.

TP53

May be altered; Not the signature event seen in high-grade serous cancer.

ARID1A: Chromatin-remodeling disruption

ARID1A encodes a component of the SWI/SNF chromatin-remodeling machinery.

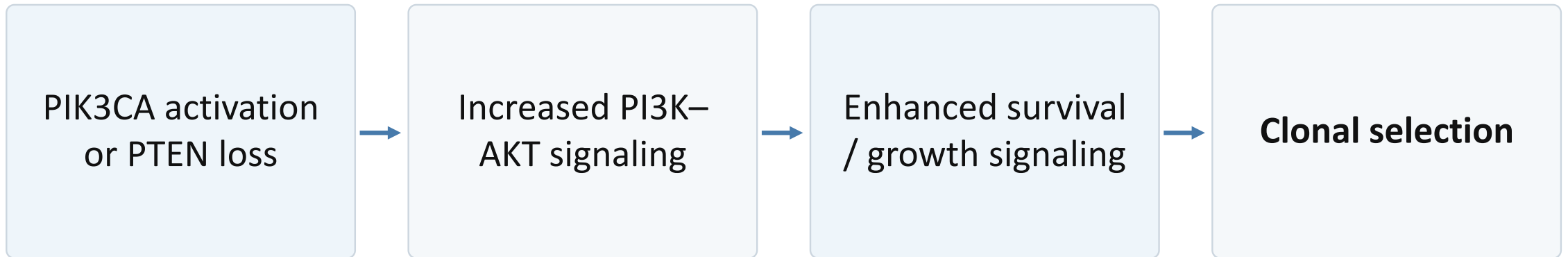
- ARID1A alterations occur in a substantial subset of ovarian clear cell carcinomas.
- Atypical endometriosis can share ARID1A loss with adjacent carcinoma.
- Loss of BAF250a expression is a surrogate for some ARID1A alterations, not a universal diagnostic criterion.

PIK3CA: Oncogenic signaling

PIK3CA encodes the catalytic PI3K α subunit.

- PIK3CA alterations are recurrent in ovarian clear cell carcinoma.
- PI3K signaling promotes cellular growth and survival.
- A molecular alteration does not replace histologic identification of the carcinoma subtype.

PI3K pathway — simplified causal relation



General pathway interpretation; A teaching schematic, not a patient-specific validated assay.

Why shared mutations do not imply identical tumor types

Molecular finding	Interpretation
ARID1A or PIK3CA alteration	May be seen in clear cell and endometrioid carcinoma.
Overlapping molecular pathways	Biological relationship, not morphological equivalence.
Histotype-specific appearance	Remains important for diagnosis and prognosis.

TP53 requires careful interpretation

TP53 mutation is characteristic of high-grade serous carcinoma, not a universal feature of clear cell carcinoma.

- TP53 among alterations reported in clear cell carcinoma.
- WHO-informed reviews describe TP53 changes as less typical for clear cell carcinoma.
- An abnormal p53 staining pattern should prompt review of morphology and differential diagnosis.

Clear cell versus high-grade serous pathways

Feature	Clear cell carcinoma	High-grade serous carcinoma
Common setting	Endometriosis-associated in a subset	Tubal fimbrial/STIC pathway prominent
Characteristic genes	ARID1A; PIK3CA	TP53; homologous-recombination pathway
Typical p53 staining	Often wild-type pattern	Usually mutation-type pattern
WT1	Usually negative	Often diffuse positive

Molecular alterations are supportive, not diagnostic alone

Morphology and histotype-directed immunohistochemistry drive classification.

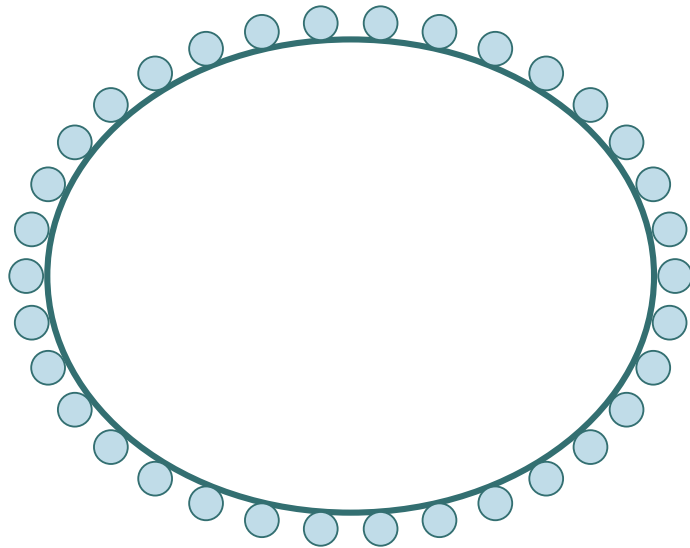
- ARID1A loss is not unique to ovarian clear cell carcinoma.
- The genotype of a tumor must be interpreted with architecture and cytology.
- Clinical site and potential metastasis can change the diagnostic question.

Gross presentation: Solid and cystic components

Ovarian clear cell carcinoma may be predominantly solid or cystic.

- Robbins explicitly describes both gross configurations.
- A tumor can contain mixed solid and cystic regions.
- Sampling must include visually different areas to characterize the lesion.

Cystic tumors: Neoplastic epithelial lining

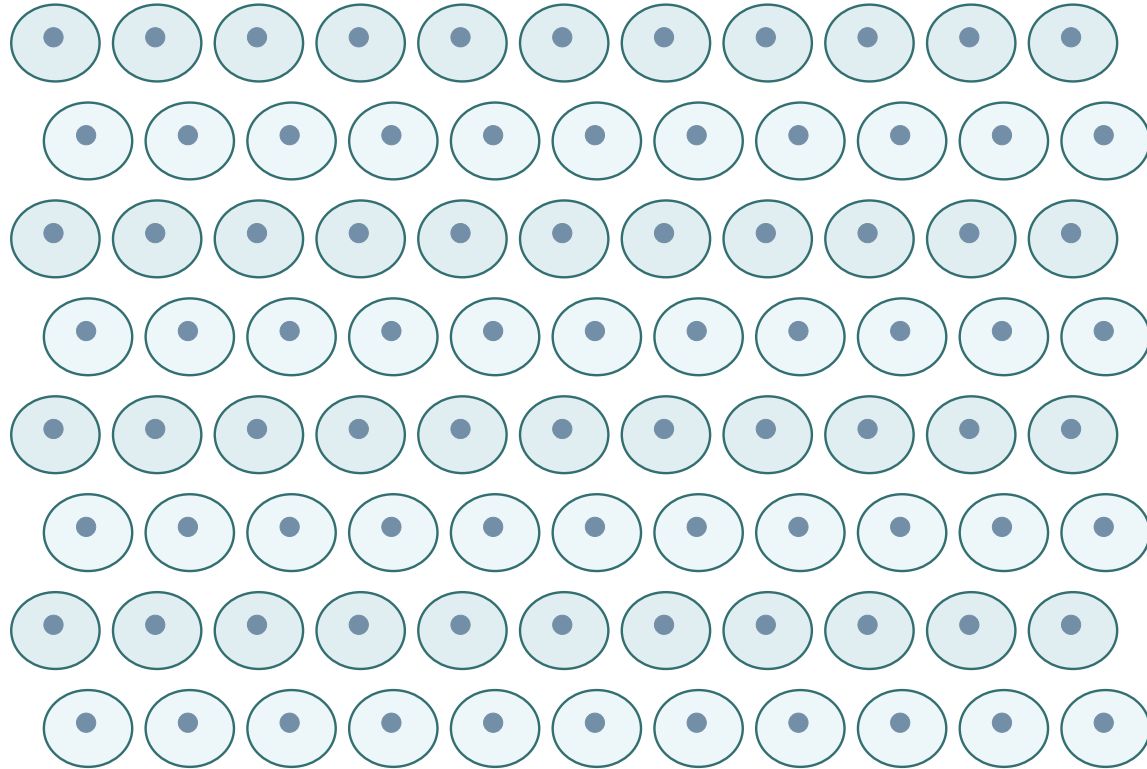


Conceptual schematic — not a histologic specimen

A cystic component is lined by neoplastic epithelial cells.

The cavity is a growth pattern, not proof of benign behavior.

Solid tumors: Epithelial sheets



Conceptual schematic — not a histologic specimen

In a solid component, neoplastic epithelial cells may form dense sheets.

Solid growth alone is not specific for this histotype.

Gross sampling priorities

Area	Why it matters
Solid focus	Can reveal epithelial cytology and additional architecture.
Cyst lining	Shows epithelial arrangement and any focal complexity.
Adjacent suspected endometriosis	Can document spatial association or transition.
Surface or capsular abnormality	Important for extent of disease; requires pathologic correlation.

Gross appearance is not a substitute for histology

A solid–cystic ovarian mass is a pattern shared by several tumor types.

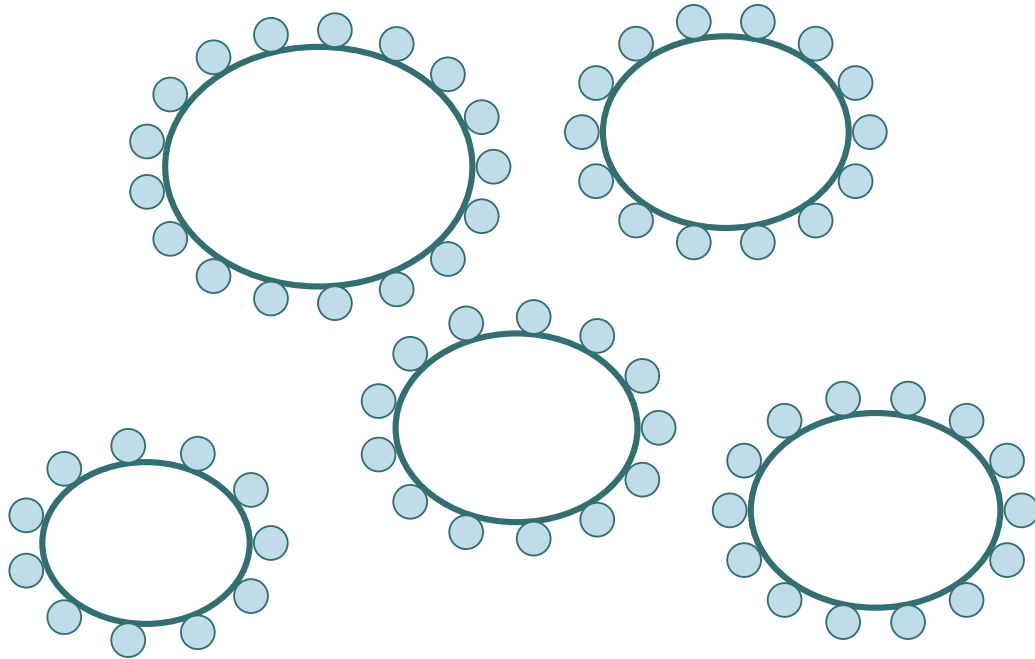
- Gross configuration helps direct sampling.
- The definitive histotype is established from microscopic findings.
- Do not infer clear cell carcinoma from cyst color or contents alone.

Three recurring microscopic architectures

Papillary, tubulocystic, and solid patterns are characteristic.

- A single tumor may display more than one architecture.
- Pattern recognition begins at low power.
- Cytologic features and supportive staining refine the diagnosis.

Tubulocystic architecture: Multiple lumina

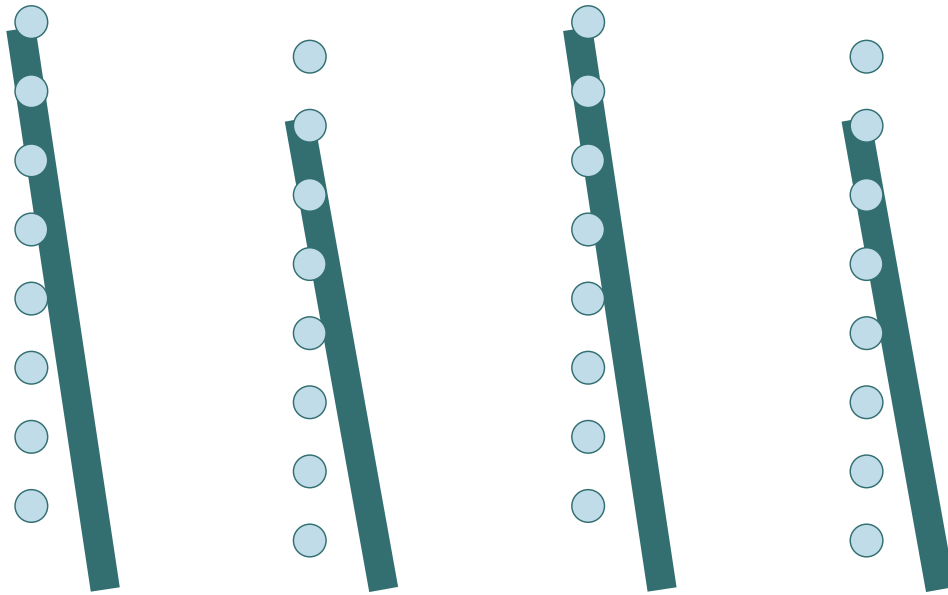


Conceptual schematic — not a histologic specimen

Variably sized glands or cystic spaces are separated by tissue stroma.

Inspect the epithelial lining for clear and hobnail cells.

Papillary architecture: Projecting fronds

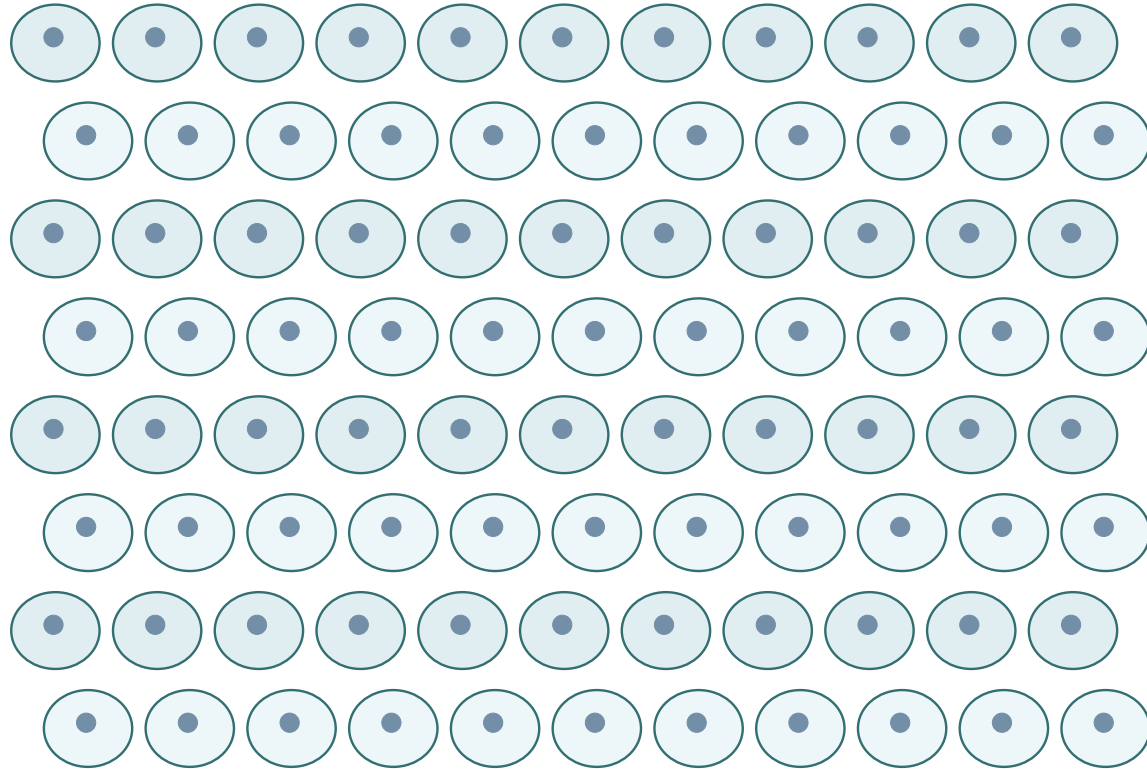


Conceptual schematic — not a histologic specimen

Tumor-lined projections
extend into spaces.

Papillary cores may
contain prominent
hyalinized material.

Solid architecture: Confluent cell groups

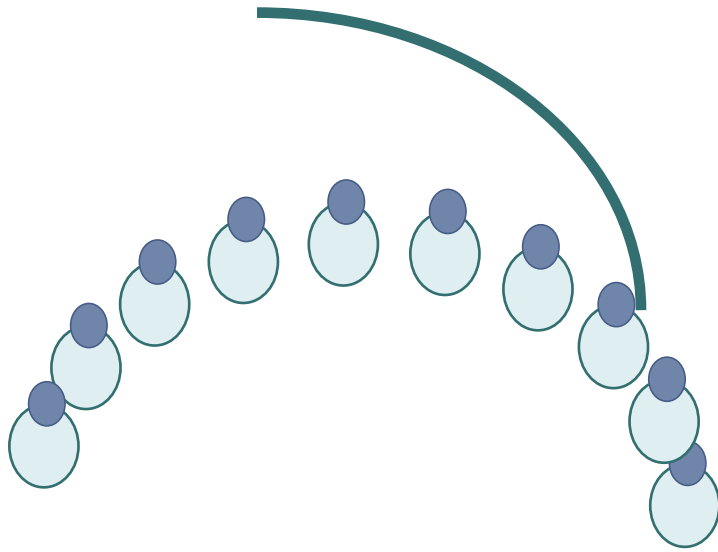


Conceptual schematic — not a histologic specimen

Confluent epithelial sheets can coexist with papillary or tubulocystic regions.

The tumor is not defined by clear cytoplasm alone.

Hobnail cells: Nucleus projects into a lumen



Conceptual schematic — not a histologic specimen

A hobnail cell has an eccentrically projecting nucleus toward the luminal surface.

This is a valuable pattern, not an obligatory finding.

Clear cytoplasm: A cytologic clue

Large cells may show abundant optically clear cytoplasm.

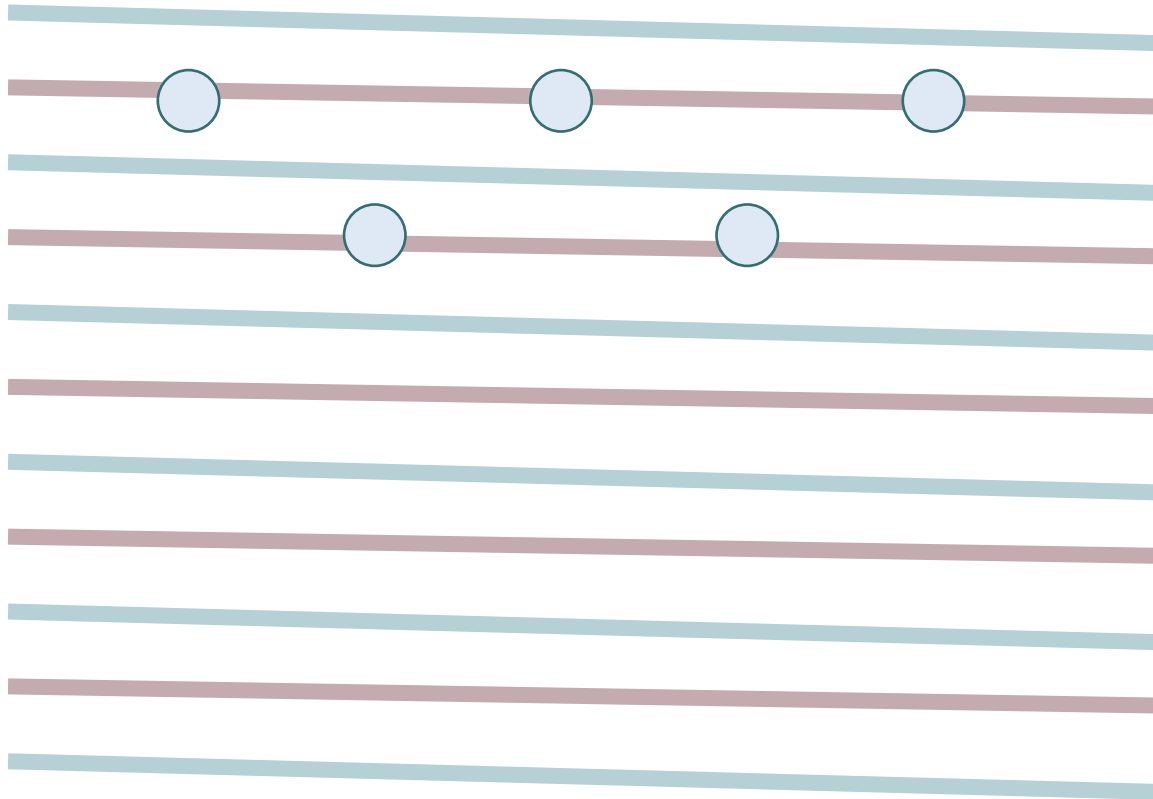
- This appearance helps explain the name “clear cell.”
- Eosinophilic cytoplasm may also occur in clear cell carcinoma.
- Other ovarian histotypes can contain clear cells.

Nuclear features are part of the diagnosis

Evaluate nuclear enlargement, atypia, and prominent nucleoli.

- The degree and distribution of atypia provide context.
- Hobnail nuclear position is a separate feature from nuclear grade.
- Atypia must be assessed in relation to the architecture.

Hyalinized cores and extracellular material



Conceptual schematic — not a histologic specimen

Dense hyaline stromal material may expand papillary cores.

This supports, but does not establish, a diagnosis of clear cell carcinoma.

Hyaline bodies: A supportive microscopic clue

Round eosinophilic hyaline bodies may be seen in ovarian clear cell carcinoma.

- Hyaline material can occur within or around tumor structures.
- Use the finding in combination with architecture and epithelial cytology.
- The absence of hyaline bodies does not exclude the histotype.

Architecture versus cytology

Architectural clue	Cytologic clue	Interpretation
Papillary growth	Clear or eosinophilic cells	One recognizable combination
Tubules / cysts	Hobnail nuclei	Another characteristic combination
Solid sheets	Large clear cells	Possible pattern; differential remains broad

A crucial pitfall: Clear cells occur in other carcinomas

Do not diagnose ovarian clear cell carcinoma from a clear cytoplasmic phenotype alone.

- High-grade serous carcinoma can show clear-cell change.
- Endometrioid carcinoma can show clear-cell areas.
- Use architecture, nuclei, immunophenotype, and full sampling.

Microscopic examination at two scales

Low-power assessment	High-power assessment
Papillary, tubulocystic, or solid growth	Clear/eosinophilic cytoplasm
Relationship of patterns and stroma	Hobnail nuclear configuration
Associated endometriosis or adenofibromatous areas	Nuclear atypia, nucleoli, hyaline bodies

The role of immunohistochemistry

Use stains to resolve a specific morphologic differential.

- Panel selection follows the histologic question.
- No single stain is perfectly sensitive and specific.
- Interpret staining pattern, localization, and internal controls together.

Core ovarian histotyping immunopanel

WT1

Often positive in high-grade serous carcinoma; Typically negative in clear cell.

P53

Mutation-type pattern suggests high-grade serous in the appropriate context.

Napsin A

Supports ovarian clear cell differentiation.

PR

Often more informative for endometrioid than clear cell carcinoma.

Napsin A: A practical diagnostic adjunct

Napsin A is frequently expressed in ovarian clear cell carcinoma.

- Cytoplasmic positivity supports clear cell differentiation.
- Negative staining does not definitively exclude the tumor.
- Napsin A is not exclusive to ovarian tumors; Clinical context matters.

HNF1 β : Supportive, not exclusive

HNF1 β nuclear expression is commonly observed in ovarian clear cell carcinoma.

- HNF1 β is linked to the clear cell differentiation phenotype.
- It can provide supportive evidence when morphology is suggestive.
- Do not use HNF1 β positivity alone to establish the primary site.

PAX8: Establishes lineage, not necessarily origin

PAX8 is commonly expressed in Müllerian ovarian carcinoma.

- PAX8 positivity supports an epithelial Müllerian-lineage differential.
- Renal clear cell carcinoma can also express PAX8.
- PAX8 alone cannot resolve ovarian versus renal primary origin.

WT1 and p53 in the key serous differential

Marker	Clear cell carcinoma	High-grade serous carcinoma
WT1	Typically negative	Usually positive
p53	Often wild-type pattern	Commonly mutation-type pattern
Napsin A	Often positive	Usually negative

Hormone receptor patterns

Marker	Typical ovarian clear cell	Typical endometrioid carcinoma
ER	Often negative	Often positive
PR	Often negative	Often positive
Interpretation	Negative receptors support when morphology matches	Receptor expression can favor endometrioid phenotype

ARID1A immunostaining: Distinguish use cases

BAF250a loss can support an altered ARID1A pathway, but is not histotype-specific.

- Loss requires retained internal positive controls.
- Endometrioid ovarian tumors may also show ARID1A alterations.
- ARID1A staining is not a substitute for morphology or the core histotyping panel.

Focused histotyping workflow

Review H&E
architecture



Form a defined
differential



Choose WT1 / p53
/ Napsin A / PR as
indicated



**Integrate IHC and
morphology**

Extend the panel according to site, history, and unusual findings.

Clear cell versus endometrioid carcinoma

Question	Favors clear cell	Favors endometrioid
Architecture	Tubulocystic / papillary / solid	Endometrial-type tubular glands
Cells	Hobnail/clear or eosinophilic	Columnar glandular cells
Immunophenotype	Napsin A / HNF1 β often positive	ER / PR often positive
Molecular overlap	ARID1A, PIK3CA possible	ARID1A, PI3K-pathway possible

Clear cell versus high-grade serous carcinoma

Question	Favors clear cell	Favors high-grade serous
Architecture	Tubulocystic / hyalinized papillae	High-grade epithelial architecture
WT1	Usually negative	Usually positive
p53	Often wild-type	Usually mutation-type
Napsin A	Often expressed	Usually absent

Metastatic renal clear cell carcinoma: Key pitfall

Feature	Ovarian clear cell	Metastatic renal clear cell
PAX8	May be positive	May be positive
CK7	Typically positive	Often negative/focal
CD10 / RCC marker	Usually not diffuse positive	Frequently supports renal origin
Deciding evidence	Full morphology + site context	Renal imaging/history + targeted panel

A diagnosis is an integrated conclusion

Architecture + cytology + immunophenotype + clinical site.

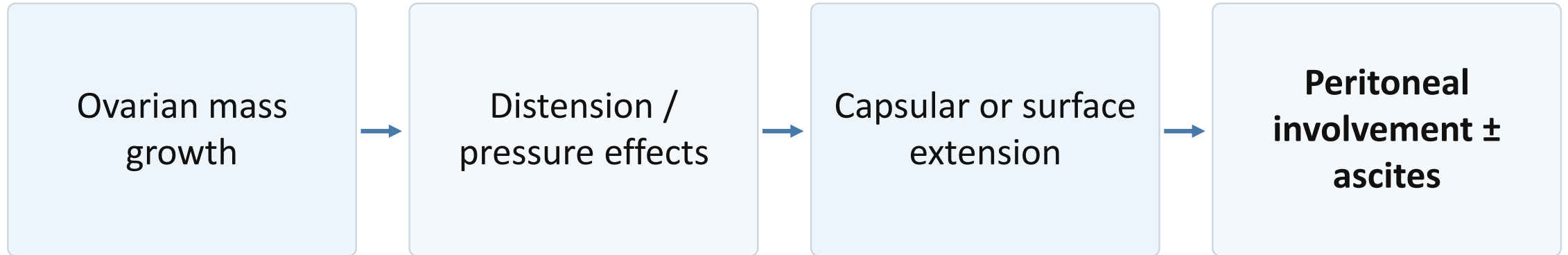
- Do not allow one aberrant stain to outweigh convincing morphology.
- Consider concurrent endometrial disease and metastatic tumors when relevant.
- State the ovarian histotype clearly when criteria are met.

Clinical presentation: Symptoms are nonspecific

Ovarian carcinomas commonly present with lower abdominal pain or abdominal enlargement.

- Pelvic pressure may produce urinary frequency or dysuria.
- Gastrointestinal complaints can accompany pelvic masses.
- Symptoms alone do not identify the histotype.

From ovarian lesion to clinical manifestations



Conceptual clinical progression; Timing and presentation vary between patients.

Peritoneal dissemination matters

Ovarian carcinoma can seed peritoneal surfaces after extracapsular spread.

- Ascites may contain exfoliated malignant cells.
- Peritoneal disease changes the extent of disease and clinical course.
- Clear cell histology does not eliminate the need for full staging assessment.

Localized disease: A comparatively favorable outcome

Approximately 90% 5-year survival when clear cell carcinoma is confined to the ovaries.

- This textbook estimate is conditional on localized disease.
- It is not an individual patient prediction.
- Do not generalize this survival figure to advanced-stage disease.

Advanced disease: The prognosis changes markedly

Poor outcome with advanced-stage clear cell carcinoma.

- Stage and spread are essential when interpreting survival.
- WHO-informed reviews report lower sensitivity to standard platinum-based therapy.
- Histotype and stage should both appear in clinicopathologic discussions.

Why stage must accompany the histologic label

Localized disease	Advanced disease
Disease confined to ovarian site.	Extension beyond the ovary and/or metastatic deposits.
Robbins cites approximately 90% 5-year survival.	Robbins describes an unfavorable outcome.
Requires complete assessment of extent.	Requires comprehensive assessment of dissemination.

CA-125: Monitoring versus screening

CA-125 is used in known ovarian carcinoma to monitor recurrence or progression.

- It is not an adequately sensitive and specific population screening tool.
- A single CA-125 value cannot assign ovarian histotype.
- Interpret serial results with disease status and imaging when appropriate.

Screening limitations and prevention

The absence of a sufficiently accurate general ovarian cancer screening assay.

- Risk-based interventions are discussed for heritable BRCA-associated susceptibility.
- Those interventions chiefly address broader ovarian cancer prevention, not a CCC-specific signature.
- Avoid treating a negative screening test as exclusion of carcinoma.

Clinical management is not defined by one stain

Treatment planning integrates histotype, extent, and patient context.

- Clear cell carcinoma is treated as ovarian carcinoma.
- Contemporary clinical guidance distinguishes epithelial ovarian histotypes.
- Staining results support diagnosis; Treatment selection requires wider assessment.

Diagnostic exercise: Morphology first

An ovarian mass shows tubulocystic and papillary epithelial growth, clear cytoplasm, and nuclei projecting into lumina.

- Name the leading histotype.
- State two supporting microscopic features.

Exercise answer: Architectural and cellular pattern

Ovarian clear cell carcinoma is the leading consideration.

- Tubulocystic / papillary architecture supports the diagnosis.
- Hobnail cells and clear cytoplasm provide cytologic support.
- An IHC panel is appropriate if the differential remains uncertain.

Diagnostic exercise: An IHC differential

An ovarian carcinoma with clear-cell morphology is WT1-negative, shows a wild-type p53 pattern, and is Napsin A-positive.

- Which histotype is supported?
- Why should the result not be interpreted from Napsin A alone?

Exercise answer: Interpret the panel together

The panel favors ovarian clear cell carcinoma when morphology is concordant.

- WT1 negativity and nonaberrant p53 argue against typical HGSC.
- Napsin A positivity supports clear cell differentiation.
- The panel must be interpreted with histology and tumor site.

Diagnostic exercise: Exclude metastasis

An ovarian clear-cell tumor is PAX8-positive in a patient with a prior renal malignancy.

- Does PAX8 positivity prove an ovarian primary?
- What additional diagnostic evidence is needed?

Exercise answer: Assign the primary site carefully

PAX8 positivity alone does not distinguish ovarian from renal clear-cell carcinoma.

- Review imaging and the known renal tumor.
- Assess CK7, CD10, RCC marker, and other targeted stains.
- Correlate architectural and cytologic features with the clinical history.

Final synthesis: Diagnostic chain

Domain	Questions answered
Setting	Is the lesion ovarian? Is there endometriosis or a competing primary?
Morphology	Is there papillary, tubulocystic, or solid growth with characteristic cells?
IHC	Do WT1, p53, Napsin A and selected adjuncts fit the histotype?
Prognosis	Is the tumor confined to the ovaries or advanced?

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