

Renal Cell Carcinoma

Pathogenesis • morphology • clinical correlations

A pathology teaching lecture

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning outcomes

- Distinguish major renal cell carcinoma subtypes by molecular and histologic features.
- Explain how VHL inactivation alters hypoxia signaling and tumor vascularity.
- Recognize the major familial predisposition syndromes.
- Connect anatomic behavior with hematuria, venous invasion, and metastasis.
- Interpret clinicopathologic clues in focused case examples.

Renal carcinoma in context

RCC is the dominant malignant epithelial tumor of the adult kidney

- RCC accounts for approximately 85% of adult renal cancers in the source textbook.
- Renal pelvic urothelial carcinoma is a different epithelial malignancy.
- Tumor classification integrates architecture with cytogenetic and genetic changes.

Demographic profile

- Most RCCs occur in the sixth and seventh decades.
- The source reports an approximately 2:1 male predominance.
- Most tumors arise sporadically rather than through inherited syndromes.
- An appreciable minority presents before symptoms develop, because of incidental imaging.

Risk factors: Exposure and host

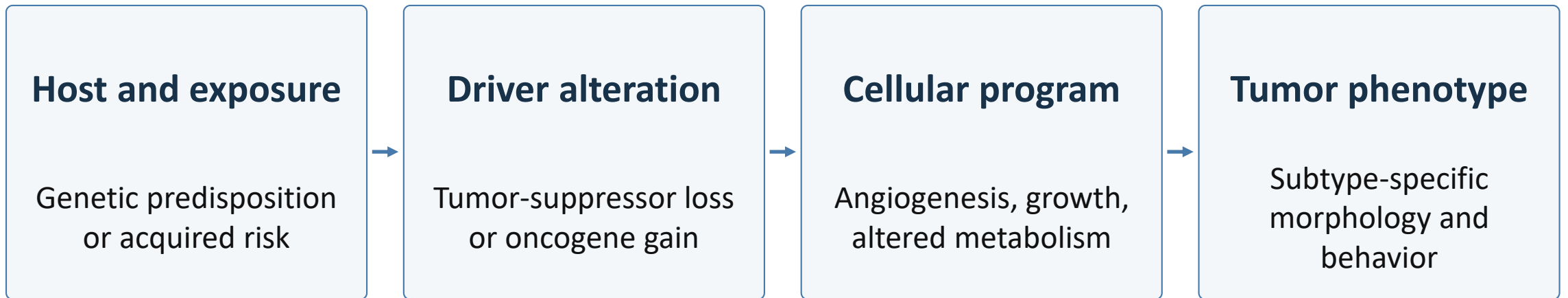
Potentially modifiable factors

- Tobacco use is emphasized as a major risk factor.
- Obesity and hypertension have been associated with RCC.
- Occupational/environmental exposures reported include petroleum products and heavy metals.

Renal disease settings

- Chronic kidney disease and end-stage kidney disease increase risk.
- Acquired cystic kidney disease is an important association.
- Tuberous sclerosis is included among predisposition settings.

A framework for renal carcinogenesis



Sporadic and familial RCC

Sporadic carcinomas

- Form the great majority of RCC cases.
- Frequently involve somatic changes in subtype-specific drivers.
- Most clear cell RCCs are sporadic.

Familial predisposition

- Usually autosomal dominant in the syndromes discussed.
- Often presents earlier in life.
- Bilaterality and multiplicity can suggest inherited susceptibility.

Inherited syndromes: Practical clues

- Young age or multifocal bilateral disease warrants attention to hereditary susceptibility.
- Extrarenal manifestations often identify a specific constitutional syndrome.
- Inherited syndromes clarify the oncogenic pathways used by sporadic tumors.
- Absence of family history does not exclude a genetically defined renal tumor.

Four important hereditary associations

VHL syndrome

Renal cysts and often bilateral, multiple clear cell renal carcinomas.

FH deficiency

Leiomyomas and an aggressive FH-deficient renal cancer phenotype.

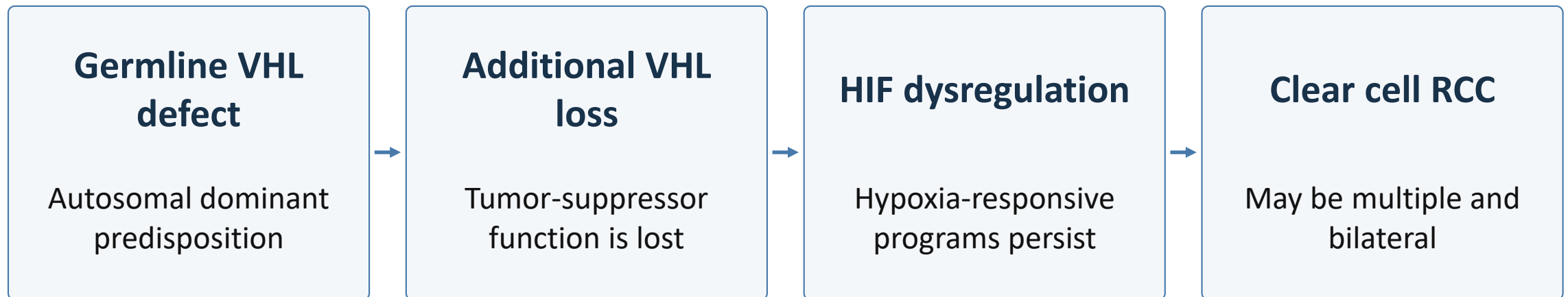
Hereditary papillary RCC

Multiple bilateral papillary tumors; Activating MET alterations.

Birt–Hogg–Dubé syndrome

Skin lesions, pulmonary cysts, and morphologically diverse renal tumors.

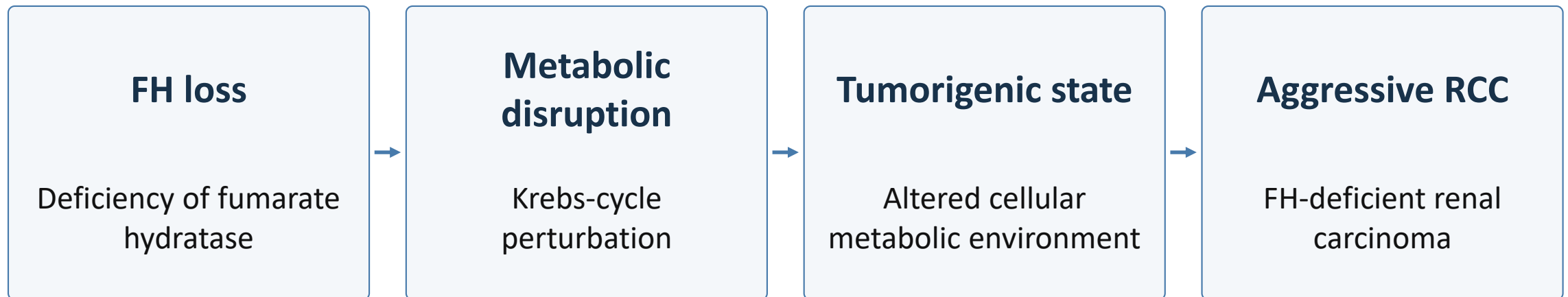
VHL syndrome and renal tumors



FH-deficient renal cell carcinoma

- The FH gene encodes fumarate hydratase, a Krebs-cycle enzyme.
- Loss-of-function is associated with hereditary leiomyomatosis and RCC syndrome.
- Skin and uterine leiomyomas may accompany the renal tumor.
- The kidney tumor can be aggressive with a propensity for metastasis.
- FH-deficient RCC may occur without an evident hereditary family history.

FH loss links metabolism with carcinogenesis



Hereditary papillary renal carcinoma

- Typically an autosomal dominant predisposition.
- Multiple bilateral papillary renal tumors are characteristic.
- Activating mutations of MET are the central genetic feature.
- Tumors are often relatively low nuclear grade in the reported syndrome.

Birt–Hogg–Dubé syndrome

- Loss of folliculin function results from mutations of the BHD/FLCN gene.
- Cutaneous findings include fibrofolliculomas and related papules.
- Pulmonary cysts or blebs are part of the syndrome.
- Renal tumors can show different morphologic patterns rather than one uniform subtype.

Hereditary syndromes compared

Syndrome	Gene / pathway	Diagnostic context
von Hippel–Lindau	VHL; HIF signaling	Cysts; multifocal/bilateral clear cell RCC
FH-deficient RCC	FH; metabolic enzyme	Cutaneous/uterine leiomyomas; aggressive RCC
Hereditary papillary	MET activation	Bilateral multifocal papillary RCC
Birt–Hogg–Dubé	BHD / folliculin	Skin papules, lung cysts, renal tumors

Principles of subtype classification

- Histology is interpreted together with cytogenetic and genetic findings.
- Clear cell, papillary, and chromophobe RCC are major categories.
- TFE3-rearranged RCC and collecting duct carcinoma are less common examples.
- Sarcomatoid change may arise across several RCC subtypes; It is not a single lineage.

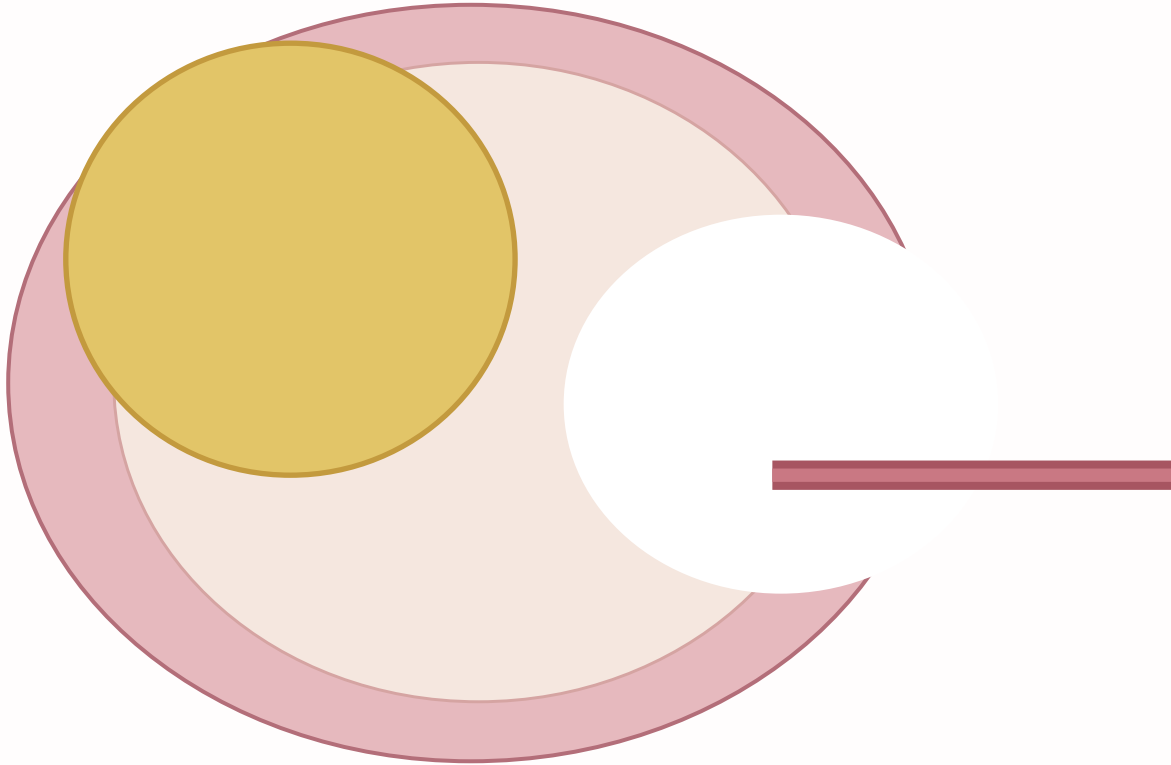
Major renal cell carcinoma subtypes

Subtype	Approximate share	Hallmark
Clear cell	70–80%	VHL/3p abnormalities; clear nests
Papillary	10–15%	7/17 gains; papillae; MET subset
Chromophobe	~5%	Multiple chromosome losses; perinuclear halo
Collecting duct	≤1%	Medullary glands with desmoplasia

Clear cell RCC: The predominant subtype

- Constitutes approximately 70–80% of RCC in the source.
- Believed to arise predominantly from proximal tubular epithelium.
- Usually presents as a solitary unilateral tumor.
- Growth patterns include nested, tubular, solid, and pseudopapillary forms.
- VHL pathway loss is a central oncogenic event.

Clear cell RCC: Gross architecture



Gross-anatomic interpretation

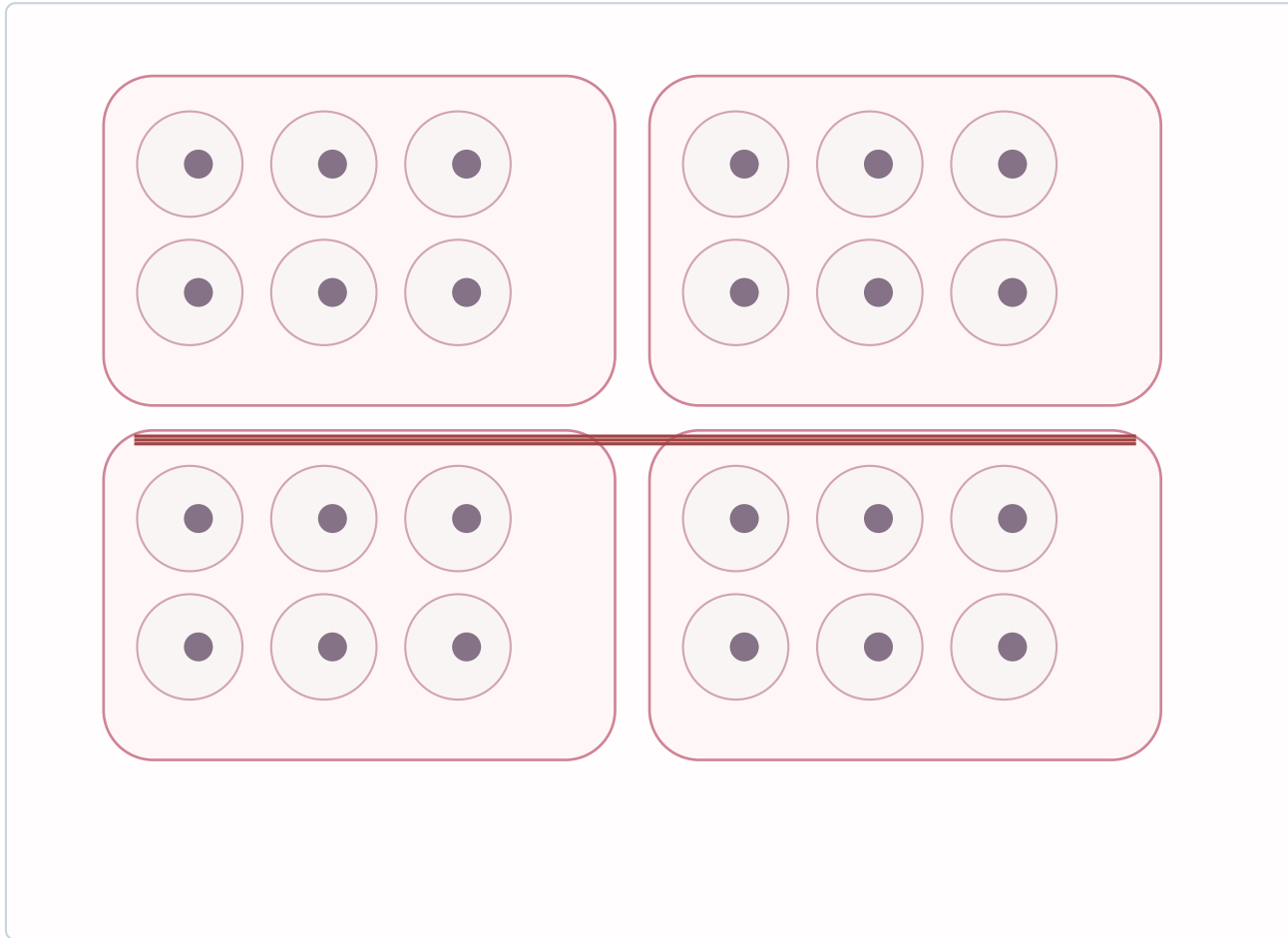
- Polar tumor location
- Distortion of renal outline
- Necrosis and hemorrhage may coexist

Simplified kidney cross-section: Diagrammatic location and spread (not a gross specimen)

Clear cell RCC: Gross specimen clues

- A rounded, well-demarcated cortical tumor may distort the kidney.
- Bright yellow coloration reflects lipid accumulation in tumor cells.
- Hemorrhagic and gray-white necrotic regions are frequent.
- The tumor may contain cystic areas or more extensive hyalinization.
- Gross appearance alone does not establish histologic subtype.

Clear cell RCC: Nested architecture



What to recognize

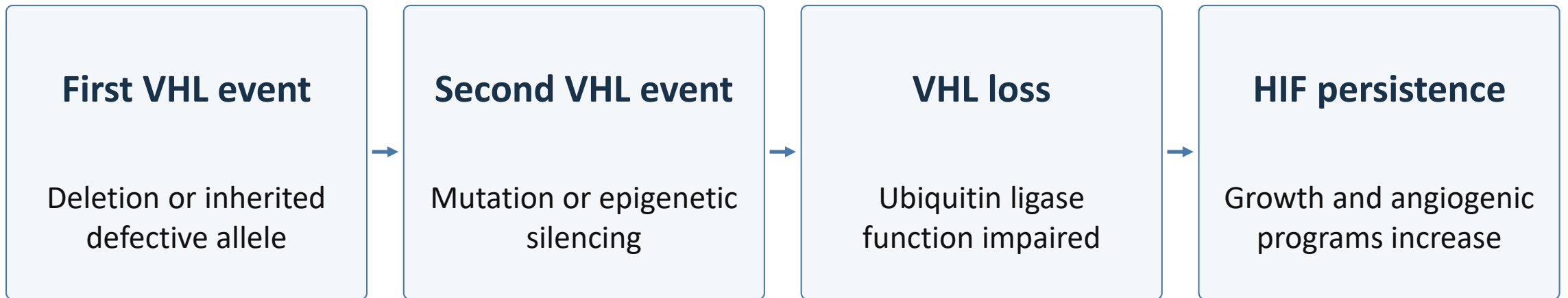
- Cells are polygonal or rounded.
- Clear or granular cytoplasm reflects lipid and glycogen content.
- Fine branching vessels separate tumor nests.
- Nuclear atypia varies from mild to striking.

Schematic architecture only — not a histologic specimen

Why does clear cell cytoplasm look clear?

- Neoplastic cells accumulate lipids and glycogen.
- Routine tissue processing removes much of the cytoplasmic lipid.
- The remaining pale cytoplasm creates the diagnostic “clear cell” appearance.
- This cytoplasmic phenotype must be interpreted with architecture and context.

VHL: The two-hit tumor-suppressor model



Oxygen sensing: Intact VHL versus loss

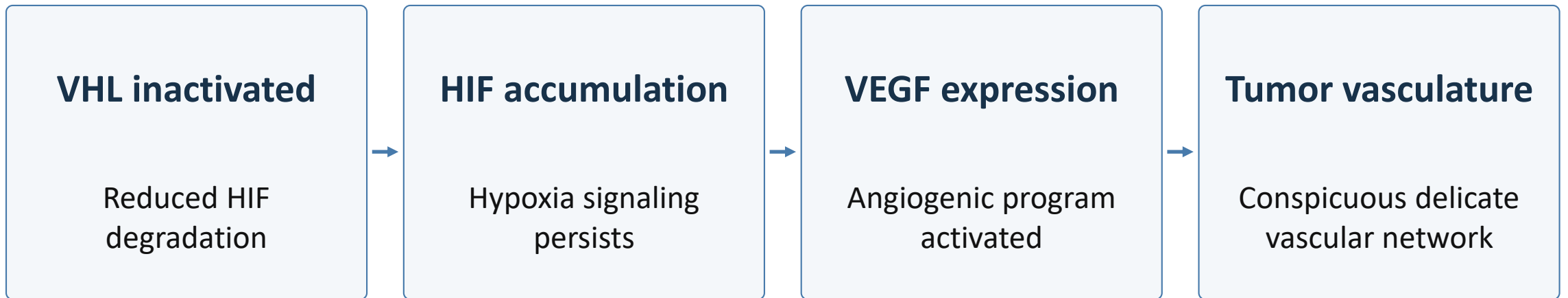
With functional VHL

- In the presence of adequate oxygen, HIF is targeted for proteolysis.
- HIF-dependent transcription is restrained.
- This oxygen-sensitive mechanism limits angiogenic signaling.

With VHL inactivation

- HIF degradation becomes impaired even with adequate oxygen.
- Persistent HIF stimulates transcription of target genes.
- VEGF and growth-promoting programs become inappropriately active.

VHL loss leads to angiogenesis



HIF controls more than angiogenesis

- HIF-dependent gene expression includes VEGF, a major angiogenic factor.
- Insulin-like growth factor-1 is among growth-promoting outputs noted in the text.
- HIF interacts with MYC-driven metabolic programs.
- The biological outcome is a microenvironment that favors tumor growth.

Clear cell RCC: Genotype to phenotype

Genetic findings

- 3p25.3 loss includes the VHL locus.
- Somatic VHL mutation or silencing can remove the second allele.
- Alterations in chromatin-regulatory genes are also frequent.

Morphologic outputs

- Lipid-rich cells create the pale, yellow gross cut surface.
- Clear cells grow in nests with a delicate vascular meshwork.
- The tumor can show necrosis, hemorrhage, and venous invasion.

Epigenetic remodeling in clear cell RCC

- Genomic studies have identified mutations involving histone-modification regulators.
- Epigenetic dysregulation provides an additional route to abnormal gene expression.
- VHL/HIF remains a core pathway but is not the entire molecular explanation.
- Altered chromatin regulation contributes to biologic heterogeneity.

Clear cell RCC: Integrated mechanism

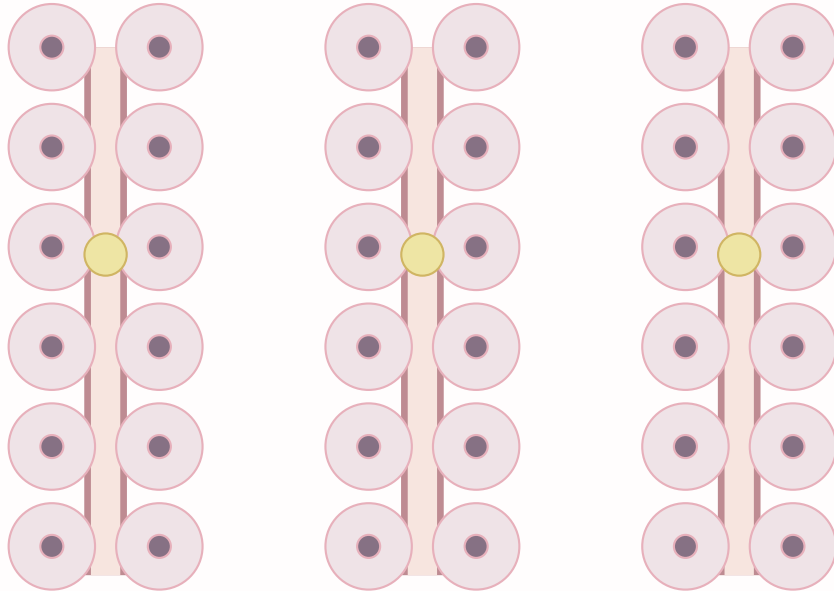
VHL loss → persistent HIF signaling → angiogenic and growth-promoting transcription

- The vascular phenotype and molecular pathway reinforce one another.
- Histologic identity still rests on the combined morphology and context.
- Targeted therapy rationale follows pathway biology, not morphology alone.

Papillary RCC: General profile

- Accounts for roughly 10–15% of RCCs.
- Architecture may be papillary, tubulopapillary, or solid.
- Sporadic and familial forms both occur.
- Multifocal tumors are more frequent than in clear cell RCC.
- The characteristic cytogenetic pathway differs from 3p/VHL loss.

Papillary RCC: Epithelial fronds



What to recognize

- Papillae contain fibrovascular cores.
- Cuboidal or low-columnar epithelial cells cover the fronds.
- Foamy macrophages may occupy papillary stalks.
- Psammoma bodies may occur.

Schematic architecture only — not a histologic specimen

Papillary RCC: Gross features

- Can be bilateral or multifocal.
- Larger lesions are commonly hemorrhagic and cystic.
- The architecture includes papillae but is not limited to them.
- Foamy histiocytes and psammoma bodies reinforce the microscopic impression.

Papillary RCC: Cytogenetic associations

Gain of chromosome 7

A recurrent finding in both familial and sporadic papillary RCC.

Gain of chromosome 17

Frequently observed in sporadic papillary RCC.

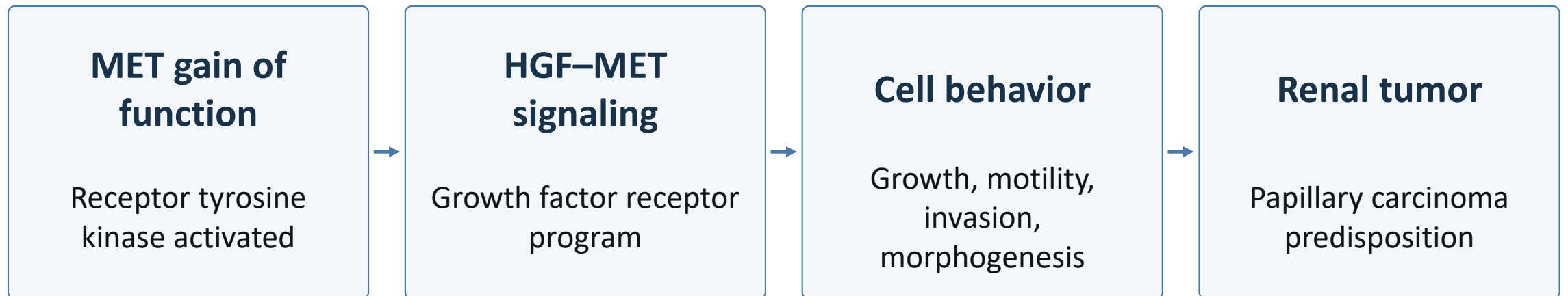
Loss of Y chromosome

Additional recurring alteration in tumors from male patients.

MET activation

Germline event in hereditary papillary RCC;
Somatic in a subset.

MET activation in hereditary papillary RCC



Papillary RCC: Familial versus sporadic

Hereditary cases

- Germline MET activation defines classic hereditary papillary carcinoma.
- Often multifocal and bilateral.
- Chromosome 7 gain is described.

Sporadic cases

- Frequently show gains of chromosomes 7 and 17.
- Loss of chromosome Y may occur in men.
- MET mutations affect only a subset.

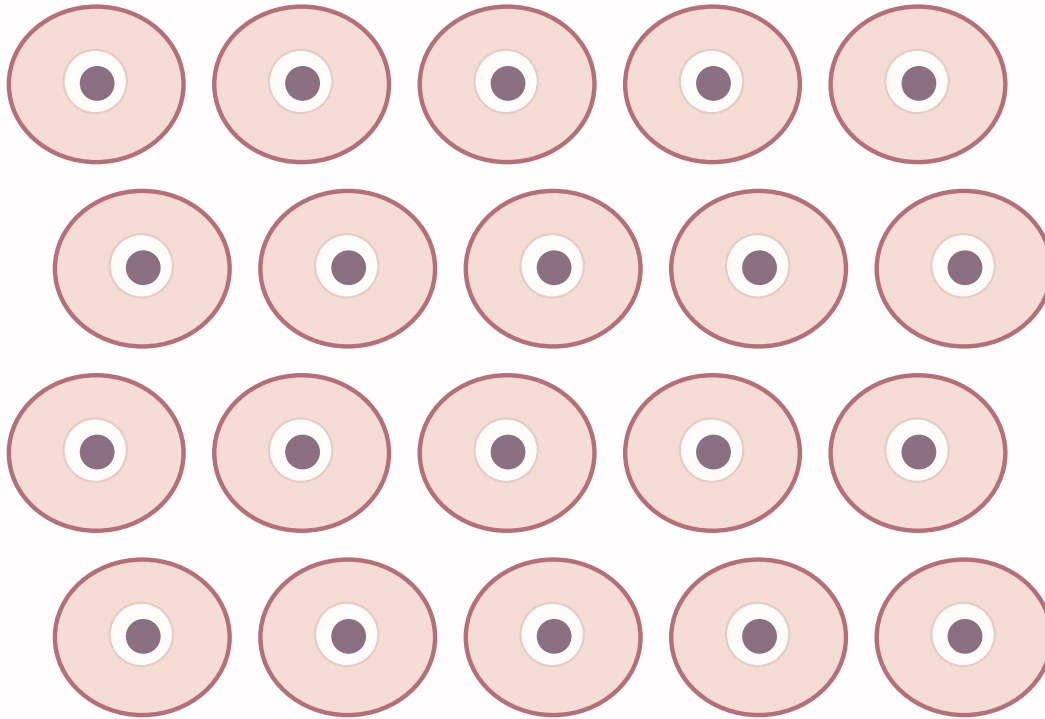
Papillary adenoma: Close morphologic mimic

- Small cortical papillary adenomas can resemble low-grade papillary RCC.
- The source describes lesions typically less than 1.5 cm.
- They may share gains of chromosomes 7 and 17 with papillary RCC.
- Size, context, and recognized diagnostic criteria are essential to classification.
- This is a practical overlap within the renal neoplasm spectrum.

Chromophobe RCC: Defining profile

- Represents approximately 5% of RCCs.
- Believed to arise from collecting-duct intercalated cells.
- Tumor cells have conspicuous membranes and pale eosinophilic cytoplasm.
- A perinuclear halo is a common cytologic feature.
- Prognosis is generally more favorable than clear cell or papillary RCC.

Chromophobe RCC: Cell borders and halos



What to recognize

- Large polygonal epithelial cells form solid sheets.
- Cell borders are particularly conspicuous.
- Perinuclear halos interrupt pale eosinophilic cytoplasm.
- Chromosome loss is a major molecular correlate.

Schematic architecture only — not a histologic specimen

Chromophobe RCC: Chromosomal pattern

- The hallmark is extensive chromosomal loss with marked hypodiploidy.
- This differs from the 3p/VHL loss pattern of clear cell RCC.
- It also differs from the recurrent gains in papillary RCC.
- Interpret chromosomal data together with cell morphology.

Chromophobe RCC versus renal oncocytoma

Chromophobe carcinoma

- Prominent membranes and perinuclear halos.
- Multiple chromosome losses are characteristic.
- Despite relatively favorable prognosis, it remains malignant.

Renal oncocytoma

- Benign epithelial neoplasm with eosinophilic, mitochondria-rich cells.
- Often homogeneous tan or mahogany-brown grossly.
- Overlapping oncocytic appearance can complicate histologic assessment.

TFE3-rearranged renal cell carcinoma

- Genetically defined by rearrangements involving TFE3 at Xp11.2.
- Often encountered in younger patients.
- Different partner genes may produce different architectural patterns.
- Histology may be nested, solid, or tubulopapillary.
- TFE3 overexpression reflects the underlying rearrangement.

TFE3-rearranged RCC: Diagnostic reasoning

Clinical context

Young patient with a renal epithelial malignancy.

Morphologic spectrum

Nested, solid, or tubulopapillary architecture;
Not pathognomonic alone.

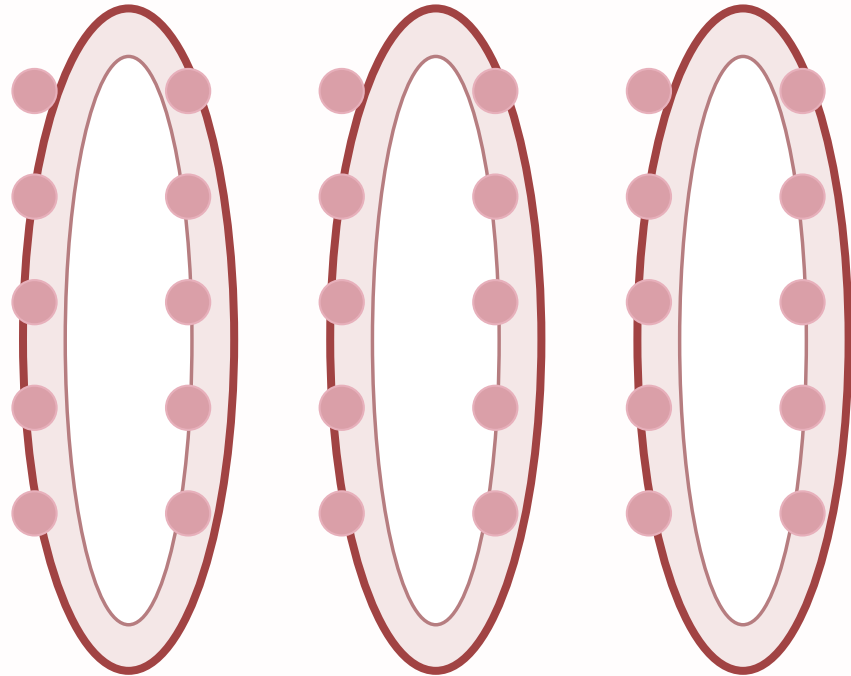
Molecular definition

Rearrangement involving the TFE3 gene at Xp11.2.

Collecting duct carcinoma: A rare aggressive pattern

- Roughly 1% or less of renal epithelial tumors in the source.
- Arises from collecting duct structures in the renal medulla.
- Infiltrative glands are set in abundant desmoplastic stroma.
- The epithelium is markedly atypical; Hobnail lining can be seen.
- Anatomic location and stromal response are important clues.

Collecting duct carcinoma: Medullary glands



What to recognize

- Medullary location is an important context clue.
- Irregular glands or channels infiltrate stroma.
- The tumor epithelium is highly atypical.
- A conspicuous desmoplastic reaction surrounds glands.

Schematic architecture only — not a histologic specimen

Renal medullary carcinoma: Important association

- Medullary carcinoma as morphologically similar to collecting duct carcinoma.
- The association with sickle cell trait is diagnostically important.
- The designation should not be inferred solely from medullary location.
- This differential requires integrated clinical and pathologic assessment.

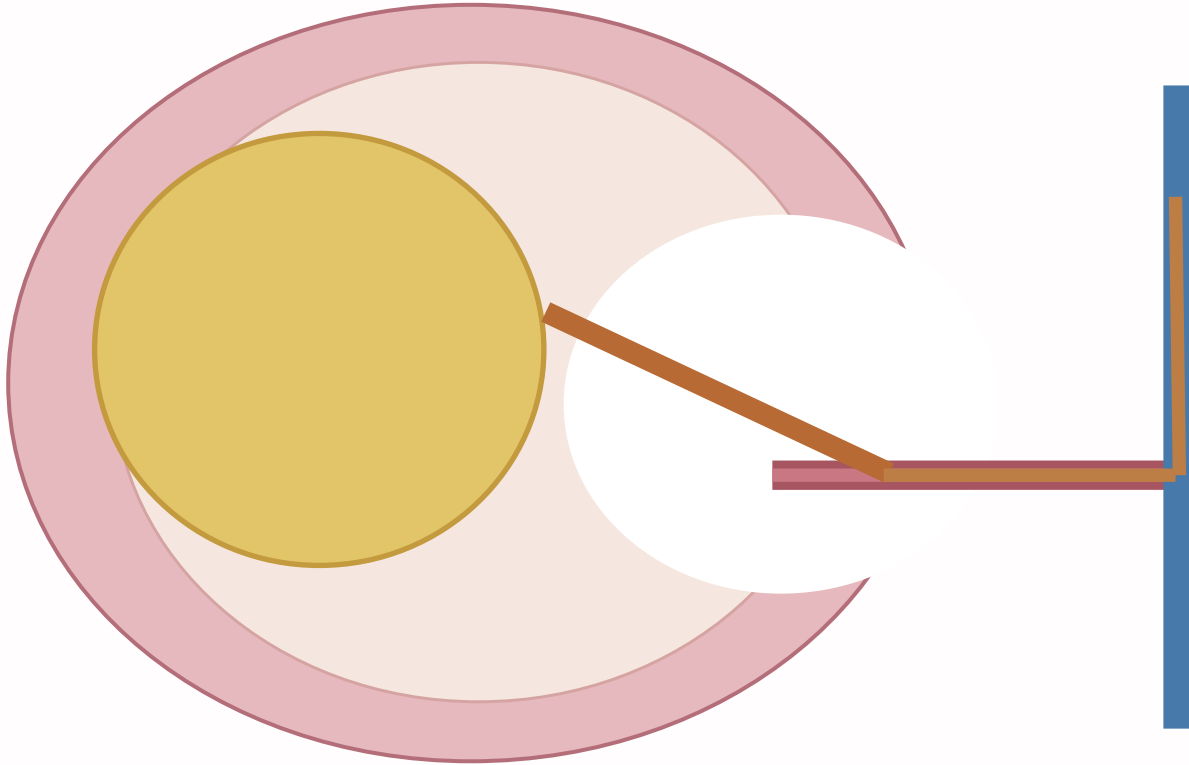
Morphology-based subtype comparison

Feature	Clear cell	Papillary	Chromophobe
Dominant pattern	Nests and delicate vessels	Papillae / tubules	Solid sheets
Cytoplasm	Clear or granular	Usually cuboidal cells	Pale eosinophilic
Key clue	Fine vascular network	Foamy macrophages	Perinuclear halos
Genetic theme	3p / VHL	7/17 gains; MET subset	Multiple losses

Sarcomatoid change: A cross-subtype warning

- Sarcomatoid transformation can occur in several RCC subtypes.
- It is associated with a markedly adverse prognosis.
- The finding describes dedifferentiation rather than a separate tubular cell lineage.
- Areas of spindle-cell morphology require correlation with an epithelial RCC component.

RCC and renal vein invasion



Gross-anatomic interpretation

- Renal vein invasion
- Extension toward the vena cava
- Potential intravascular tumor column

Simplified kidney cross-section: Diagrammatic location and spread (not a gross specimen)

Why venous invasion matters

- Clear cell RCC may extend as a solid tumor column within the renal vein.
- Contiguous intravascular growth can reach the inferior vena cava.
- Rarely, extension may approach the right side of the heart.
- Venous spread changes surgical and prognostic assessment.
- Do not equate visible venous extension with distant metastasis.

How RCC extends locally

- Expanding tumors distort the renal parenchyma and may approach the capsule.
- Bulging into the calyceal system may produce collecting-system involvement.
- Advanced tumors may extend into the renal pelvis or ureter.
- Anatomic tumor extent is distinct from the histologic subtype.

The classic clinical triad

Hematuria + flank pain + palpable mass

- All three occur together in only a minority of cases (~10% in the source).
- Hematuria may be intermittent or only microscopic.
- Absence of the complete triad does not exclude substantial disease.

Hematuria: The key local symptom

- Hematuria as a reliable clinical clue.
- Bleeding may be intermittent and escape attention.
- Microscopic hematuria can precede obvious urinary symptoms.
- An occult lesion may grow for years before becoming clinically apparent.

Why RCC is often discovered incidentally

- Many tumors produce no local signs at early stages.
- Cross-sectional imaging is frequently performed for unrelated reasons.
- Incidental CT or MRI therefore detects a growing share of RCCs.
- Imaging discovery does not replace tissue-based subtype classification.

Constitutional manifestations

- Fever, malaise, weakness, and weight loss can dominate the presentation.
- Advanced disease may cause systemic symptoms before focal renal symptoms.
- This clinical diversity contributes to RCC being a “great mimic.”
- Constitutional findings are nonspecific and require clinical context.

Paraneoplastic manifestations: Map the syndrome

Hematologic

Polycythemia, eosinophilia, or leukemoid reactions

Mineral and vascular

Hypercalcemia and hypertension

Hepatic / endocrine

Hepatic dysfunction, Cushing syndrome, or sexual-hormone effects

Protein deposition

Amyloidosis may occur

Two systemic manifestations to recognize

Polycythemia

- Renal neoplasm can be associated with inappropriate hormone production.
- Unexpected erythrocytosis may accompany an occult tumor.
- Correlate blood findings with renal imaging and clinical context.

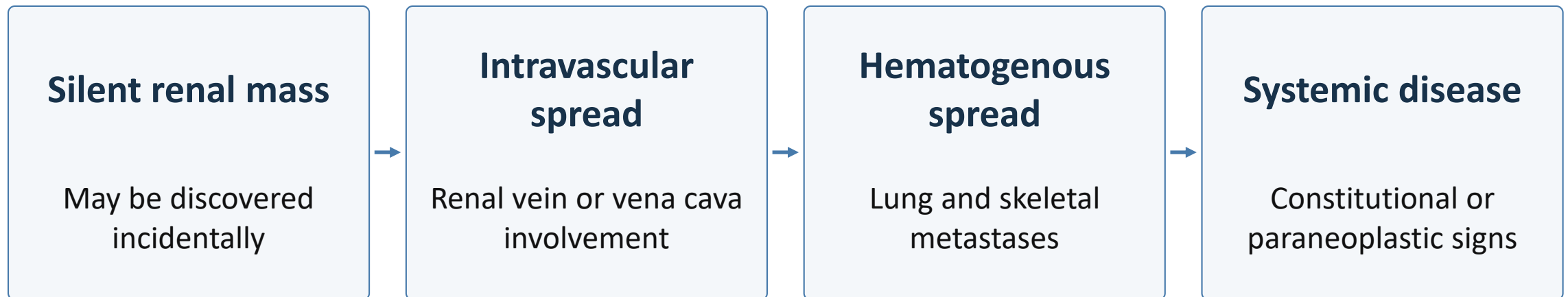
Hypercalcemia

- A recognized systemic syndrome of RCC.
- Can contribute to nonspecific weakness and systemic illness.
- Requires evaluation beyond the local renal tumor findings.

RCC: Metastatic behavior

- Renal cell carcinoma may metastasize before local symptoms develop.
- The text reports radiologically evident metastasis in approximately 15% at diagnosis.
- Lung and bone are major sites of distant involvement.
- Other metastatic destinations include nodes, liver, adrenal glands, and brain.

Clinical progression is not always linear



Common metastatic sites

Site	Clinical implication
Lungs	Frequent distant target; chest assessment is important
Bone	May present with pain or pathologic fracture
Regional lymph nodes	Locoregional dissemination
Liver, adrenal, brain	Potential extrapulmonary disease sites

Prognosis: Stage and spread matter

- Absence of distant metastasis is associated with substantially better survival.
- Extension to renal vein or perinephric fat worsens prognosis.
- Sarcomatoid differentiation is an adverse microscopic feature.
- Histologic type contributes to risk but cannot replace anatomic assessment.

Prognostic assessment: Separate the axes

Anatomic extent

Organ-confined versus local extension and venous invasion

Distant dissemination

Metastatic disease fundamentally changes prognosis

Histologic biology

Subtype and sarcomatoid differentiation affect behavior

Clinical state

Symptoms and systemic effects influence clinical management

Treatment principles in the source

- Surgery is central for localized RCC.
- Nephron-sparing surgery is recommended for small T1a lesions where feasible.
- Additional tumors may be suitable for renal-preserving resection if technically possible.
- VEGF/kinase-directed agents and immunotherapy are discussed for advanced disease.
- Drug sequencing and current treatment algorithms require separate guideline verification.

A case of hematuria without the triad

A 62-year-old has episodic microscopic hematuria and no palpable renal mass

- Would absence of flank pain and a palpable mass exclude RCC?
- What investigation commonly reveals clinically silent renal tumors?
- Which renal tumor can invade the renal vein while remaining relatively well circumscribed?

Case resolution: Hematuria and a renal mass

- No: The complete triad occurs in only a minority of patients.
- Cross-sectional imaging often detects occult renal masses.
- Clear cell RCC has a notable tendency for renal vein invasion.
- The combination of imaging findings and pathology establishes tumor context.

A case of bilateral papillary tumors

A young adult has multiple papillary renal tumors in both kidneys

- Which inherited syndrome becomes a major consideration?
- Which proto-oncogene is characteristically activated?
- Which chromosomal gains commonly characterize the papillary pathway?

Case resolution: Hereditary papillary RCC

- Hereditary papillary renal carcinoma should be considered.
- Activating MET mutations define the classical familial form.
- Chromosome 7 gain is seen; Sporadic tumors often also gain chromosome 17.
- Multifocality and bilaterality are important clinical clues.

High-yield differential: RCC versus pelvic urothelial cancer

Renal cell carcinoma

- Tumor of renal parenchymal epithelial lineage.
- Clear cell, papillary, chromophobe, and other subtypes.
- Venous invasion and distant spread are important behaviors.

Renal pelvic urothelial carcinoma

- Originates from urothelium of the collecting-system pelvis.
- May cause early hematuria or urinary obstruction.
- Histologically parallels urothelial neoplasia of the bladder.

Morphology → mechanism → clinical behavior

Clear cell

VHL/HIF dysregulation → vascular clear-cell nests → venous invasion

Papillary

Chromosome 7/17 changes ± MET → papillary cores → often multifocal

Chromophobe

Multiple chromosomal losses → pale cells with halos → favorable relative outcome

Collecting duct

Medullary origin → desmoplastic infiltrating glands → aggressive presentation

Five principles to retain

- Histology and genetics jointly define RCC subtypes.
- VHL loss stabilizes HIF and links clear cell RCC to angiogenesis.
- MET activation characterizes classic hereditary papillary RCC.
- Chromophobe RCC has prominent membranes, perinuclear halos, and multiple losses.
- Venous invasion and occult metastatic spread are central to clinical assessment.

References

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Chapter 20: The Kidney. Renal cell carcinoma, pp. 863–865.
- Adjacent source context: Renal papillary adenoma and renal oncocytoma, pp. 862–863; urothelial carcinoma of renal pelvis, p. 865.
- Textbook Fig. 20.46 summarizes the genetic patterns of clear cell and papillary RCC.
- Textbook Figs. 20.47–20.48 depict gross and histologic RCC morphology.