

Malignant Neoplasms of the Kidney

Renal cell carcinoma: carcinogenesis, morphology, and clinicopathologic interpretation

Medical pathology lecture

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Classify malignant renal epithelial tumors using morphology and molecular alterations.
- Explain how VHL loss stabilizes HIF and promotes clear cell carcinogenesis.
- Recognize major hereditary syndromes and their renal tumor associations.
- Link gross and microscopic findings to clinical manifestations and routes of spread.
- Interpret major prognostic patterns and distinguish RCC from renal pelvic urothelial carcinoma.

Two major epithelial locations

Renal tubular epithelium



Renal cell carcinoma

Renal pelvic urothelium



Urothelial carcinoma

Most of this lecture: Renal cell carcinoma. Pelvic tumors are contrasted briefly, then taught separately.

The clinical burden of renal cell carcinoma

Adult renal cancers

~85%

Represented by RCC

New US cancers

~3%

RCC contribution

Sex ratio

2 : 1

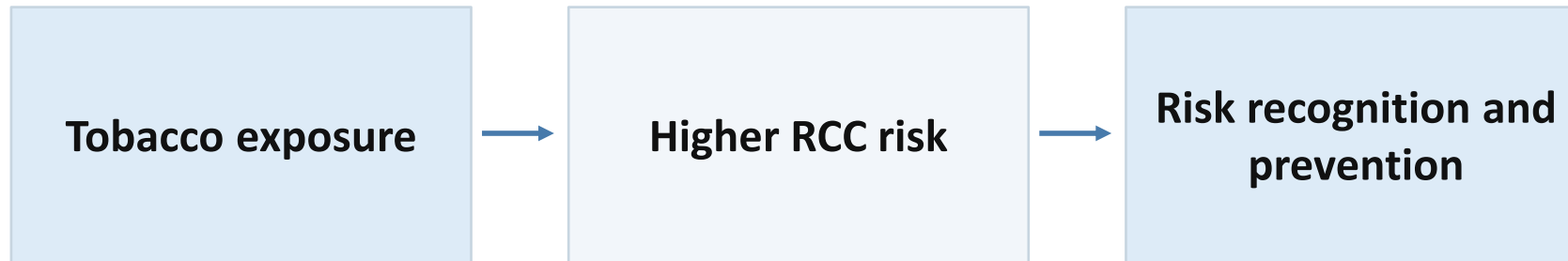
Male predominance

Textbook epidemiologic estimates (11th edition); Figures may change across populations and years.

Age distribution and clinical context

- RCC occurs most often in the sixth and seventh decades of life.
- Men are affected approximately twice as often as women.
- Many cancers are sporadic and arise without a recognizable inherited syndrome.
- Hereditary disease commonly presents at a younger age and may be bilateral or multifocal.

Tobacco exposure: The principal risk factor



Smoking as the most significant risk factor and reports an approximately twofold incidence among cigarette smokers.

Recognized risk contexts

General risk associations

- Obesity; Stronger association noted in women.
- Hypertension.
- Unopposed estrogen therapy.

Occupational or environmental

- Asbestos exposure.
- Petroleum products.
- Heavy metals.

Renal disease also changes cancer risk



Robbins additionally identifies tuberous sclerosis as an increased-risk condition.

Sporadic and inherited renal cancer

Sporadic cases

- Comprise the large majority of RCC.
- Often solitary and unilateral.
- Acquired somatic changes may target the same genes as familial disease.

Hereditary cases

- About 4% of RCC in the source.
- Often present at younger age.
- Bilateral, multiple neoplasms are characteristic of several syndromes.

When should an inherited syndrome be considered?

- A young patient with a renal malignancy warrants evaluation of hereditary context.
- Multiple or bilateral renal tumors increase suspicion of a familial predisposition.
- Associated skin, pulmonary, or uterine findings can provide syndromic clues.
- The specific histologic and molecular subtype helps direct further classification.

Clinical interpretation based on Robbins pp. 863–864; No formal genetic-testing algorithm supplied.

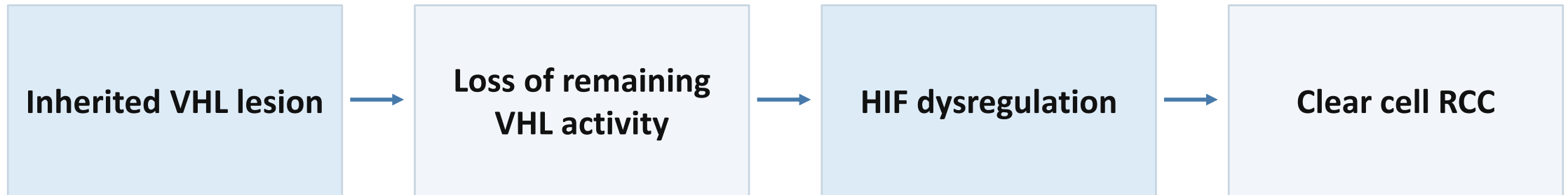
Hereditary RCC syndromes: Molecular map

Syndrome	Altered gene	Renal/other clue
von Hippel–Lindau	VHL	Multiple, bilateral RCCs and renal cysts
FH-deficient RCC syndrome	FH	Cutaneous/uterine leiomyomas; aggressive RCC
Hereditary papillary RCC	MET	Multiple bilateral papillary tumors
Birt–Hogg–Dubé	BHD / folliculin	Skin fibrofolliculomas; lung cysts; varied renal tumors

VHL syndrome: Renal manifestations

- Autosomal dominant tumor predisposition associated with loss of VHL function.
- Renal cysts and often multiple bilateral RCCs can develop.
- Renal involvement in one-half to two-thirds of affected people; Penetrance rises with age.
- The VHL pathway is also commonly inactivated in sporadic clear cell RCC.

VHL provides a mechanistic bridge

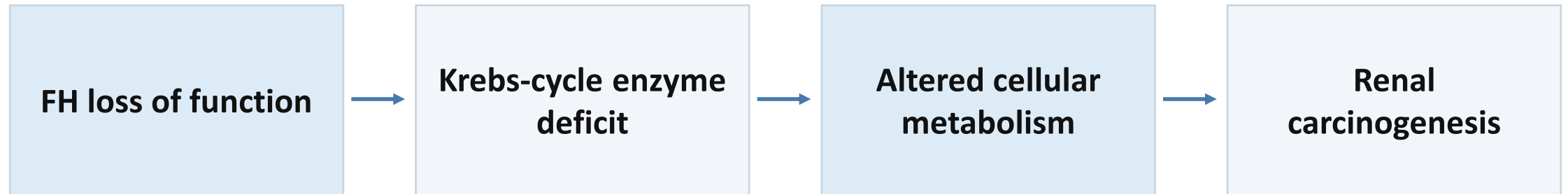


Inherited VHL disease illustrates how loss of tumor suppressor function alters HIF-dependent gene expression.

FH-deficient renal cell carcinoma

- Hereditary leiomyomatosis and RCC syndrome is autosomal dominant.
- Loss-of-function alterations affect FH, encoding fumarate hydratase.
- Associated tumors may be high-grade and aggressive with metastatic propensity.
- The descriptive entity FH-deficient RCC also includes cases without a family history.

Fumarate hydratase connects metabolism and cancer



FH encodes fumarate hydratase, illustrating metabolic alterations in oncogenesis.

Hereditary papillary renal carcinoma

- Autosomal dominant disorder associated with activating MET alterations.
- Characteristically multifocal and bilateral papillary tumors.
- Tumors often have low nuclear grade in the described hereditary form.
- Familial MET alterations identify a central receptor tyrosine kinase pathway.

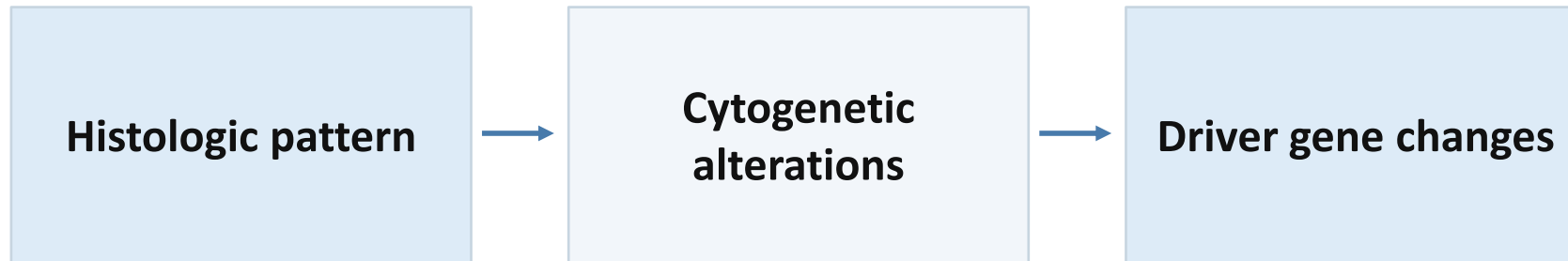
Birt–Hogg–Dubé syndrome

- Autosomal dominant syndrome caused by BHD gene loss of function.
- BHD encodes folliculin, a tumor-suppressor protein.
- Skin findings include fibrofolliculomas, trichodiscomas, and acrochordons.
- Pulmonary cysts or blebs coexist with renal tumors of varied morphologic types.

Hereditary phenotype: Which gene fits?

Presentation clue	Mechanistic association
Renal cysts + bilateral clear cell tumors	VHL pathway
Leiomyomas + aggressive RCC	FH loss
Multiple papillary RCCs, often low-grade	MET activation
Fibrofolliculomas + lung cysts + renal tumors	BHD / folliculin loss

Classification uses three complementary dimensions



No single growth pattern alone defines every renal carcinoma subtype.

Major RCC histologic types

Clear cell

70–80%

VHL/3p-associated

Papillary

10–15%

Chromosomes 7, 17; MET

Chromophobe

~5%

Multiple chromosome losses

Collecting duct

≤1%

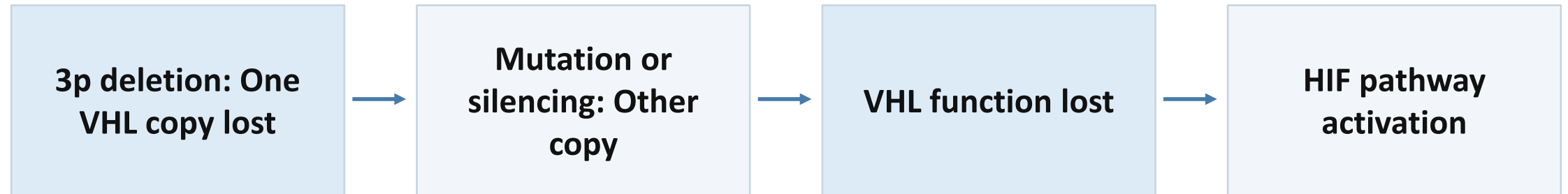
Medullary, desmoplastic

Approximate proportions given by Robbins; Minor categories are not all included.

Clear cell RCC: Molecular hallmark

- Clear cell carcinoma is the most prevalent RCC histologic subtype.
- The VHL locus resides at chromosome 3p25.3.
- Most cases have loss of chromosome 3p material involving one VHL allele.
- Inactivation of the second VHL copy frequently occurs by mutation or promoter hypermethylation.

The VHL two-hit model



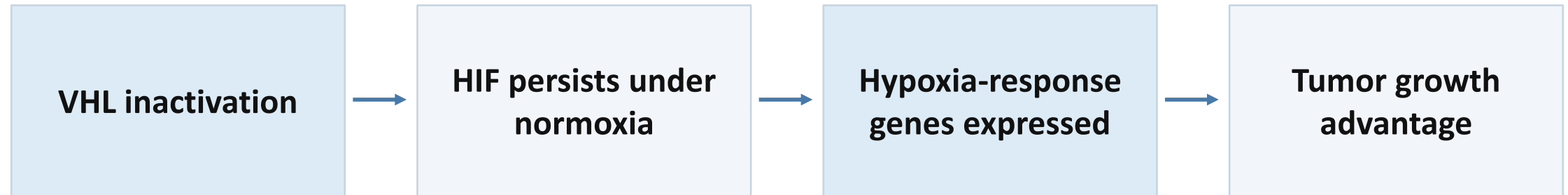
The source reports 3p deletion in 98% and second-copy inactivation in up to 80% of clear cell carcinomas; These are source-specific estimates.

In normal oxygenation, VHL limits HIF



VHL complex promotes HIF-1 turnover in an oxygen-dependent manner.

When VHL is inactive, HIF escapes degradation



Even when oxygen is available, failure of HIF degradation allows inappropriate expression of target genes.

HIF transcriptional targets reshape the tumor



HIF-dependent VEGF and IGF-1 exemplify proangiogenic and proliferative outputs.

Metabolism and epigenetics in clear cell RCC

- HIF collaborates with MYC in complex changes to cellular metabolism.
- Reprogrammed metabolic pathways can support tumor cell growth.
- Genome sequencing reveals recurrent defects in histone-modifying genes.
- Thus genetic, epigenetic, and metabolic disturbances reinforce RCC development.

Clear cell appearance follows cellular biochemistry

**Lipid and glycogen
accumulate**



**Cytoplasm appears
optically clear**



**Nests or solid tumor
architecture**

Clear and granular cells may coexist.

Clear cell RCC: Characteristic gross appearance

- Usually a unilateral, solitary, rounded cortical mass, often in a renal pole.
- Bright yellow areas reflect abundant lipid in tumor cells.
- Hemorrhage, necrosis, and cystic degeneration may create variegation.
- The mass is often sharply demarcated, although it can invade adjacent structures.

Clear cell RCC: Nested architecture



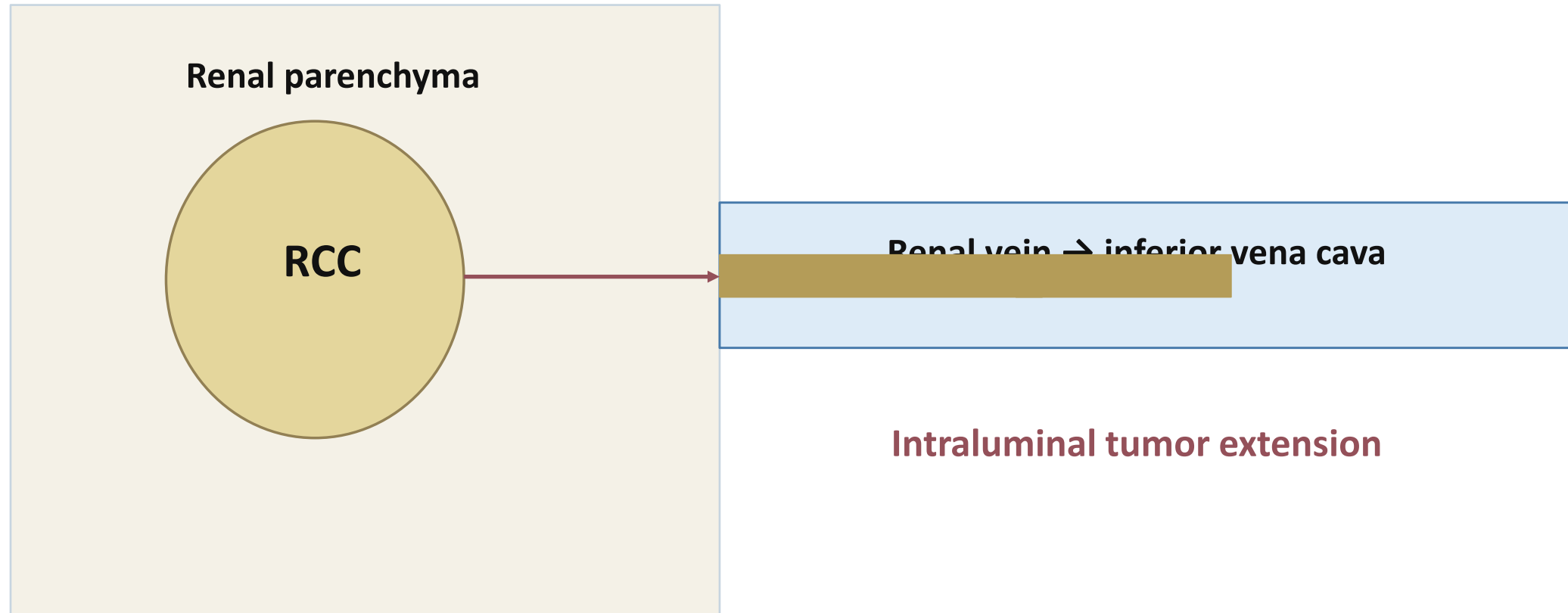
Clear or granular cytoplasm;
Nests separated by delicate
branching vascular channels.

Schematic — not a histologic specimen

Clear cell RCC: Histologic variations

- Growth can be nested, tubular, solid, or pseudopapillary.
- Cells may have abundant clear or granular cytoplasm.
- Delicate branching microvasculature is a recurring feature.
- Larger lesions may show cysts or hyalinized areas; High-grade tumors may show bizarre nuclei and giant cells.

Renal vein invasion: A defining local spread pattern



Schematic — not gross pathology or imaging

Papillary RCC: Major genetic distinctions

- Papillary RCC contributes approximately 10%–15% of RCC in the source.
- It is not characterized by the 3p loss typical of clear cell RCC.
- Trisomies of chromosomes 7 and 17 occur in sporadic tumors.
- Activation of MET is causal in hereditary papillary carcinoma and occurs in a subset of sporadic cases.

Papillary RCC: Sporadic versus familial

Feature	Sporadic papillary RCC	Hereditary papillary RCC
Cytogenetics	Gains of chromosomes 7 and 17; Y loss in men	Trisomy 7
MET	Activated in a small subset	Activating MET mutation is characteristic
Multiplicity	Often multifocal	Often multiple and bilateral

MET signaling and papillary carcinogenesis

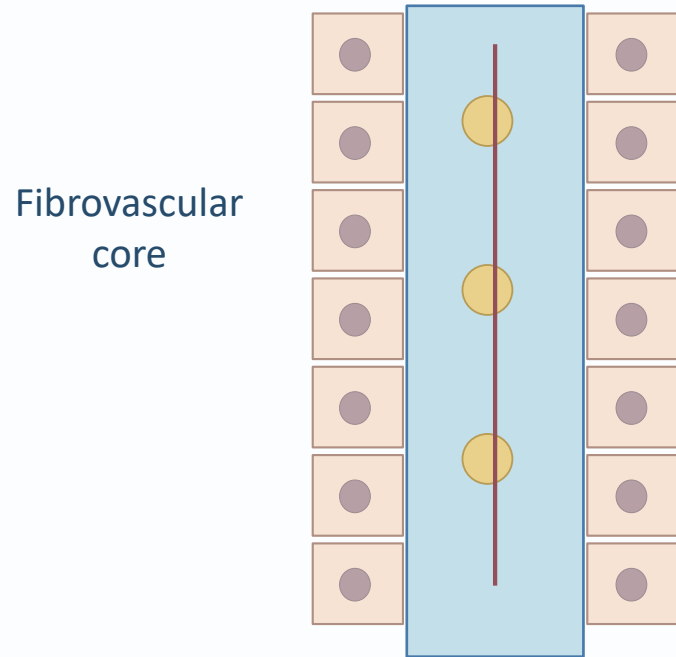


MET is encoded on chromosome 7 and is the hepatocyte growth factor receptor.

Papillary RCC: Gross and distribution pattern

- Unlike clear cell tumors, papillary RCC is frequently multifocal.
- Papillary neoplasms may also affect both kidneys.
- Large tumors are often hemorrhagic and cystic.
- Papillary, tubulopapillary, and solid configurations may coexist.

Papillary RCC: Papillary architecture



Papillary frond with cuboidal/columnar epithelial lining and foam histiocytes enclosed within the stalk; Psammoma bodies may occur.

Schematic — not a histologic specimen

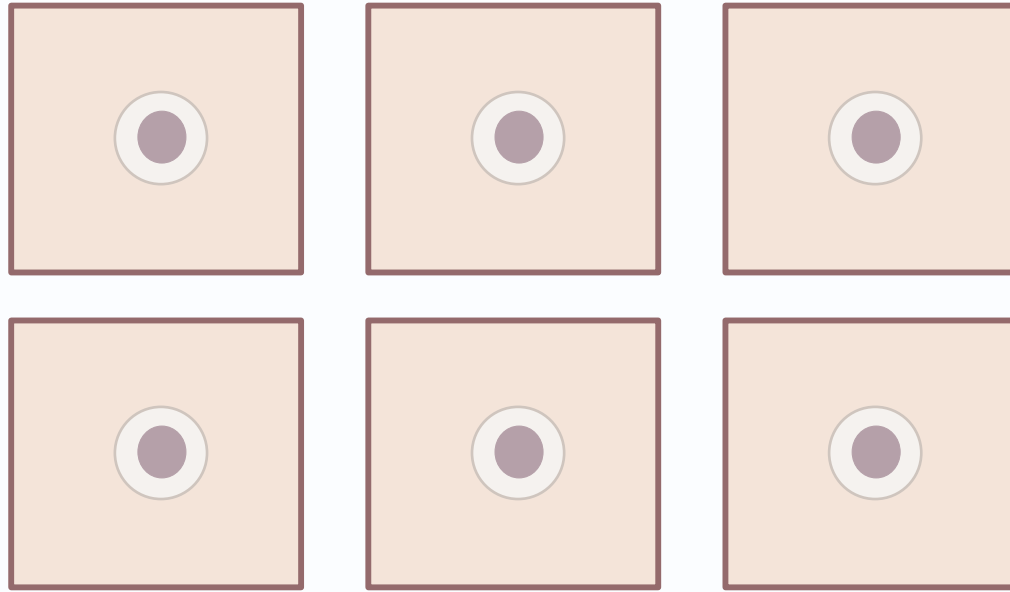
Papillary RCC: Microscopy details

- Papillae are lined by cuboidal to low columnar epithelial cells.
- Foamy macrophages commonly occur in papillary cores.
- Lamellated psammoma bodies may be present.
- The full architectural spectrum includes papillary, tubulopapillary, and solid regions.

Chromophobe RCC: Genotype and origin

- Chromophobe RCC accounts for approximately 5% of RCC.
- Chromosomal losses across multiple chromosomes are typical.
- Extreme hypodiploidy may result.
- The source describes a likely origin from intercalated cells of collecting ducts.

Chromophobe RCC: Cell morphology



Pale eosinophilic cells with prominent membranes and perinuclear halos; Usually solid sheets.

Schematic — not a histologic specimen

Chromophobe carcinoma versus oncocytoma

Chromophobe RCC

- Malignant renal epithelial neoplasm.
- Pale eosinophilic cells with perinuclear halos.
- Strong cell borders; Multiple chromosome losses.

Oncocytoma (differential)

- Benign renal epithelial tumor.
- Can resemble eosinophilic chromophobe cells.
- Histologic separation may be difficult.

TFE3-rearranged RCC

- Defined by a rearrangement involving TFE3 at chromosome Xp11.2.
- Different fusion partners lead to TFE3 overexpression.
- Often occurs in younger patients.
- Morphology varies with fusion partner: Nested, solid, and tubulopapillary patterns occur.

Collecting duct carcinoma

- Rare subtype, accounting for approximately 1% or less of renal epithelial tumors.
- Typically arises in the renal medulla from collecting duct epithelium.
- Irregular malignant glands are embedded in a prominent desmoplastic stroma.
- Cells can line gland-like channels with highly atypical, hobnail architecture.

Renal medullary carcinoma: Clinical association



Robbins provides an association and morphologic comparison but no detailed treatment algorithm.

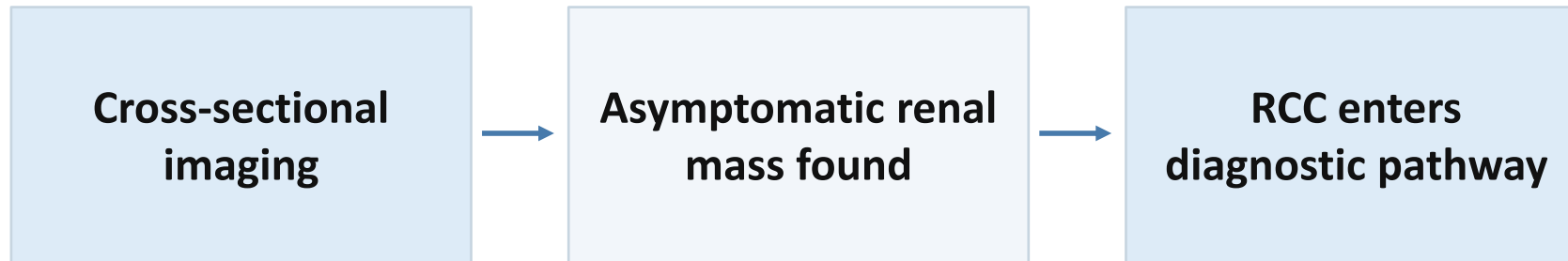
Sarcomatoid change signals aggressive disease

- Sarcomatoid morphology can occur in multiple RCC histologic types.
- It is a pattern of high-grade transformation, not one exclusive molecular subtype.
- Sarcomatoid change is associated with particularly poor prognosis.
- Reporting should recognize both underlying type and aggressive component when possible.

Major renal carcinoma subtypes compared

Subtype	Core finding	Molecular / context clue
Clear cell	Lipid-rich clear cells; fine vascular nests	3p/VHL loss; HIF signaling
Papillary	Papillae; foam macrophages; possible psammoma	Trisomy 7/17; subset MET activation
Chromophobe	Strong membranes; perinuclear halos	Multiple chromosome losses
TFE3-rearranged	Variable nested or papillary growth	TFE3 fusion; often younger
Collecting duct	Medullary infiltrating glands; desmoplasia	Rare; medullary origin

Why incidental detection is increasingly common



Textbook notes rising incidental detection on CT and MRI; No quantified current prevalence.

The classic RCC clinical triad is uncommon

- Flank or costovertebral pain.
- Palpable renal mass.
- Hematuria.
- All three together occur in only about 10% of cases, according to the text.

Hematuria: An important but imperfect clue

- Hematuria is the most reliable of the classic symptoms.
- Bleeding may be intermittent or only microscopic.
- A large primary tumor may develop before local symptoms become evident.
- Absence of visible blood does not exclude a clinically significant RCC.

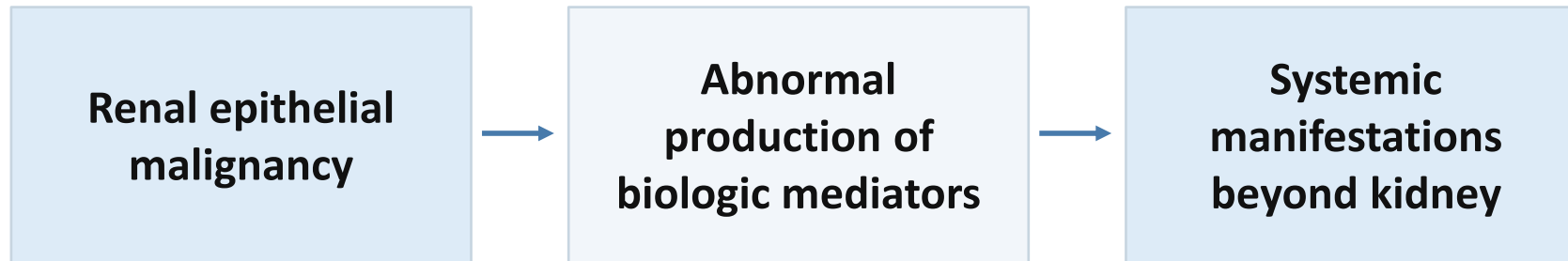
Systemic symptoms may dominate presentation

- Fever, malaise, weakness, and weight loss can occur.
- These complaints may accompany large tumors.
- RCC can act as a systemic disease long before kidney-specific symptoms appear.
- This broad clinical profile underlies its reputation as a medical “great mimic.”

Paraneoplastic phenomena in RCC

Category	Examples reported by Robbins
Hematologic	Polycythemia; eosinophilia; leukemoid reactions
Mineral/endocrine	Hypercalcemia; hypertension; Cushing syndrome
Hormonal phenotype	Feminization or masculinization
Other systemic	Hepatic dysfunction; amyloidosis

Paraneoplastic syndromes: Diagnostic logic



Clinical manifestations may reflect ectopic or excessive mediator production rather than local invasion.

Local progression can obstruct the collecting system



Source documents progressive tumor bulging/fungation into the collecting system.

RCC can spread through the venous system



The primary tumor can form a solid column of cells into major veins.

RCC may metastasize before it is symptomatic

- A major diagnostic difficulty is early distant spread without local signs.
- Radiologic metastasis at initial presentation in approximately 15% of new patients.
- Lung and bone are frequent sites of distant spread.
- Lymph nodes, liver, adrenal glands, and brain are additional common locations.

Sites of metastasis reported in RCC

Lung

>50%

Overall metastasis-site frequency

Bone

33%

Overall metastasis-site frequency

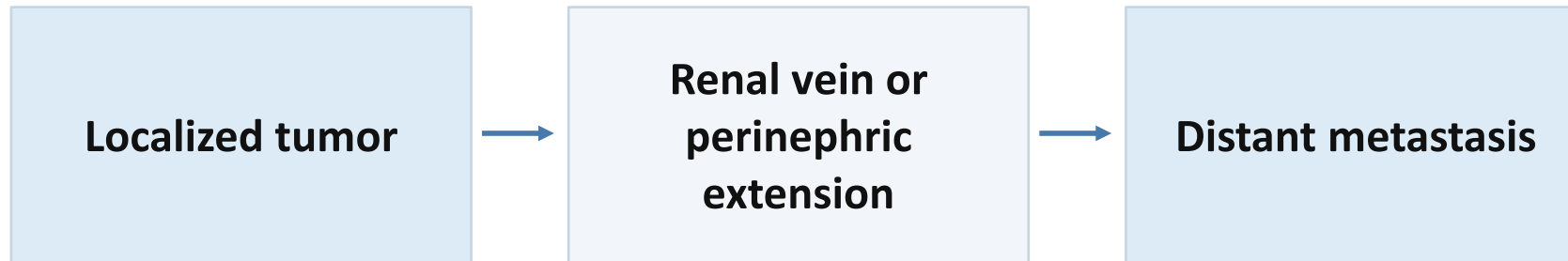
Other

—

Nodes, liver, adrenal, brain

Patients may have disease at more than one metastatic site; Do not add these percentages.

Prognosis tracks anatomic disease extent



Increasing spread generally reduces survival.

Textbook five-year survival estimates

No distant metastasis

Near 100%

Textbook estimate

Renal vein / fat invasion

~60%

Textbook estimate

Overall average

~70%

Textbook estimate

Survival depends on stage and clinical context; Estimates shown are approximate statements from the source.

Treatment principles in the pathology context

Surgical management

- Nephrectomy historically used for localized RCC.
- Nephron-sparing surgery preserves renal function.
- The source supports partial nephrectomy for T1a tumors and selected larger resectable tumors.

Advanced or metastatic disease

- VEGF pathway inhibitors are used in systemic therapy.
- Tyrosine kinase inhibitors target oncogenic signaling.
- Immunotherapy is an important treatment class; Specific regimens require current guidance.

RCC versus renal pelvic urothelial carcinoma

Feature	Parenchymal RCC	Renal pelvic urothelial carcinoma
Cell of origin	Renal tubular epithelial compartment	Urothelial lining of pelvis
Hallmark genetics in source	VHL/3p, MET, chromosomal losses	Not detailed in the kidney section
Typical gross position	Parenchyma; often renal pole	Pelvis / collecting system
Clinical clue	Often incidentally detected	Early hematuria with small lesion

Case application: Yellow renal cortical mass

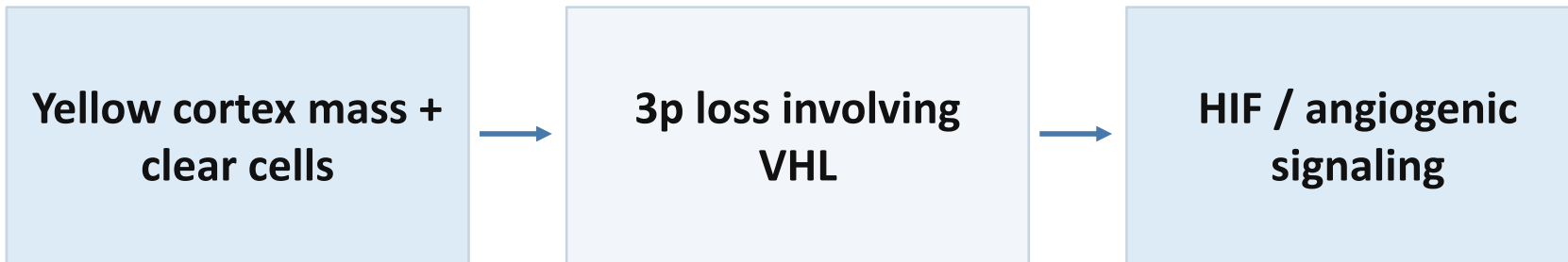
A patient is found to have a solitary golden-yellow renal cortical tumor.

CLUES

- Microscopy shows cells with abundant clear cytoplasm.
- Tumor cells form nests interspersed by delicate vascular channels.
- Molecular analysis identifies loss affecting chromosome 3p.

Which subtype and tumor-suppressor pathway best explain these findings?

Case interpretation: Clear cell carcinoma



Clear-cell phenotype reflects lipid/glycogen while 3p/VHL loss supports molecular classification.

Case application: Multiple papillary tumors

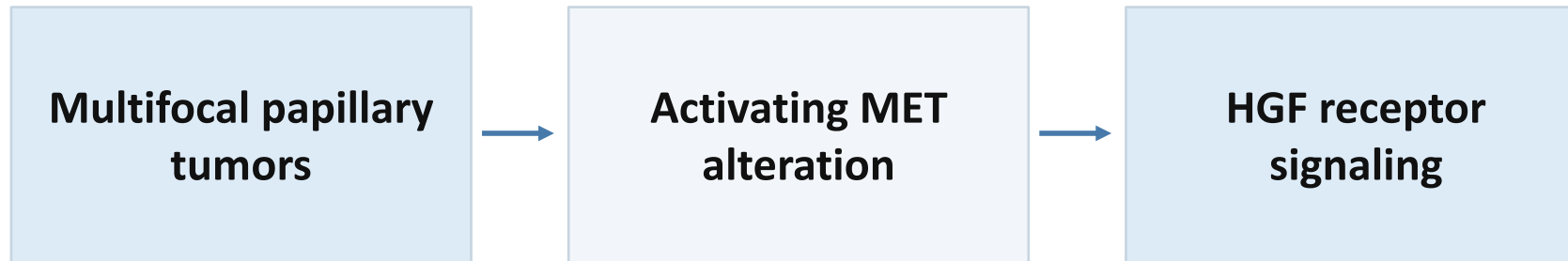
A relatively young adult presents with bilateral renal masses.

CLUES

- Histology demonstrates papillary architecture and foam histiocytes.
- Several tumors are identified in both kidneys.
- A germline activated receptor tyrosine kinase is suspected.

Which oncogene and growth-factor receptor are implicated?

Case interpretation: MET-associated papillary RCC



MET encodes hepatocyte growth factor receptor tyrosine kinase.

Integration: Morphology and genotype are complementary

Observed pattern	Most useful next mechanistic inference
Clear cells + delicate vascular nest	VHL loss → persistent HIF target expression
Papillary fronds + foam histiocytes	Papillary RCC; chromosome 7/17 changes; subset MET
Strong cell borders + halos	Chromophobe RCC; multiple chromosome losses
Medullary glands + desmoplasia	Consider collecting duct carcinoma
Any RCC with sarcomatoid change	Aggressive behavior across different RCC types

Core diagnostic and clinical principles

- RCC is a molecularly heterogeneous group of renal epithelial cancers.
- Clear cell RCC centers on VHL/HIF dysregulation; Hereditary papillary RCC centers on MET activation.
- Gross appearance and microscopic architecture narrow the differential but can overlap.
- Tumor extent, especially venous invasion and distant metastasis, is central to prognosis.
- Hereditary syndromes provide mechanistic insights into sporadic renal carcinogenesis.

Primary reading and source limitations

Primary source

Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026). Chapter 20, The Kidney, pp. 863–865; “Malignant Neoplasms” and “Renal Cell Carcinoma.”

Scope and interpretation

- Figures, subtype proportions, and survival estimates are textbook statements, not independently updated registry data.
- Original source chapter PDF and copyrighted diagnostic figures were not available for direct image verification.
- All mechanisms and illustrative diagrams are editable schematics; no clinical histopathology or gross specimen images are claimed.