Updated Classification of Renal cell carcinoma

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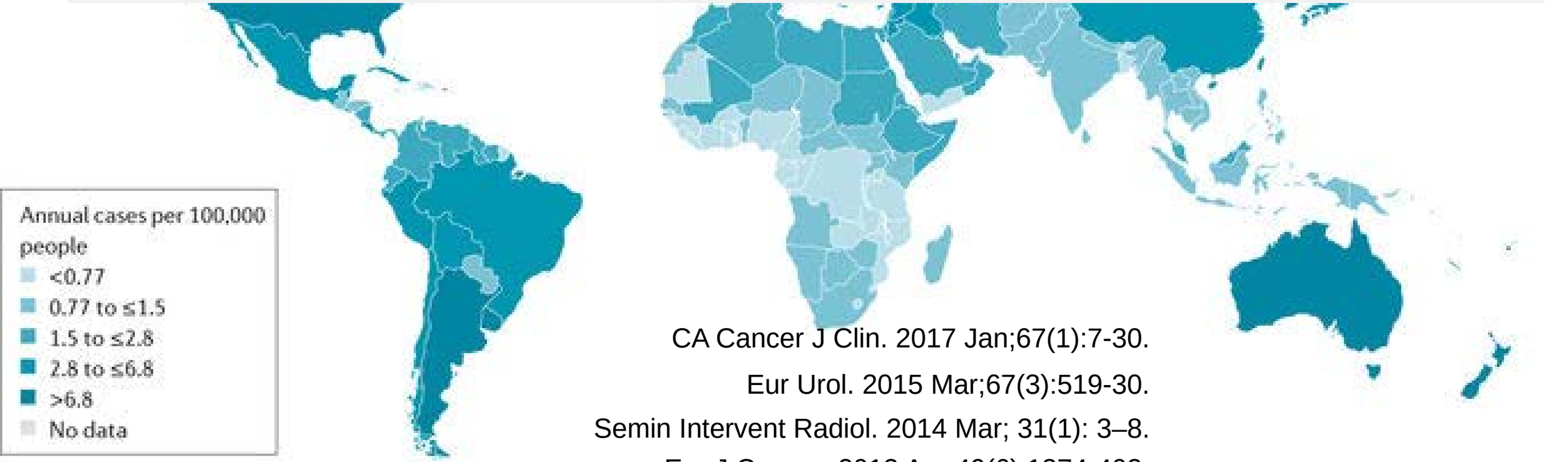
Incidence:

Global: 338,000 new cases, 130,000 deaths annually (4/100,000)
Czech Republic: male 24.1/100,000, female 10.5/100,000
United States: 64,000 new cases and almost 14,000 deaths (15.3/100,000)
European Union: 84,000 new cases and 35,000 deaths
China: 2.8/100,000



CA Cancer J Clin. 2017 Jan;67(1):7-30.

Eur Urol. 2015 Mar;67(3):519-30.

Semin Intervent Radiol. 2014 Mar; 31(1): 3–8.

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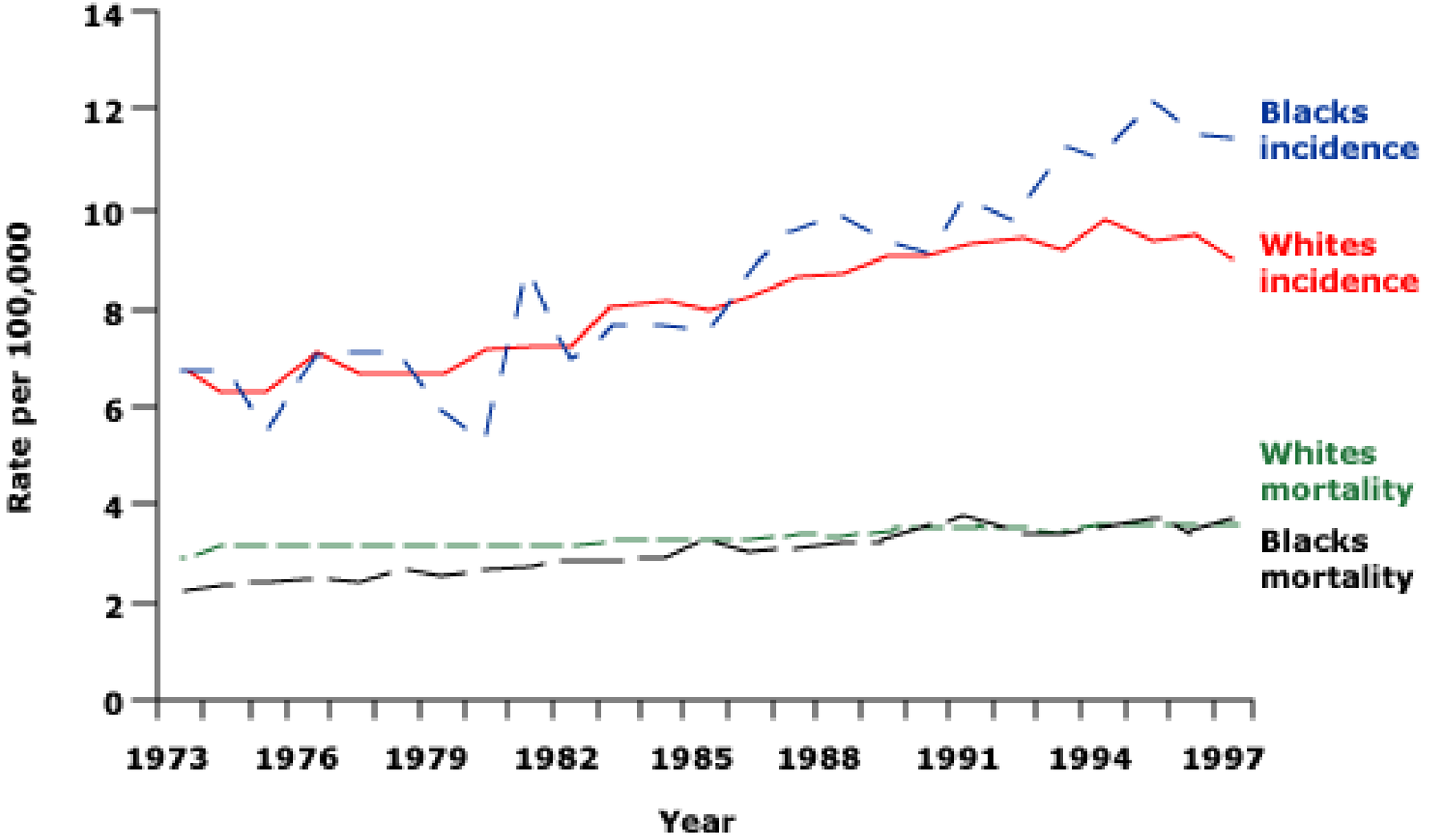
Nature Reviews | Disease Primers



Incidence rates are rising three times faster than mortality rates, suggesting an improvement in overall survival in patients with renal cell cancer over the last 25 years.

Pantuck, AJ, et al, J Urology 2001; 166:1612.

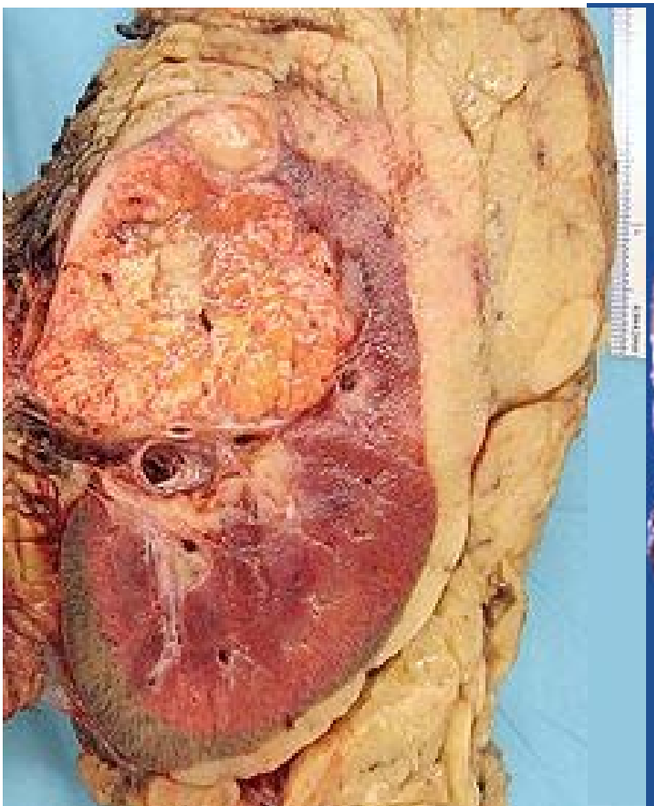
The five-year survival rate of patients with kidney cancer

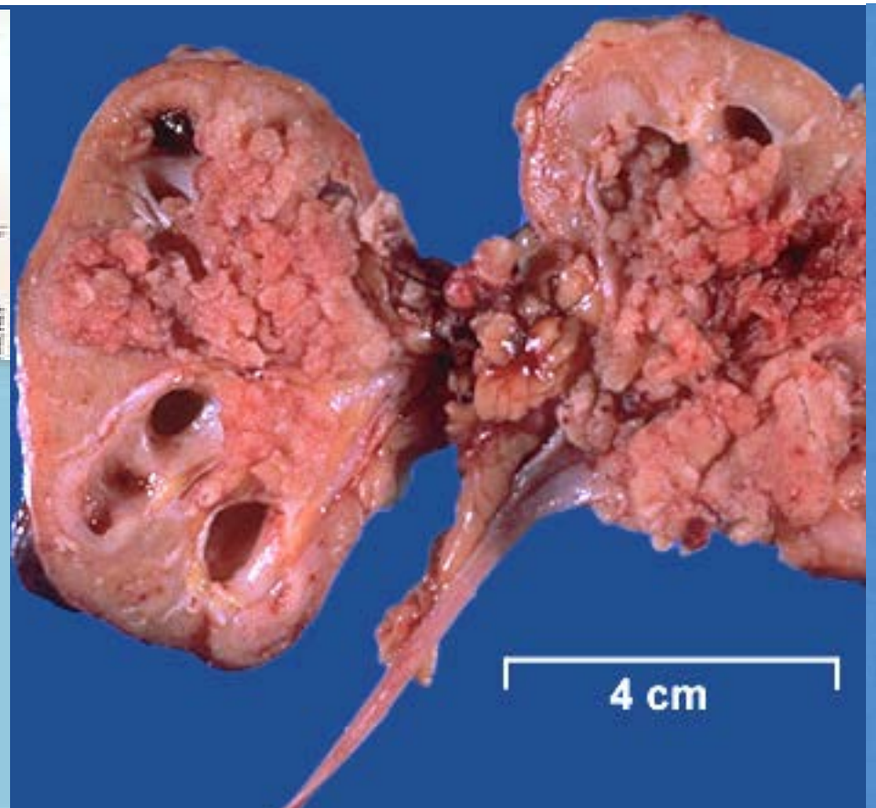
- 34 % in 1954
- 62 % in 1996
- 73 % in 2005 to 2011

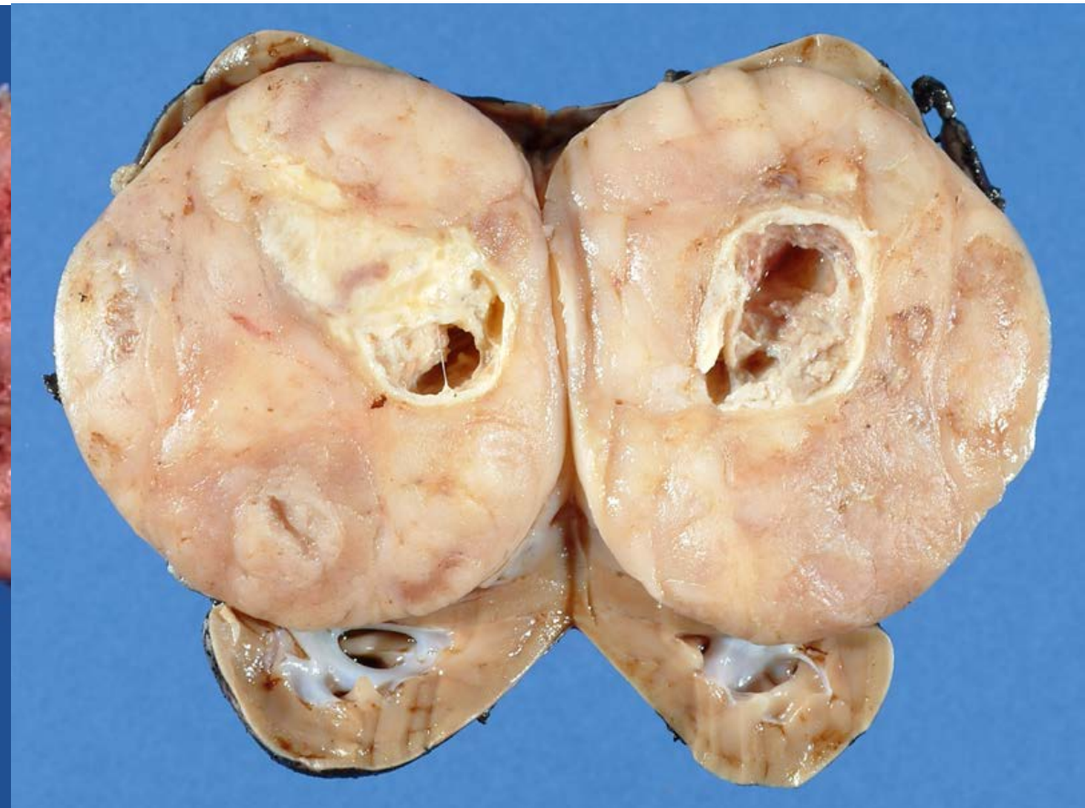
This improved survival and case-fatality rate is mostly due to earlier detection of these tumors at smaller sizes (ie, <4 cm) and curative surgical treatment.

Primary Renal Tumors

80-85% Renal cell carcinomas (RCCs)
8% Transitional cell carcinomas
5-6% Nephroblastoma or Wilms' tumor (common in children)
Oncocytomas, collecting duct tumors, and renal sarcomas
Renal medullary carcinoma (sickle cell disease)

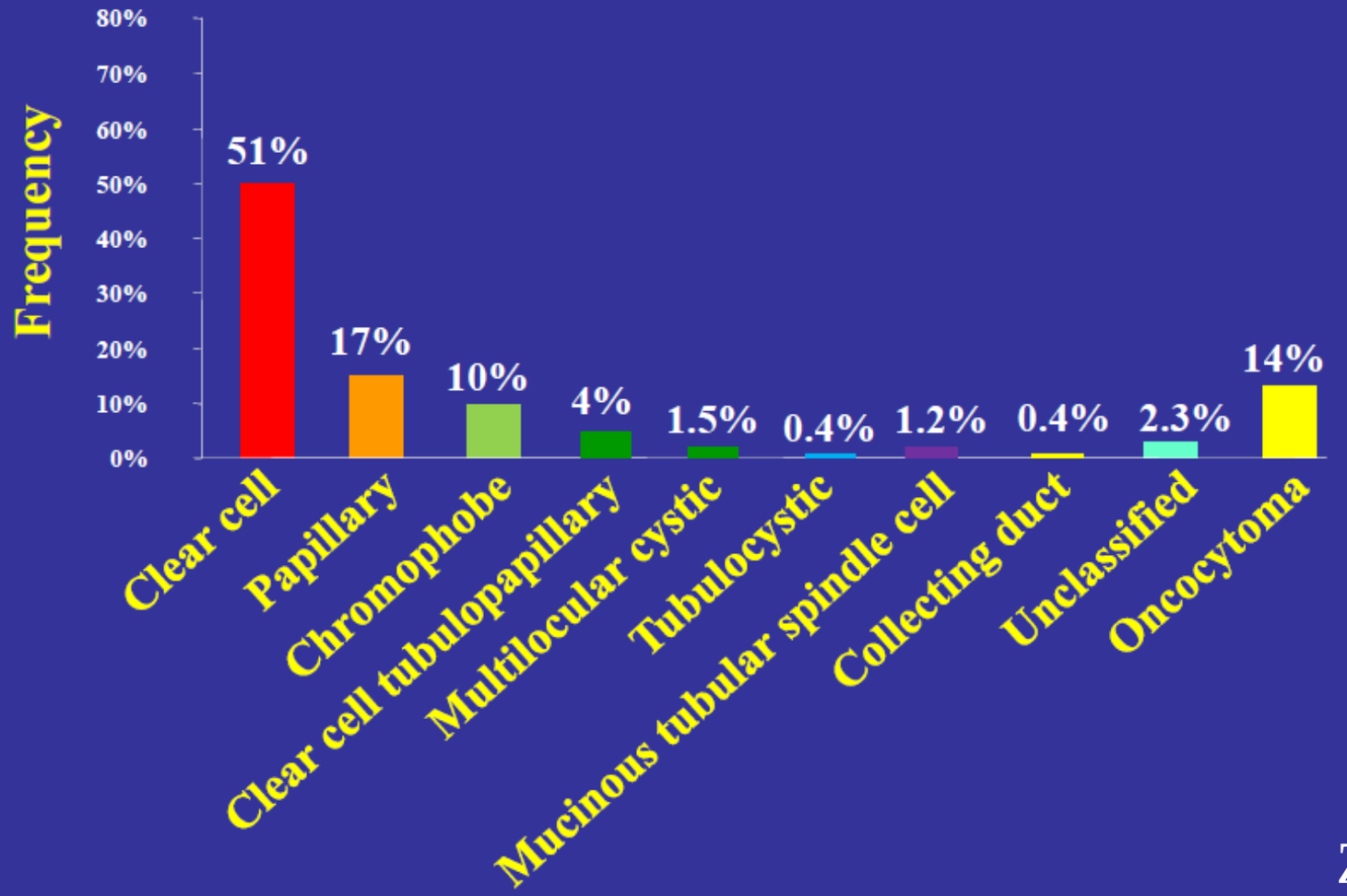






Frequency of Histological Subtypes of Renal Tumors

(NYU, 260 cases)



Zhou M.

RISK FACTORS

Cigarette smoking: The relative risks for RCC for all smokers, current smokers, and former smokers were 1.31, 1.36, and 1.16, respectively. (24 meta-analysis studies)

Hypertension: The underlying biological explanations linking HT to RCC remain unknown.

Obesity: A prospective analysis of over 300,000 participants in the National Institutes of Health and American Association for Retired Persons (NIH-AARP) Diet and Health Study. The relative risk (RR) of RCC increased progressively with BMI.

Occupational exposure:

Toxic compounds, such as cadmium, asbestos, and petroleum by-products associated with an increased risk of RCC. In one international multicenter study of over 1700 patients with RCCs and 2300 controls, an increased risk of cancer was observed in

- Asbestos (RR 1.4, 95% CI 1.1-1.8),
- Cadmium (RR 2.0, 95% CI 1.0-3.9),
- Gasoline (RR 1.6, 95% CI 1.2-2.0).

Increased exposure to such carcinogens may be associated with mutations in genes associated with the pathogenesis of RCC, such as the von Hippel-Lindau (VHL) tumor suppressor gene.

Analgesics: Prolonged ingestion of analgesic combinations, particularly compounds containing phenacetin (acetaminophen) and aspirin, -> CRF -> increased risk for renal pelvic and urothelial tumors.

Heavy use of aspirin, NSAIDS, and acetaminophen -> increased risk of RCC.

The largest prospective studies: 77,525 women followed >16 years and 49,043 men followed > 20 years.

The regular use of aspirin or acetaminophen was not associated with the development of RCC .

The routine use of nonaspirin NSAIDs was associated with a greater risk of RCC (hazard ratio [HR] 1.51, 95% CI 1.12-2.04), which increased with more frequent use and longer period of use.

Data from 1217 RCC cases and 1235 controls in the US Kidney Cancer Study, and 98,807 participants in the US Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) found that non-prescription acetaminophen use increased the risk of developing RCC.

Acquired cystic disease of the kidney

30-50% in chronic dialysis, 6% develop RCC

Genetic factors:

Most RCCs are sporadic.
Several syndromes associated with RCC have been described.
Factors favor a hereditary contribution without a clear genetic disease include
- First degree relatives with a tumor,
- Onset before the age of 40,
- Bilateral or multifocal disease.

Other individuals with a clear genetic contribution have abnormalities on chromosome 3.

Inherited polycystic disease may have an increased risk of RCC.

One cohort study in a Chinese population: the risk of RCC was increased in patients with inherited polycystic kidney disease and no history of renal disease compared to a matched control group (adjusted HR 2.5, 95% CI 1.3-4.7)

Cytotoxic chemotherapy: The use of cytotoxic chemotherapy in childhood for malignancies, autoimmune disorders, or bone marrow transplant conditioning has been associated with the subsequent development of translocation RCC.

Chronic hepatitis C infection: An epidemiologic study of over 67,000 patients found that chronic infection with hepatitis C virus was associated with a significantly increased risk of RCC after correcting for age, ethnicity, gender, and the presence of chronic kidney disease (HR 1.77, 95% CI 2.05-2.98).

Sickle cell disease: Patients with sickle cell trait and sickle cell disease are at risk for renal medullary carcinoma.

Kidney stones: A history of kidney stones may be associated with both RCC and transitional cell carcinoma of the upper urinary tract. In a meta-analysis from almost 63,000 patients with kidney stones, the risk ratio of developing RCC was 1.96 (95% CI 1.24-2.49), and the increased risk appeared to be largely limited to men. The risk ratio for transitional cell carcinoma was 2.14 (95% CI 1.35-3.40).

OTHER FACTORS THAT MODIFY RISK

Diabetes mellitus: associated with a modest increase in the risk of renal cell carcinoma (RCC) in some studies but not in others. This may be mediated through an increase in the incidence of hypertension.

Polycystic kidney disease: It does not increased frequency compared with the general population. The tumors are more often **bilateral at presentation** (12 versus 1 to 4 percent in sporadic RCC in the general population), **multicentric** (28 versus 6 percent), and **sarcomatoid** (33 versus 1 to 5 percent)

Alcohol: Associated with a **protective effect** on the risk of RCC in both men and women. The protective effect of alcohol on the risk of RCC was shown in a 2012 meta-analysis of 20 studies.

Other factors:
Dietary factors such as the intake of nitrite from processed meat sources,
reproductive factors (eg, increasing number of pregnancies),
prior radiation therapy (RT). For women, the use of oral contraceptives may reduce risk.

PATHOLOGY:

Previously, renal cell carcinomas (RCCs) were classified by cell type and growth pattern.

This classification was changed to more accurately reflect the morphology, growth pattern, cell origin, histochemical, and molecular basis of the different types of adenocarcinomas.

1810: First renal carcinoma published by Meri…

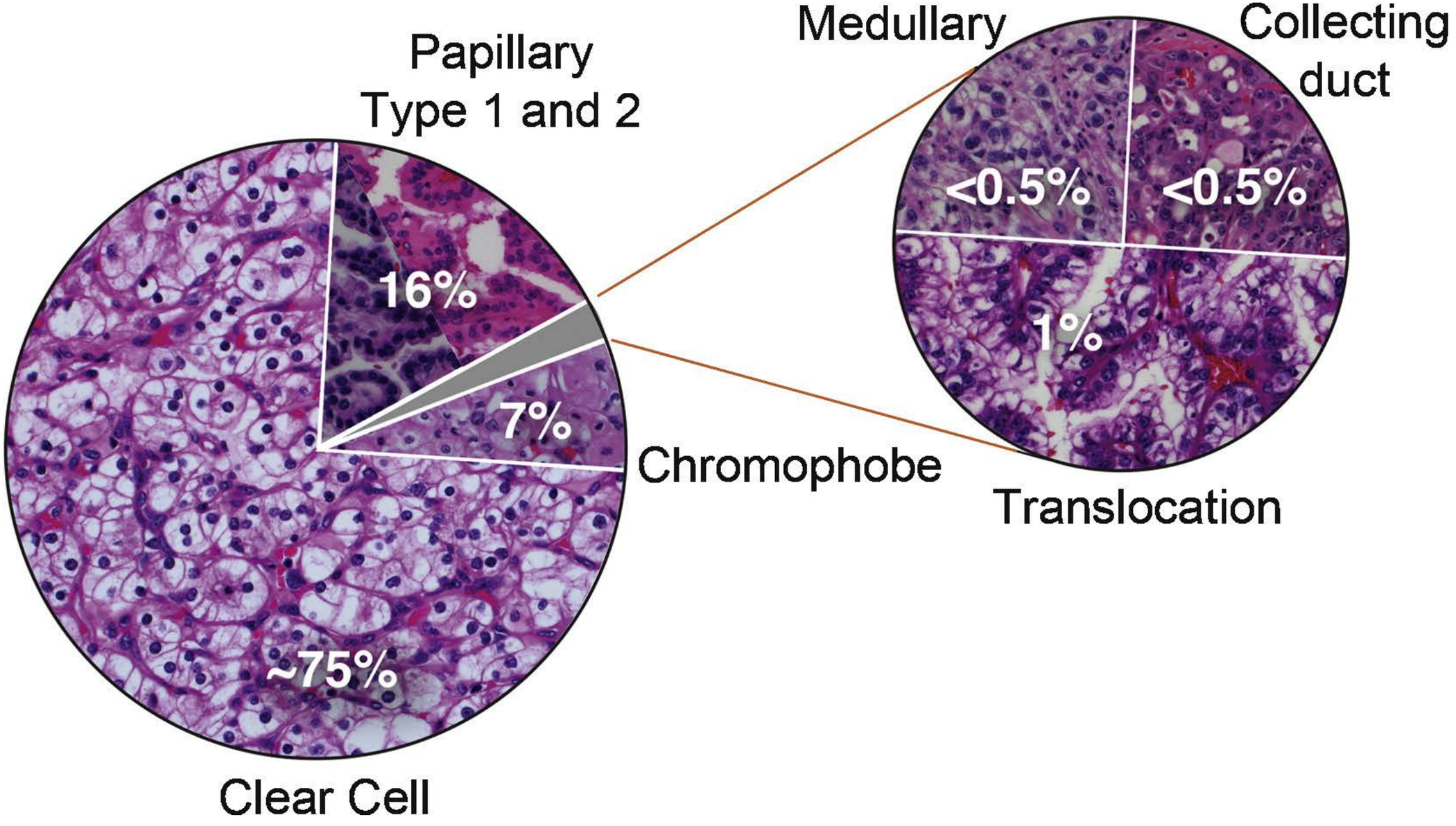
1613: Daniel Sennert …

1826: Koenig classified renal tumors based on clinical and gross morphology

1880–1920

Hypernephroma

Grawitz Tumor



EUROPEAN UROLOGY 67 (2015) 85–97

Renal cell tumours	
Clear cell renal cell carcinoma	8310/3
Multilocular cystic renal neoplasm of low malignant potential	8316/1*
Papillary renal cell carcinoma	8260/3
Hereditary leiomyomatosis and renal cell carcinoma–associated renal cell carcinoma	8311/3*
Chromophobe renal cell carcinoma	8317/3
Collecting duct carcinoma	8319/3
Renal medullary carcinoma	8510/3*
MiT family translocation renal cell carcinomas	8311/3*
Succinate dehydrogenase–deficient renal carcinoma	8311/3
Mucinous tubular and spindle cell carcinoma	8480/3*
Tubulocystic renal cell carcinoma	8316/3*
Acquired cystic disease–associated renal cell carcinoma	8316/3
Clear cell papillary renal cell carcinoma	8323/1
Renal cell carcinoma, unclassified	8312/3
Papillary adenoma	8260/0
Oncocytoma	8290/0
Metanephric tumours	
Metanephric adenoma	8325/0
Metanephric adenofibroma	9013/0
Metanephric stromal tumour	8935/1
Nephroblastic and cystic tumours occurring mainly in children	
Nephrogenic rests	
Nephroblastoma	8960/3
Cystic partially differentiated nephroblastoma	8959/1
Paediatric cystic nephroma	8959/0

Mesenchymal tumours	
Mesenchymal tumours occurring mainly in children	
Clear cell sarcoma	8964/3
Rhabdoid tumour	8963/3
Congenital mesoblastic nephroma	8960/1
Ossifying renal tumour of infancy	8967/0
Mesenchymal tumours occurring mainly in adults	
Leiomyosarcoma	8890/3
Angiosarcoma	9120/3
Rhabdomyosarcoma	8900/3
Osteosarcoma	9180/3
Synovial sarcoma	9040/3
Ewing sarcoma	9364/3
Angiomyolipoma	8860/0
Epithelioid angiomyolipoma	8860/1*
Leiomyoma	8890/0
Haemangioma	9120/0
Lymphangioma	9170/0
Haemangioblastoma	9161/1
Juxtaglomerular cell tumour	8361/0
Renomedullary interstitial cell tumour	8966/0
Schwannoma	9560/0
Solitary fibrous tumour	8815/1
Mixed epithelial and stromal tumour family	
Cystic nephroma	8959/0
Mixed epithelial and stromal tumour	8959/0

The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs

New diagnostic entities
Clear cell papillary RCC
Hereditary leiomyomatosis and RCC- associated RCC
Succinate dehydrogenase–deficient RCC
Tubulocystic RCC
Acquired cystic disease–associated RCC

Evolving RCC classification, such as transcription elongation factor B subunit 1 (TCEB1)– mutated RCC/RCC with angioleiomyoma-like stroma/ RCC with leiomyomatous stroma, RCC associated with anaplastic lymphoma receptor tyrosine kinase (ALK) gene rearrangement, thyroid-like follicular RCC, and RCC in neuroblastoma survivors.

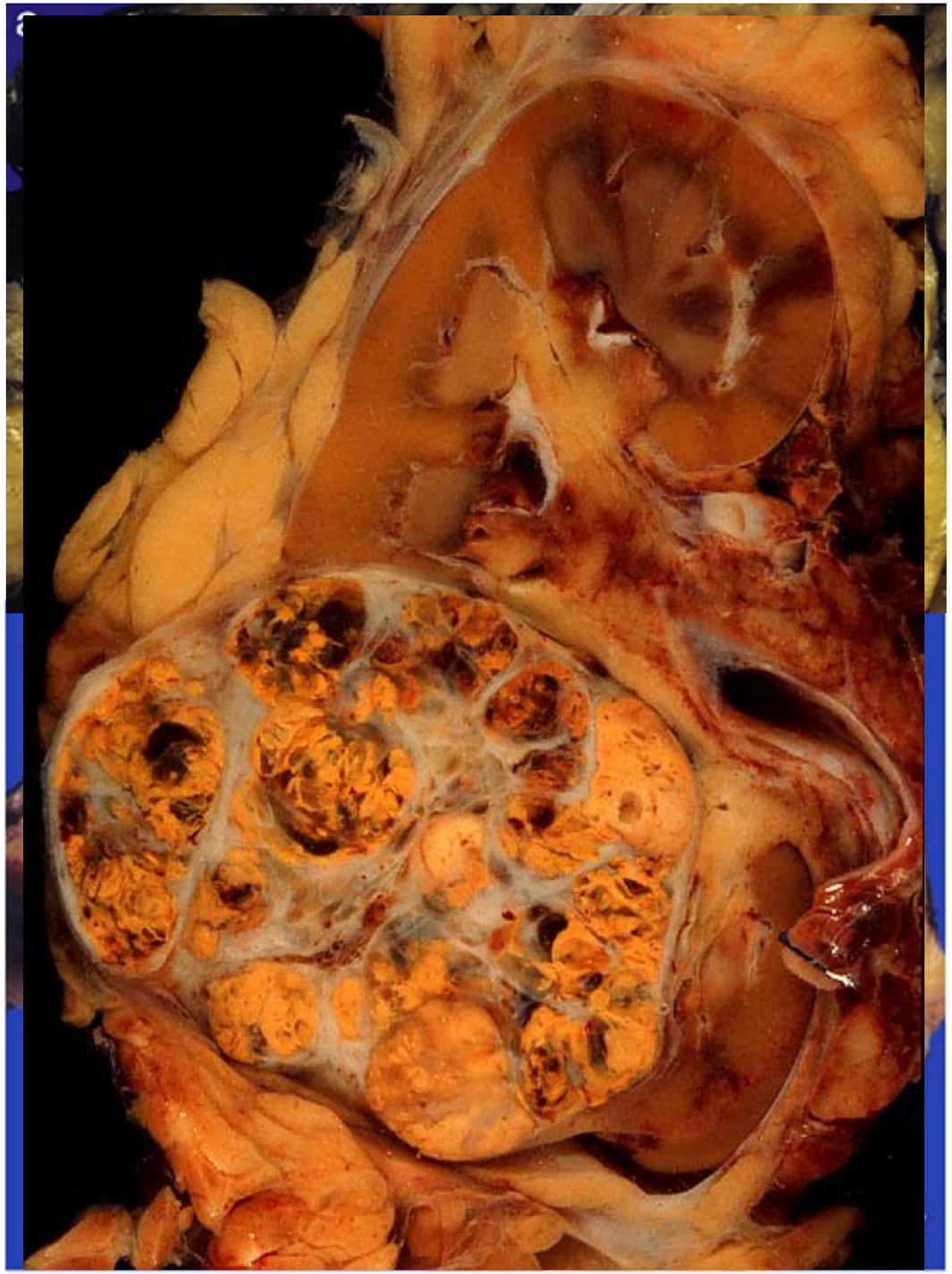
Clear cell carcinomas:

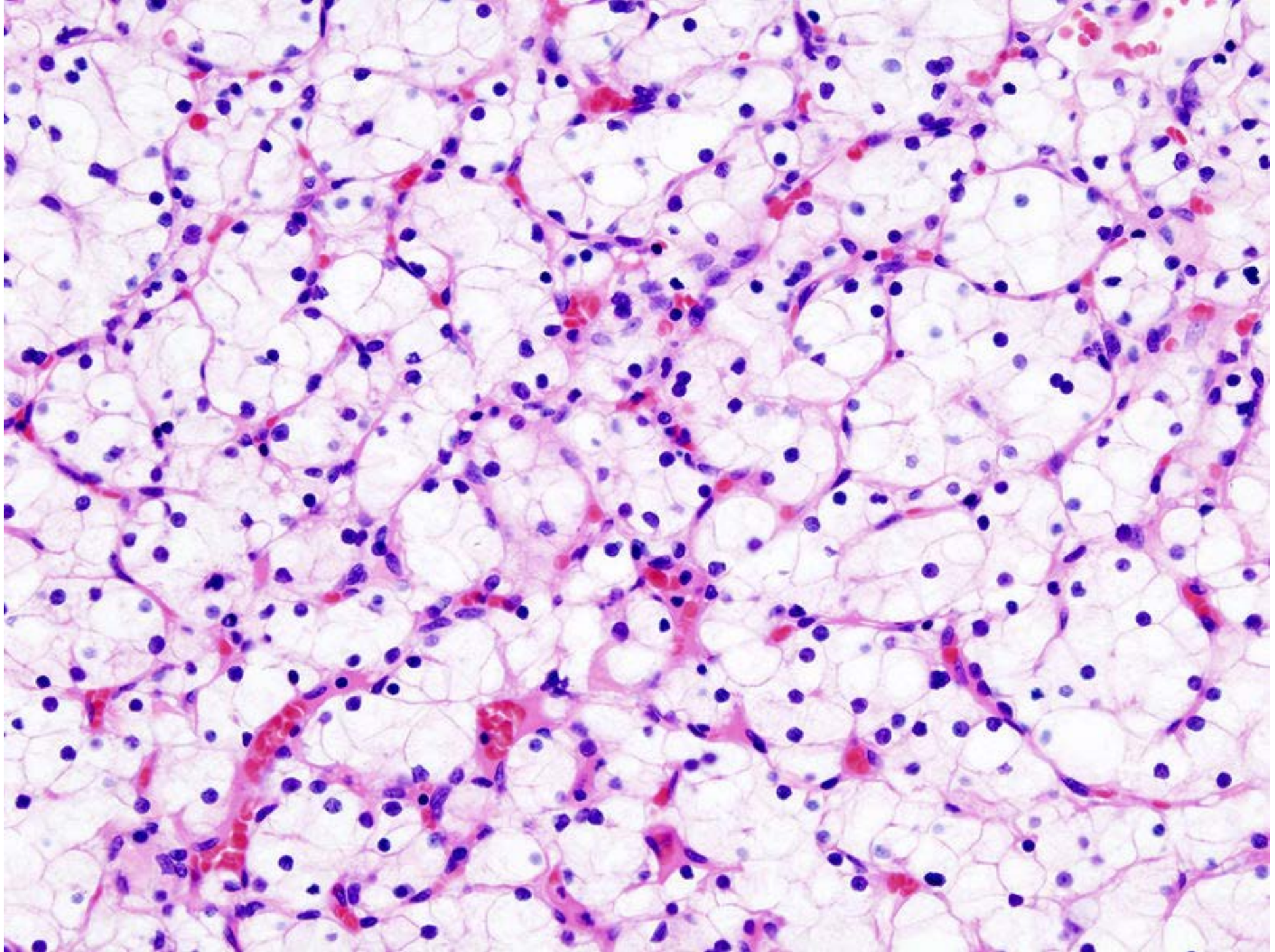
Typically have a deletion of 3p.

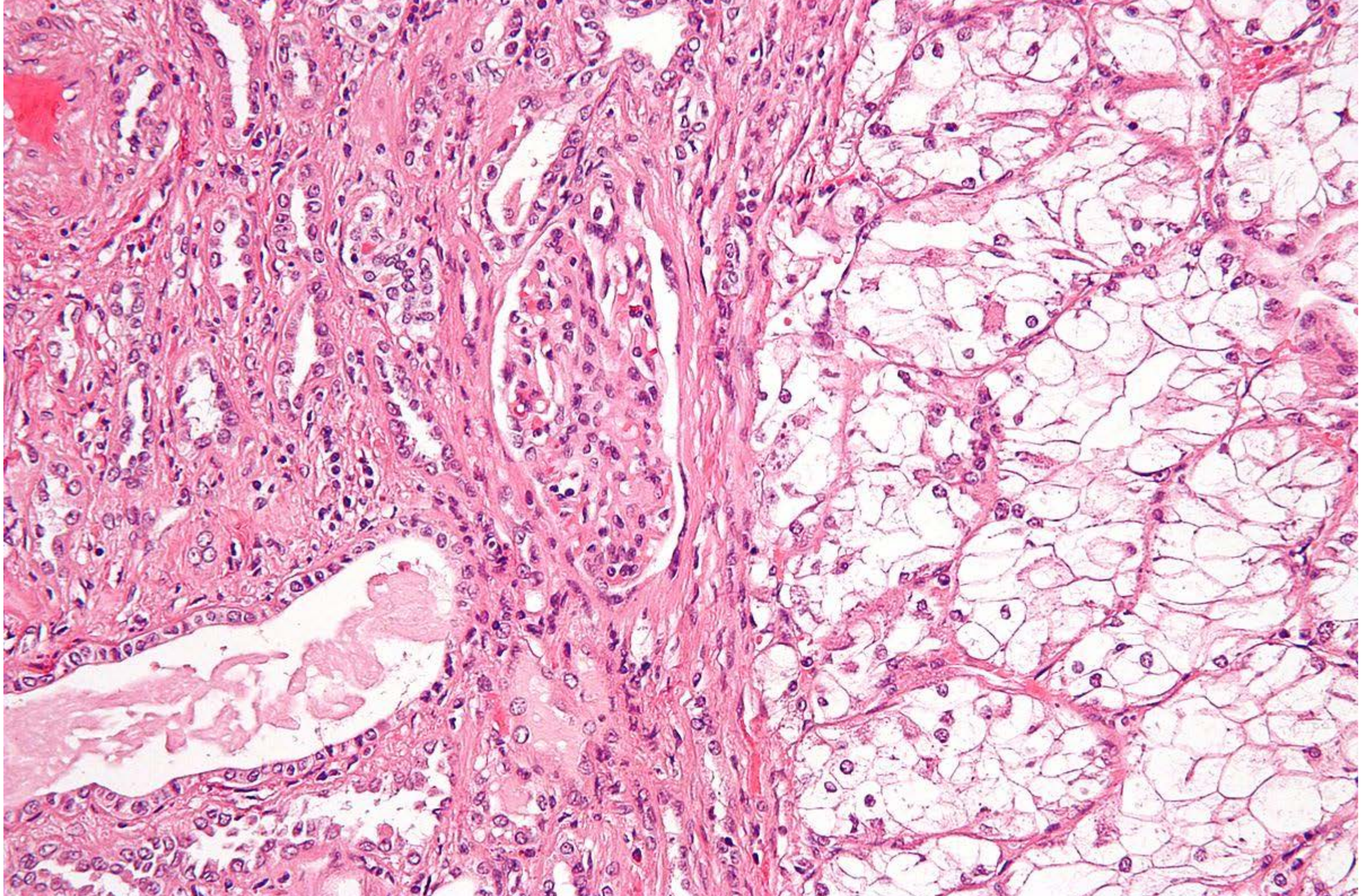
Arise from the proximal tubule.

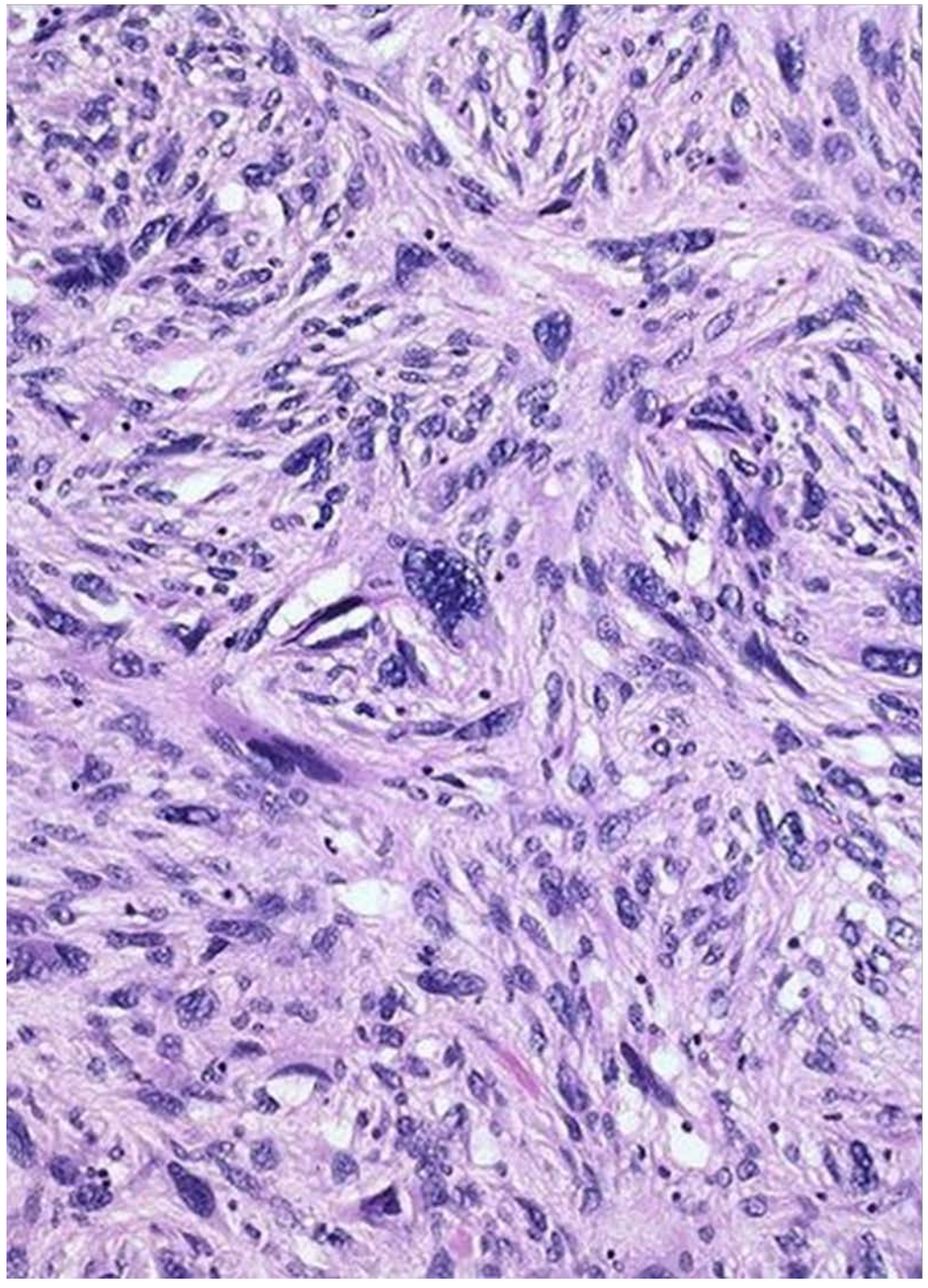
Macroscopically: solid or cystic.

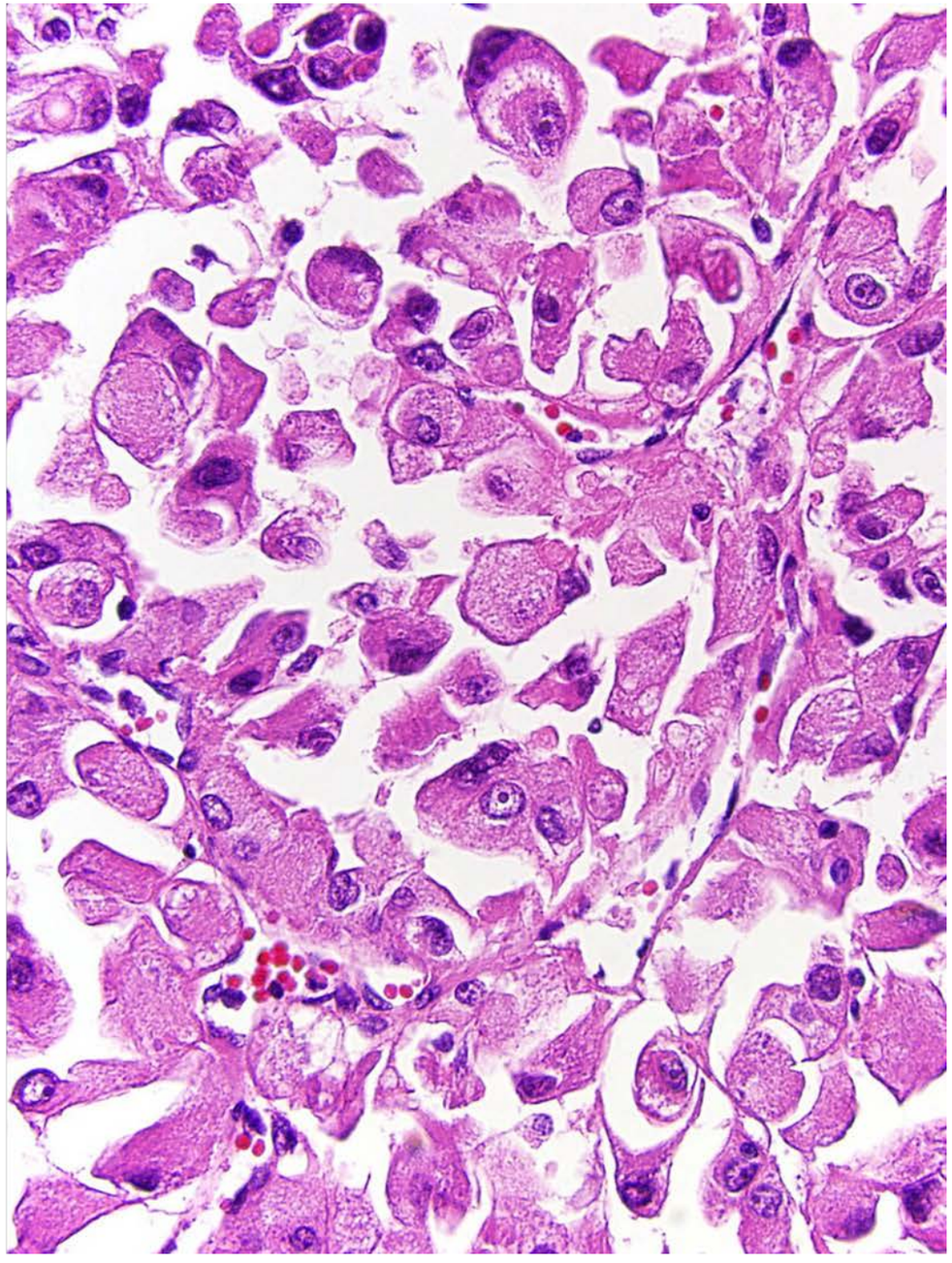
In addition to occurring in sporadic disease, clear cell carcinomas are specifically associated with von Hippel-Lindau disease.











Sarcomatoid feature

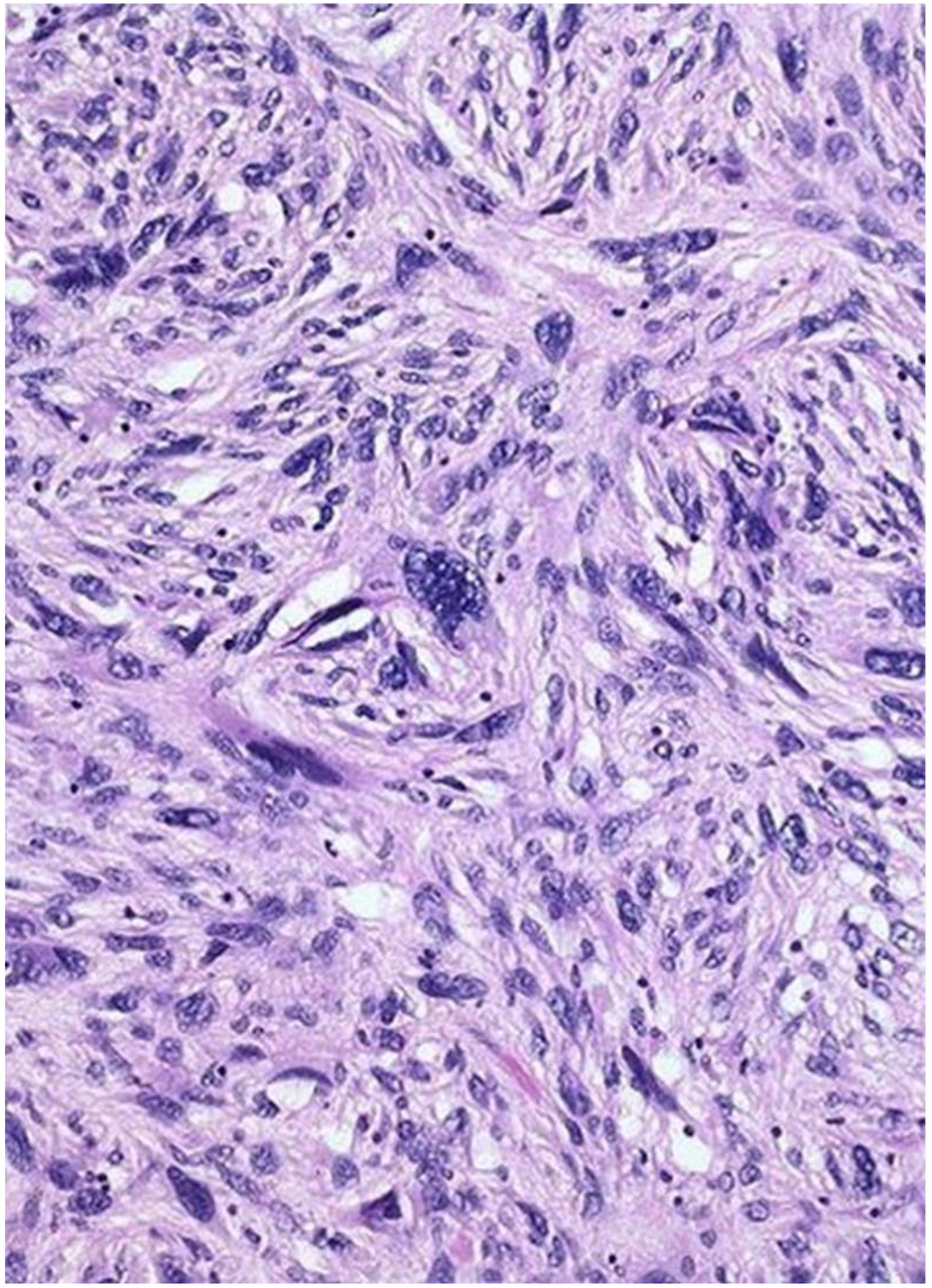
Not a subtype of renal cell carcinoma but is considered as a pattern of dedifferentiation.

Associated with an adverse outcome.

May be found in any histologic subtypes of renal cell carcinomas.

WHO/ISUP grading system as grade 4.

Percentage of sarcomatoid component in a renal cell carcinoma has prognostic importance.



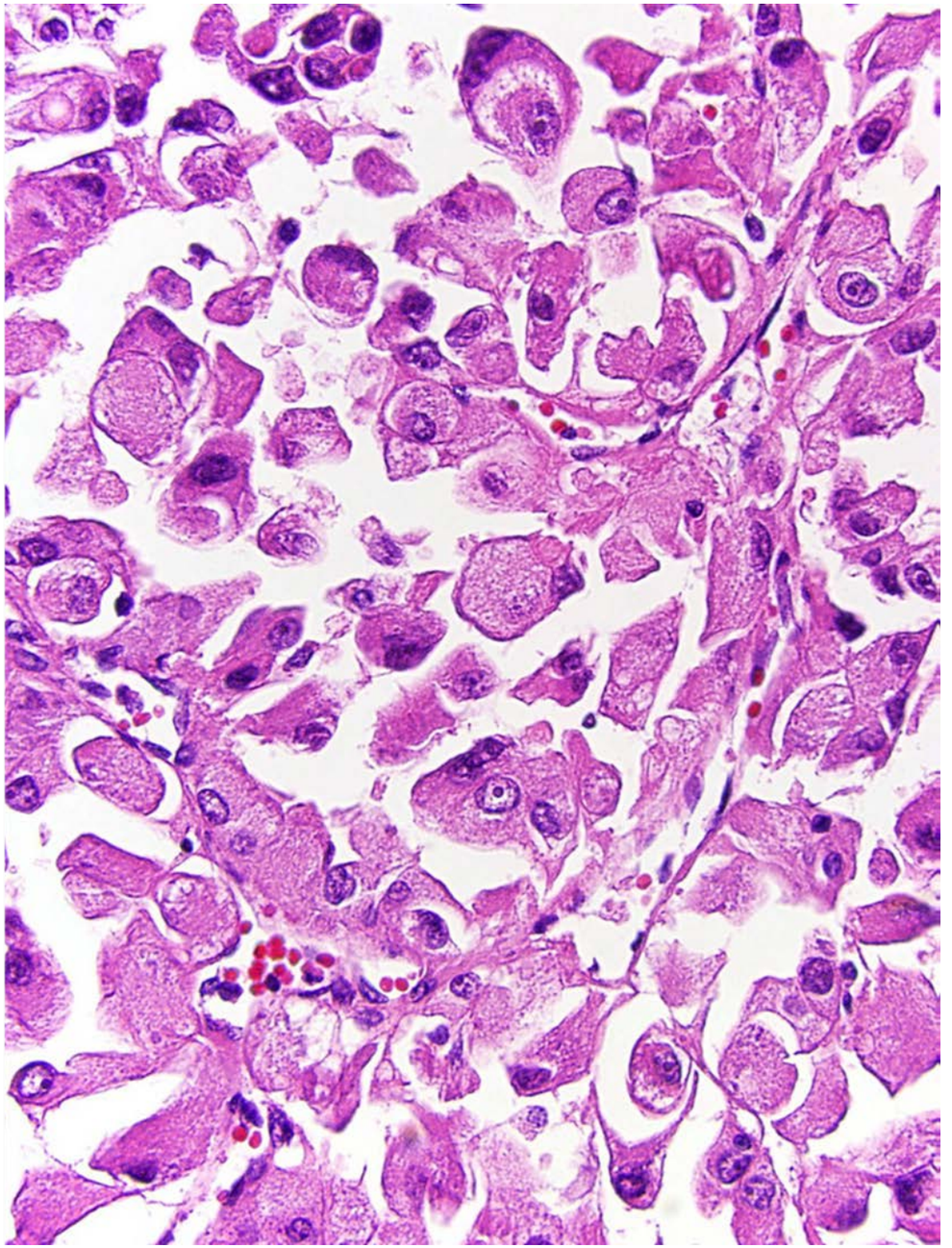
Rhabdoid feature

Characteristic of high-grade disease.

Rhabdoid cells: abundant eosinophilic cytoplasm, eccentric nucleus, prominent nucleolus.

Associated with an adverse outcome. 25% of them also show sarcomatoid features.

WHO/ISUP grading system grade 4.



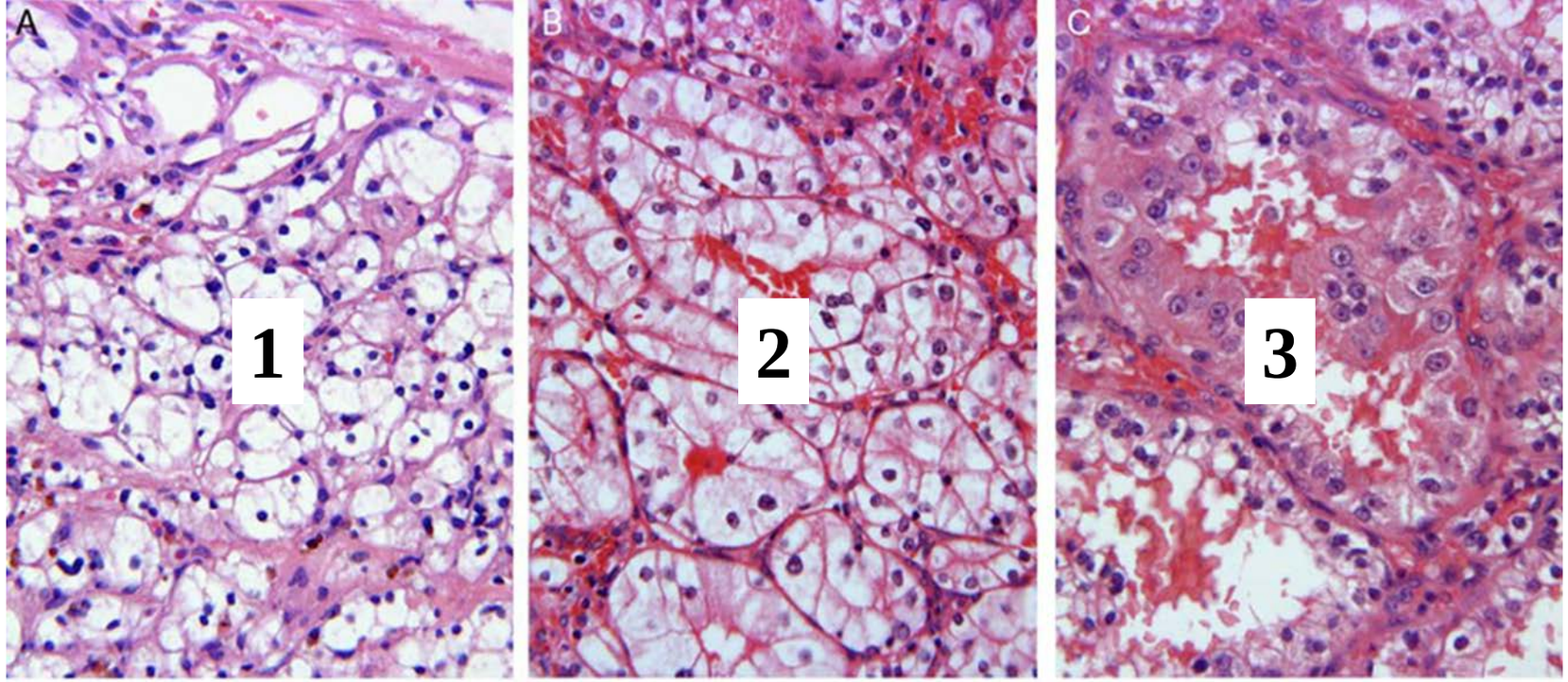
Histologic Grade
The WHO/ISUP grading system has supplanted the Fuhrman system

Validated for both clear cell and papillary renal cell carcinoma.

Chromophobe renal cell carcinoma not be graded.

Not applicable
Grade X - Cannot be assessed
Grade 1 - Nucleoli absent or inconspicuous and basophilic at 400x.
Grade 2 - Nucleoli conspicuous and eosinophilic at 400x, visible but not prominent at 100x
Grade 3 - Nucleoli conspicuous and eosinophilic at 100x
Grade 4 - Extreme nuclear pleomorphism and/or multinuclear giant cells and/or rhabdoid and/or sarcomatoid differentiation

Grade should be assigned based on the single high-power field showing the greatest degree of pleomorphism.

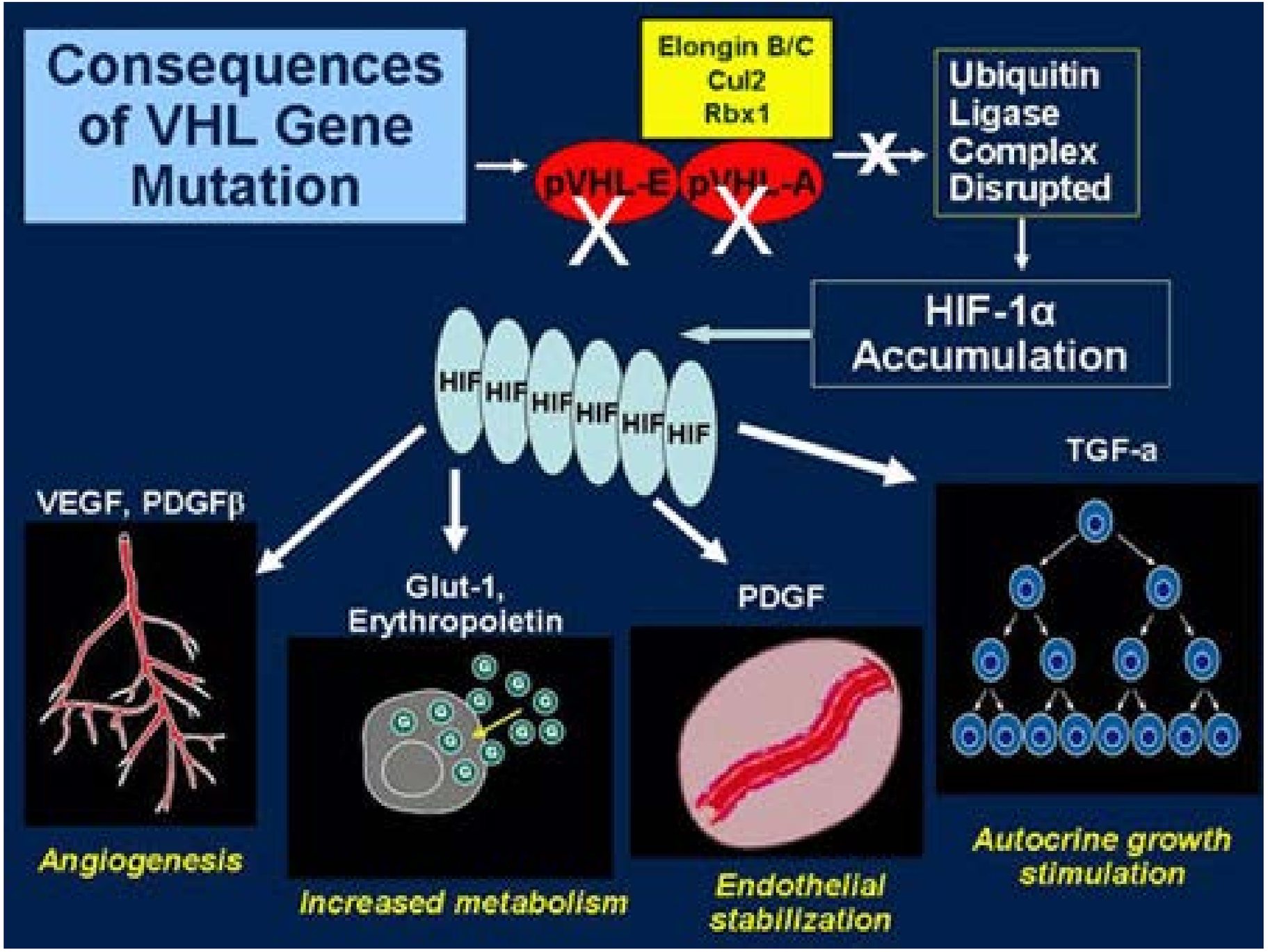

A
1
B
2
C
3

Von Hippel Lindau gene:

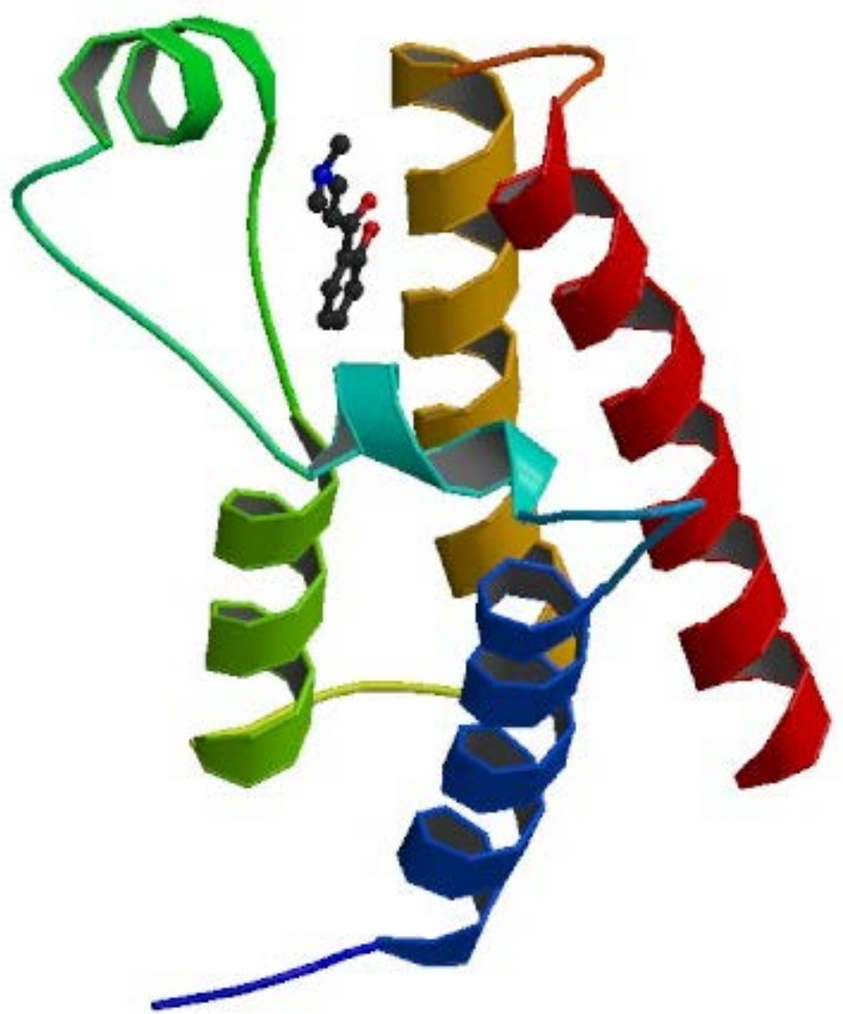
Found on chromosome 3 (3p25 to 26)
Plays a pivotal role in the development of clear cell RCC in patients with VHL disease.
VHL gene alterations be important in the pathogenesis of sporadic RCC.

187 patients with sporadic RCC, somatic mutations or promoter hypermethylation in the VHL gene was observed in 58 percent of cases.

Other reports using high throughput methodologies have demonstrated improved identification of VHL alterations; up to 91 percent of patients with clear cell RCC harbor a VHL gene alteration through genetic or epigenetic mechanisms


Consequences of VHL Gene Mutation
Elongin B/C
Cul2
Rbx1
pVHL-E
pVHL-A
Ubiquitin Ligase Complex Disrupted
HIF-1α Accumulation
HIF
HIF
HIF
HIF
HIF
HIF
VEGF, PDGFβ
Glut-1, Erythropoietin
PDGF
TGF-a
Angiogenesis
Increased metabolism
Endothelial stabilization
Autocrine growth stimulation

PBRM1 gene: Recently, the Switch/Sucrose NonFermentable (SWI/SNF) chromatin remodeling complex gene PBRM1 was found to be a second major clear cell RCC gene, with truncating mutations in 92 of 227 (41%) cases. Interestingly, PBRM1 maps to chromosome 3p21 and is a tumor-suppressor gene.



BAP1 gene:

BRCA1 associated protein-1 (BAP1), located at 3p, is mutated in 15 percent of clear cell RCC. encodes a nuclear deubiquitinase. It is part of the large ubiquitin-mediated proteolysis pathway (UMPP).

BAP1-mutant tumors are more likely to be aggressive and display adverse pathologic features, leading to worse survival.

Combined loss of BAP1 and PBRM1 in a few RCCs was associated with rhabdoid features

Nature Genetics 44, 751–759 (2012)

Inactivation of histone-modifying genes:

Inactivating mutations in two genes encoding enzymes involved in histone including

- SET domain containing protein 2 (SETD2)
- Jumonji AT-rich interactive domain 1C (JARID1C).

Chromatic modification machinery may be important to the pathogenesis of RCC.

Ubiquitin-mediated proteolysis pathway (UMPP):

UMPP is an important pathway for protein degradation through the proteasome. Alterations in UMPP result in similar functional consequences (ie, hypoxia) as VHL inactivation. In one study, UMPP was the most frequently altered pathway in clear cell RCC. Of note, the VHL and BAP1 genes are members of this pathway.

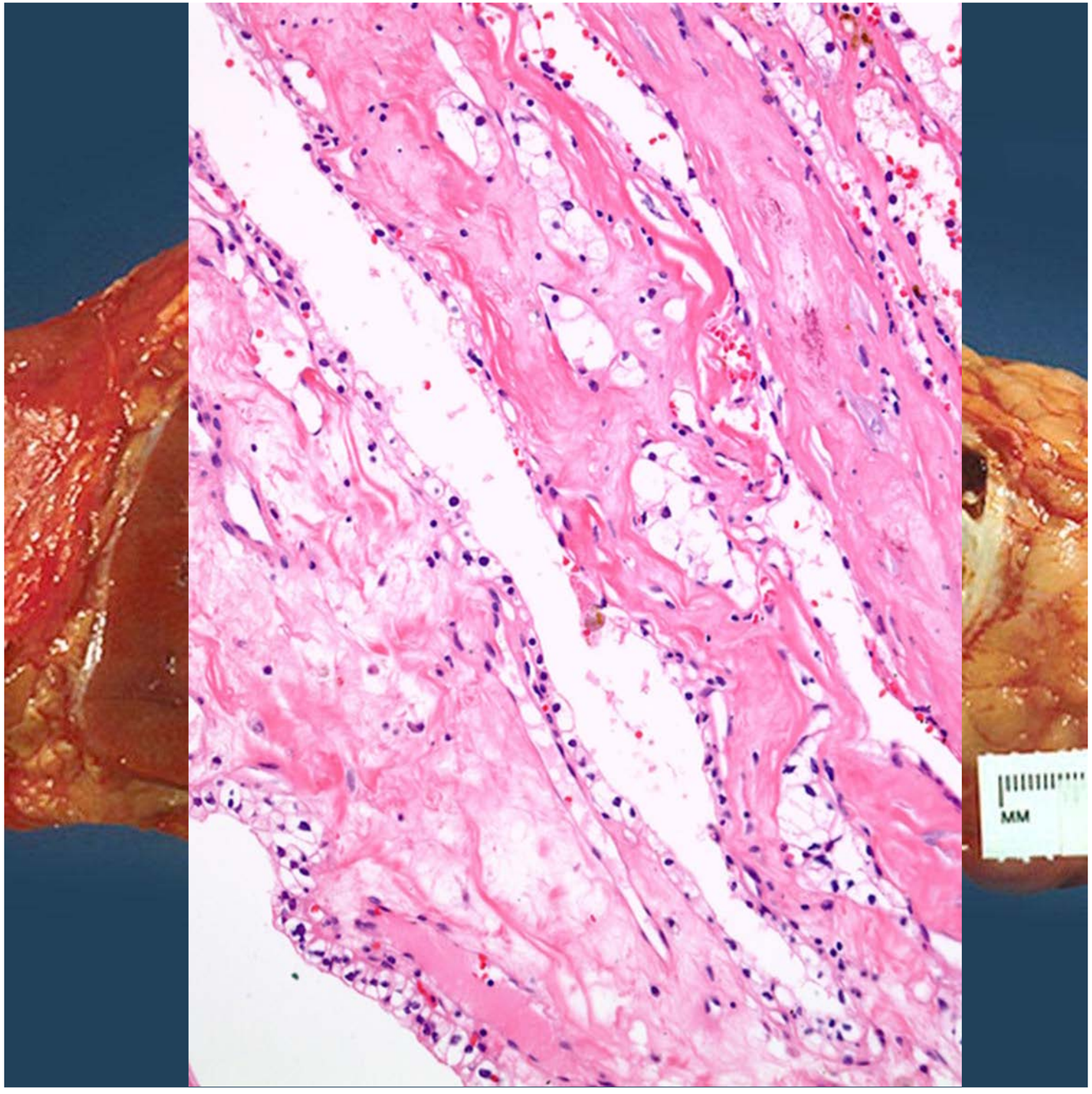
Abnormalities in cellular division:

Development of RCCs involve abnormalities in genes that control cell division include
Ras family genes and the p53 tumor suppressor gene.
Mutations in the p53 gene are identified infrequently in RCCs,
Overexpression of p53 protein is detected in approximately one-half of tumors and associated with more aggressive behavior and a worse prognosis.
Series of 175 patients, in which the ten-year disease-specific survival was lower for patients whose tumors stained for p53 (48% versus 78%, compared with those not overexpressing p53).

Genetic alterations in clear cell carcinoma:

Genome-wide analysis and gene expression profiles on 90 RCC tumors. Common genetic abnormalities in sporadic von-Hippel Lindau (VHL)-null RCC include the following:

- Loss of 3p (94 %), which contains several genes associated with RCC, including the VHL, BRCA1 associated protein-1 (BAP-1), and protein polybromo-1 (PBRM1) genes
- Gain of 5q (69 %)
- Monosomy or partial loss of 14q (42 %)
- 7q gain (20 %)
- 8p deletion (32 %)
- 9p loss (29 %)

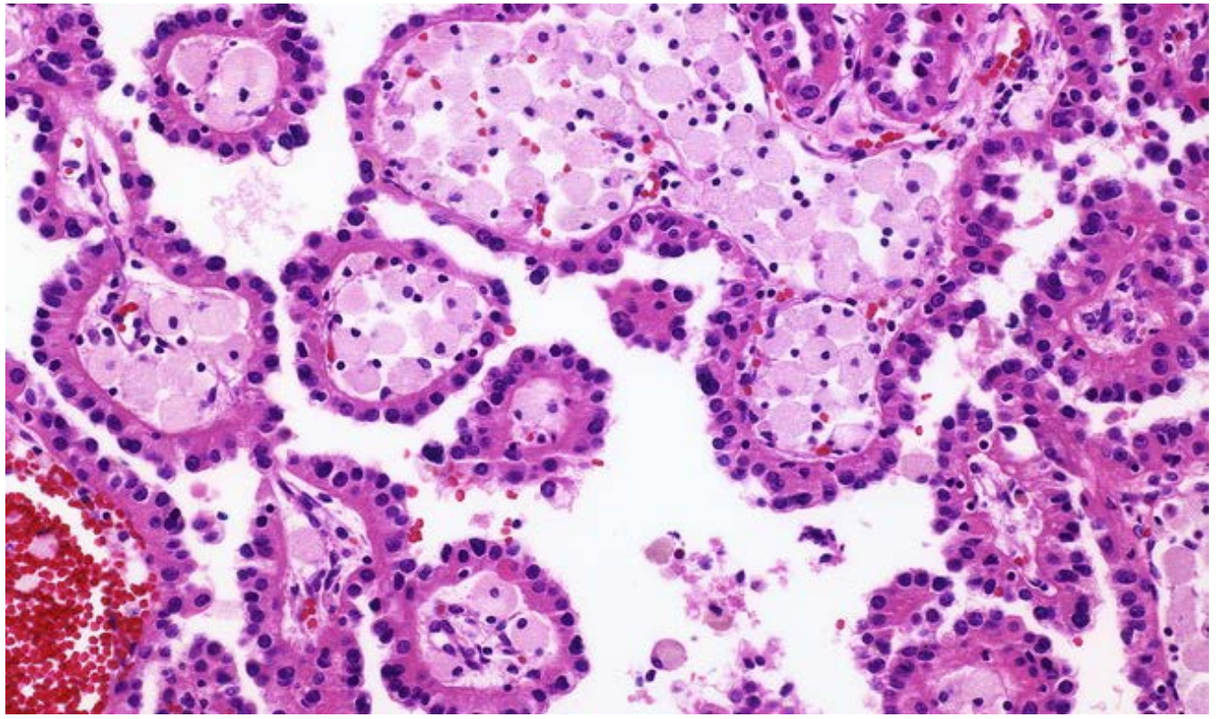

MM

A more favorable prognosis has been associated with the rare multilocular variant of cystic clear cell RCC compared with other clear cell carcinomas.

Multilocular cystic renal neoplasm of low malignant potential

Papillary renal cell carcinoma:

15 % of all kidney cancers
Divided into type 1 and type 2 lesions based upon histopathologic features.
Type 1 and type 2 papillary carcinomas differ in both clinical features and underlying genetic abnormalities.
Originates from the proximal tubule, but these tumors are morphologically and genetically distinct malignancies.



Type 1 papillary RCC:

Typically presents with stage I or II disease.

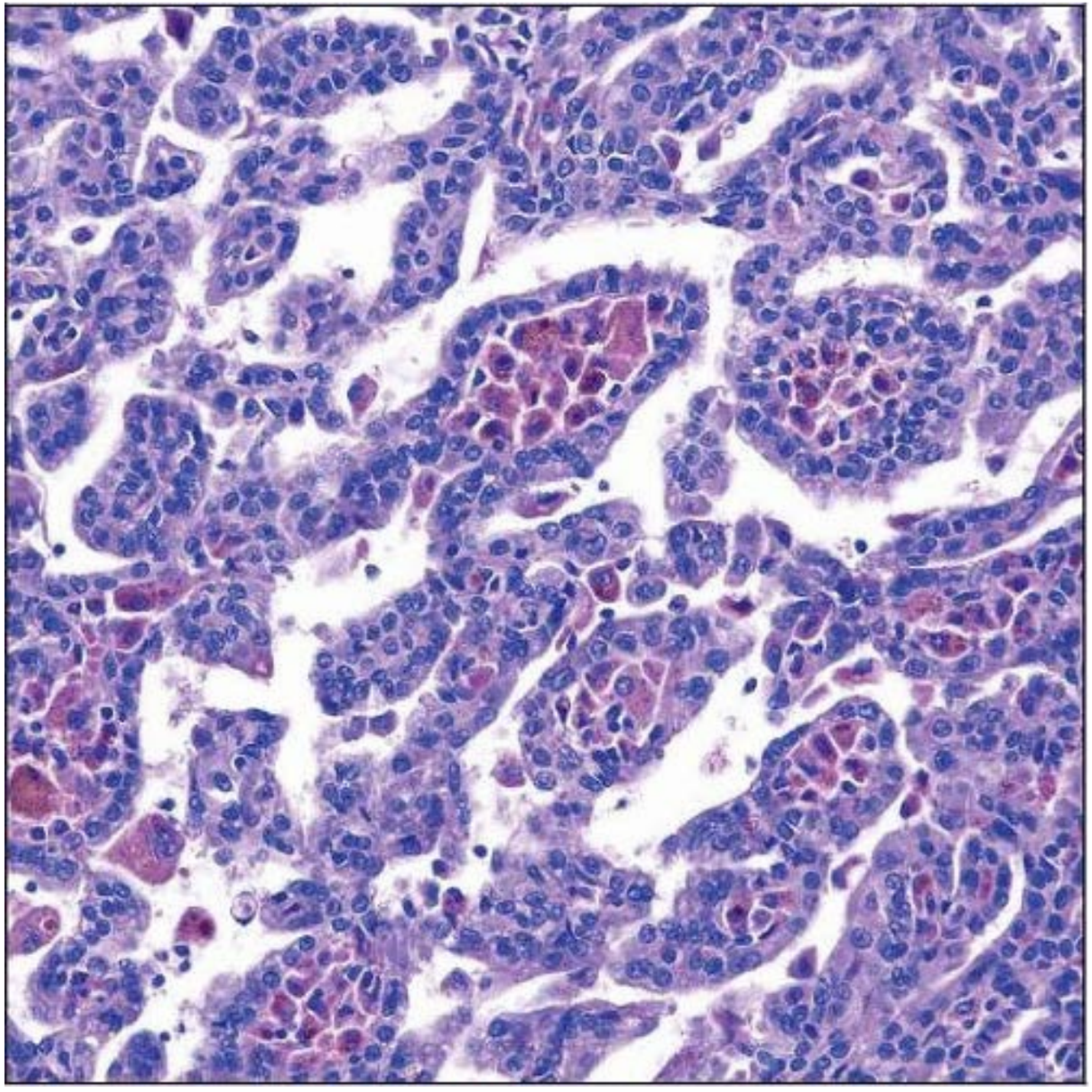
Relatively favorable prognosis.

Occur in patients with hereditary papillary RCC, the majority of these are sporadic.

In the hereditary form, activating germline mutations are seen in MET.

In nonhereditary form, somatic mutations in MET have been identified in 10-20%of cases.

Altered MET status or increased chromosome 7 copy number was identified in 81% of type 1 papillary RCCs.

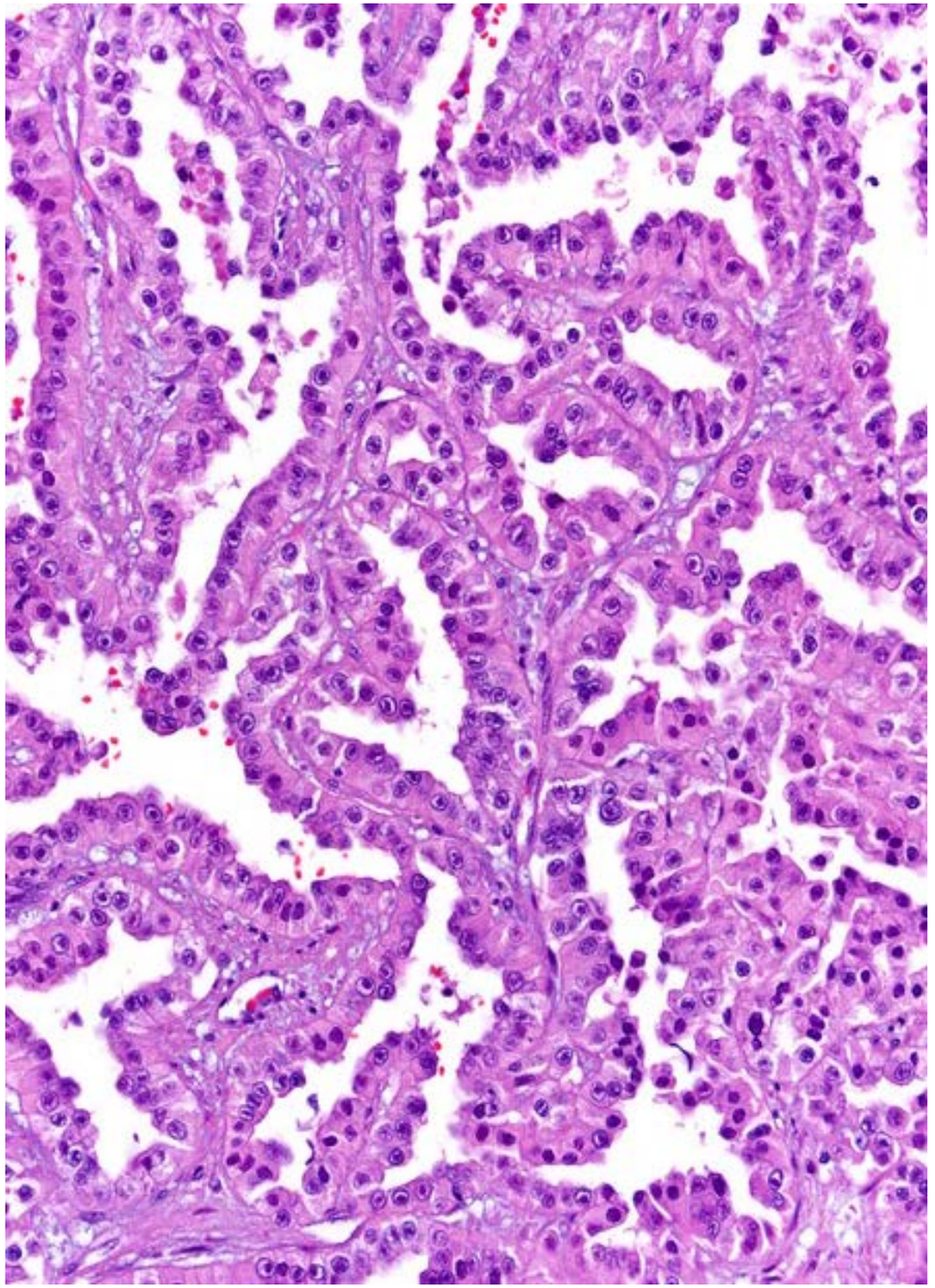


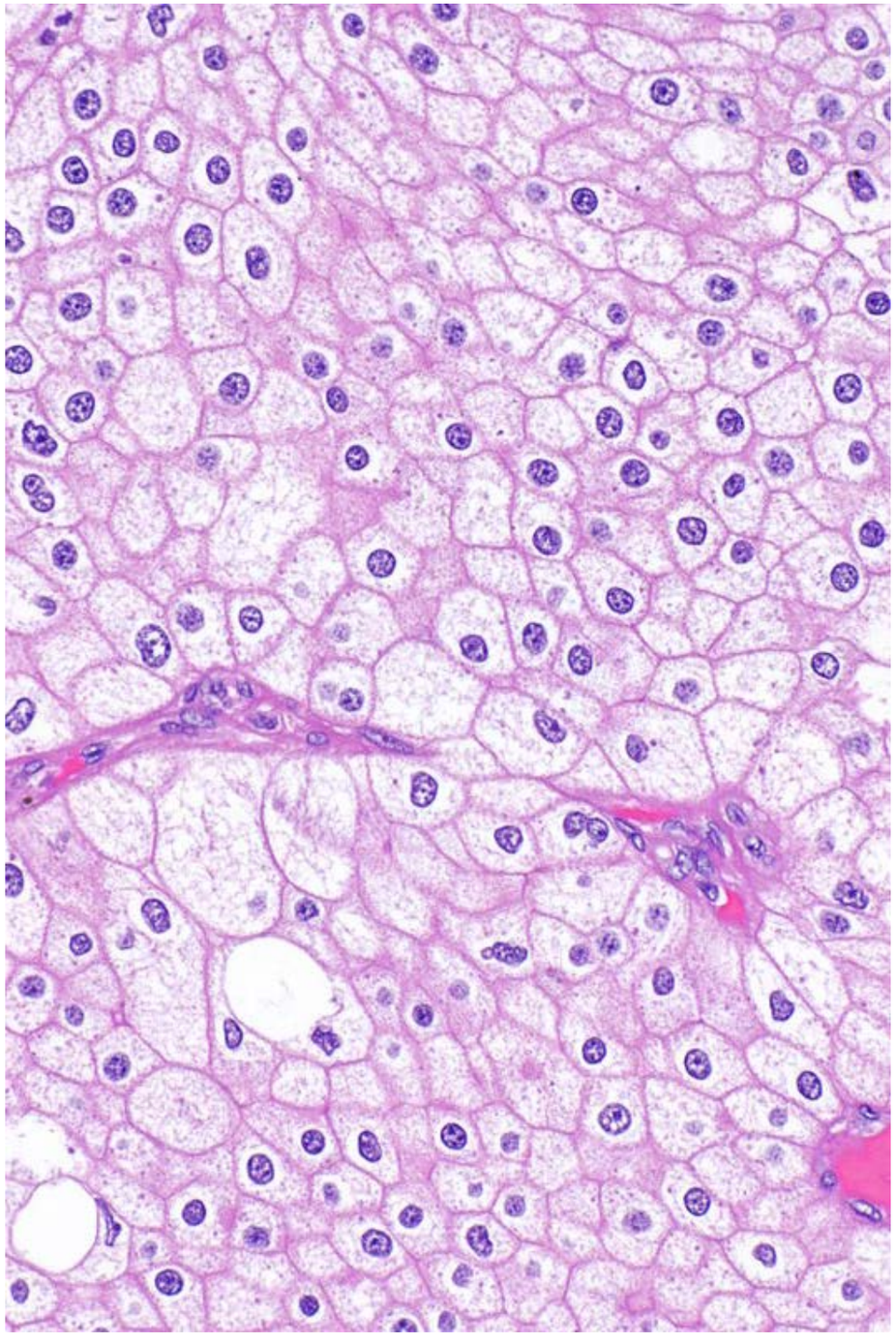
Type 2 papillary RCC:

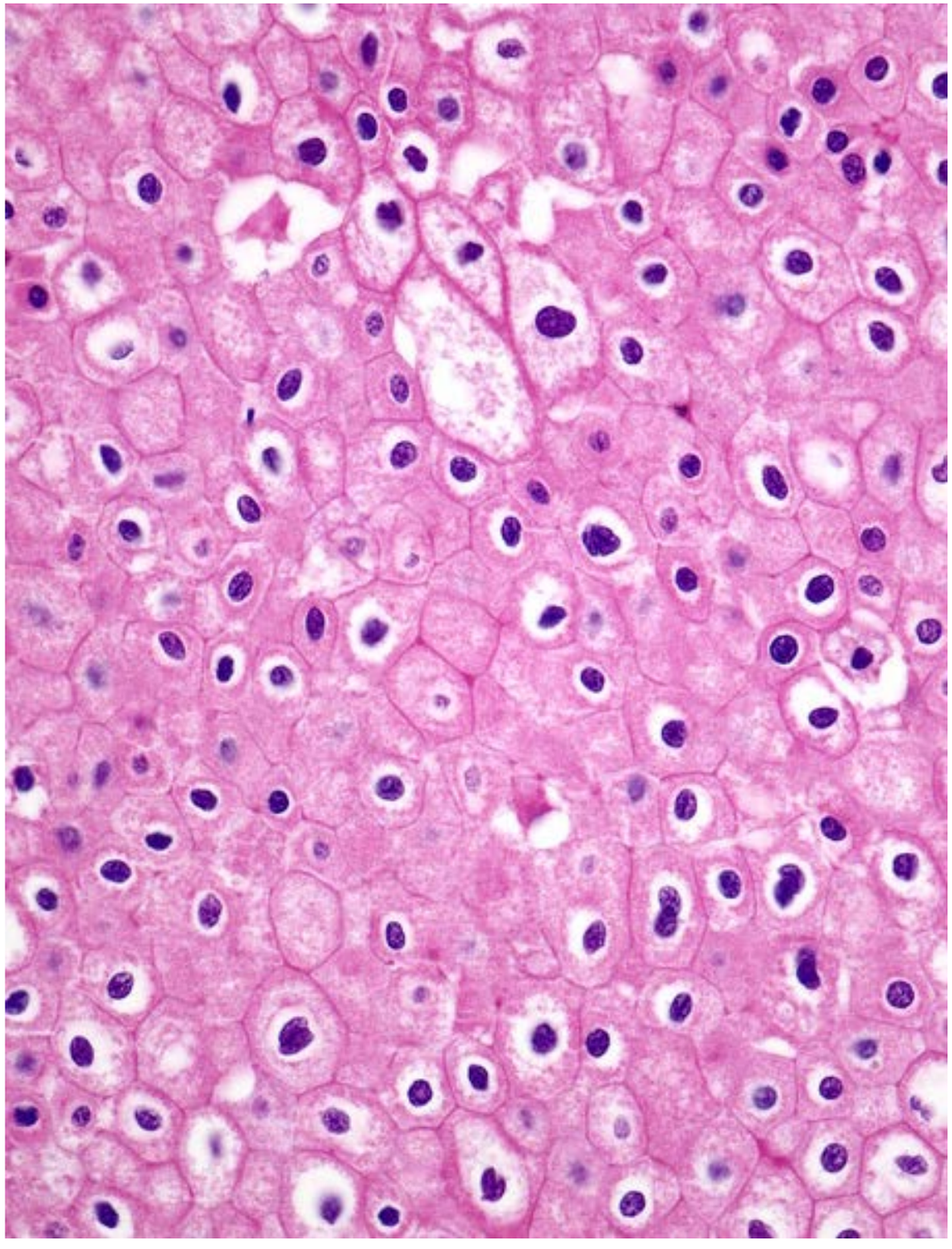
Frequently associated with aggressive tumors that are stage III or IV at presentation and associated with a poor prognosis.

Seen in the hereditary leiomyomatosis and renal cell cancer syndrome, caused by germline mutation in the gene for fumarate hydratase (FH).
In this syndrome, aggressive type 2 renal cell carcinomas are observed and are associated with activation of the NRF2-antioxidant response element (ARE) pathway.

Very few patients had alterations in the MET pathway.







Chromophobe renal cell carcinoma:

Histologically composed of sheets of cells that are darker than clear cell carcinoma.
Lack the abundant lipid and glycogen that is characteristic of most RCCs.

Originate from the intercalated cells of the collecting system.

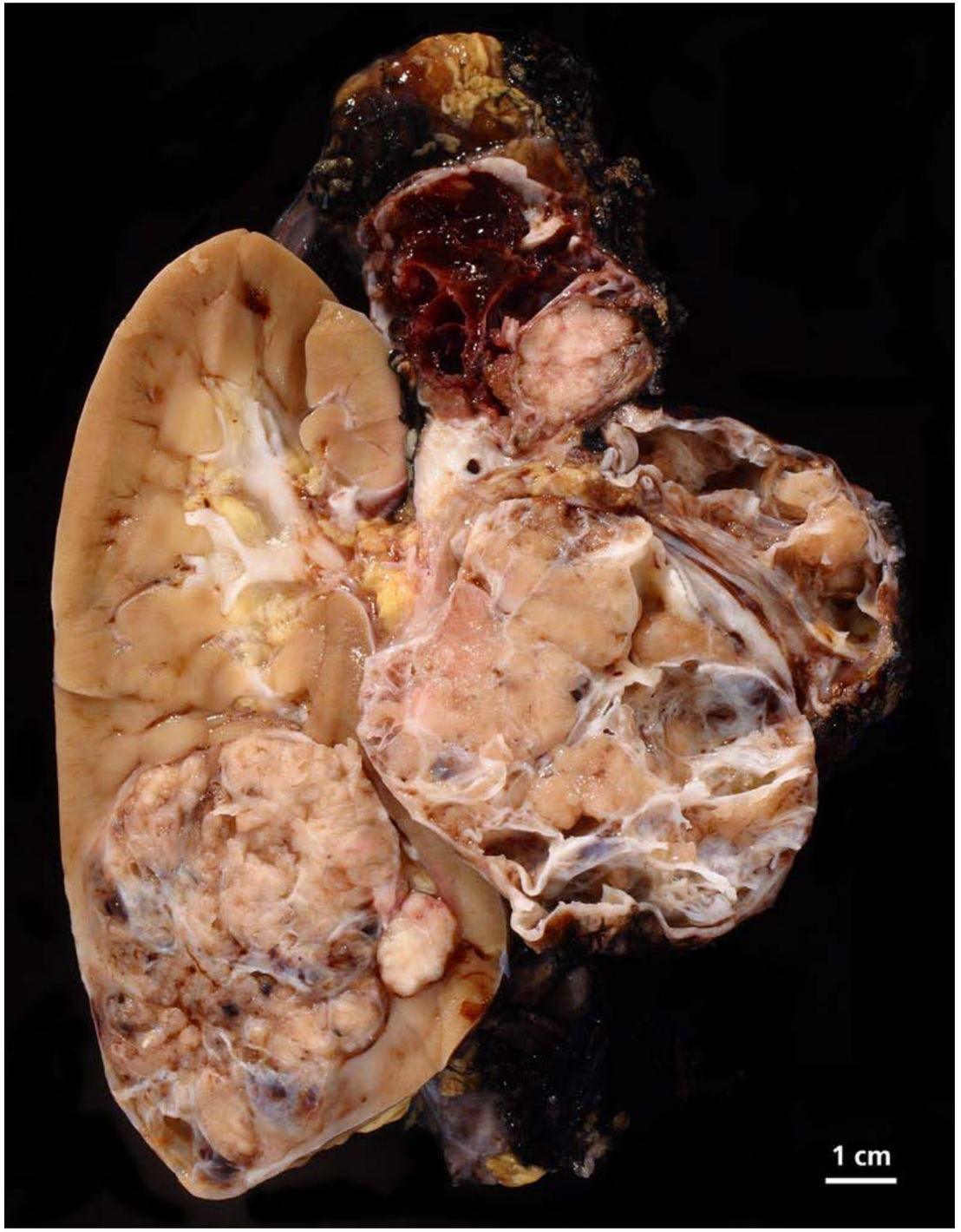
Hypodiploid number of chromosomes, but have not deleted the 3p chromosomal genetic locus.

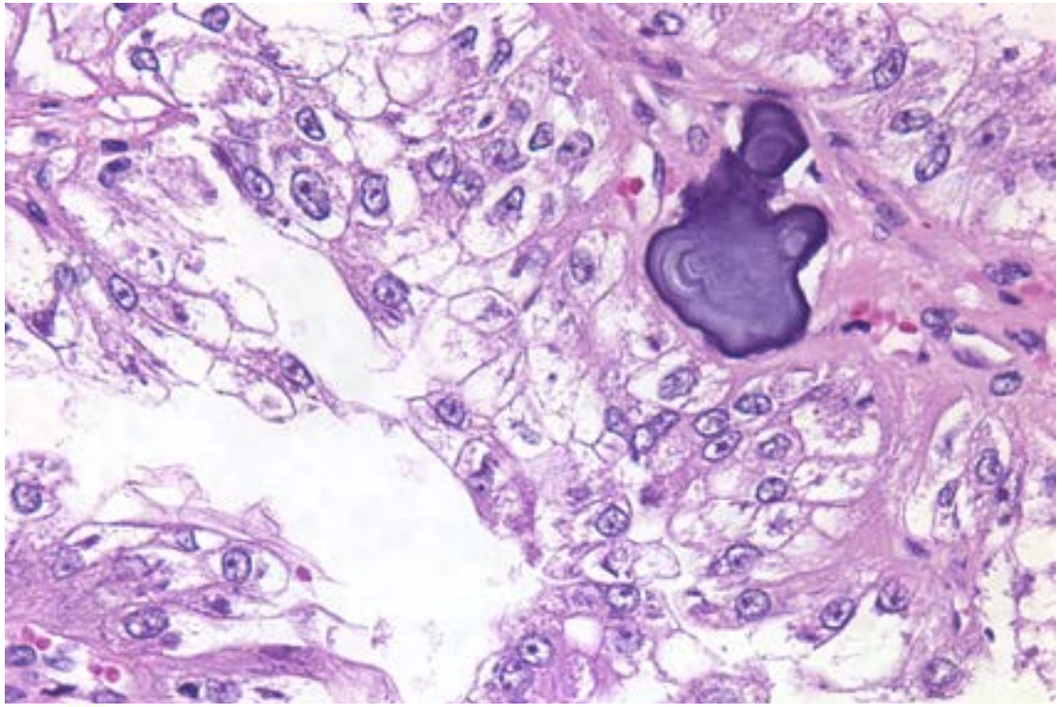
Comparative genomic hybridization found that 17 of 19 tumors exhibited a wide variety of abnormalities, including various combinations of the loss of chromosomes 1, 2, 6, 10, 13, 17, or 21.

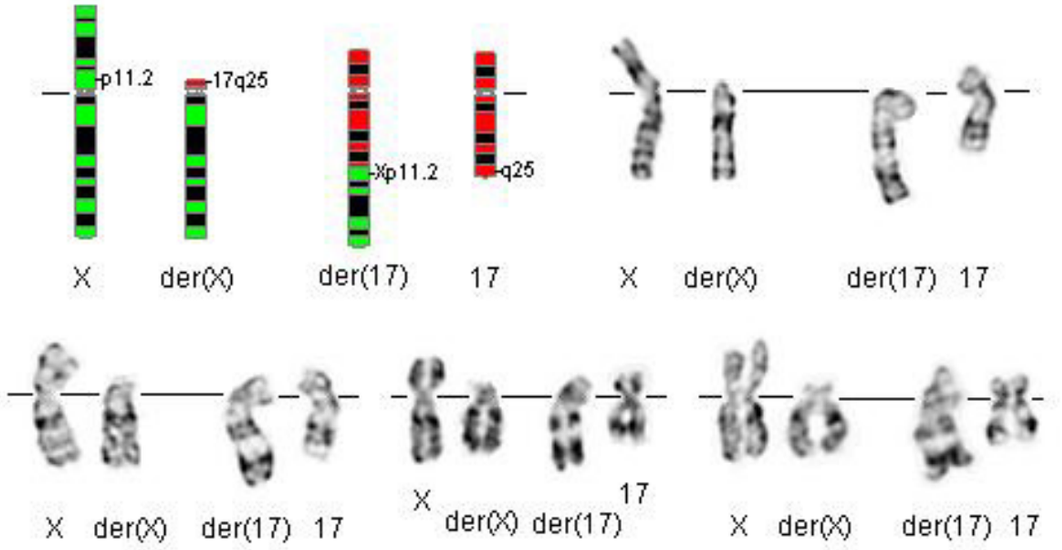
The **KIT** oncogene was found to be upregulated specifically on the cell membranes of chromophobe RCC.

Lower risk of disease progression and death compared with clear cell carcinomas, although this is likely due to the fact that patients present at a lower stage.

66 chromophobe RCCs were analyzed. Mitochondrial DNA and gene expression analysis suggested mitochondrial function as an important component of the disease biology. Genomic rearrangements showed recurrent structural breakpoints within the telomerase reverse transcriptase (TERT) promoter region, which correlates with highly elevated TERT expression.







Renal Cell Carcinoma Associated with Xp11.2 Translocation 46,X,t(X;17)(p11.2;q25)

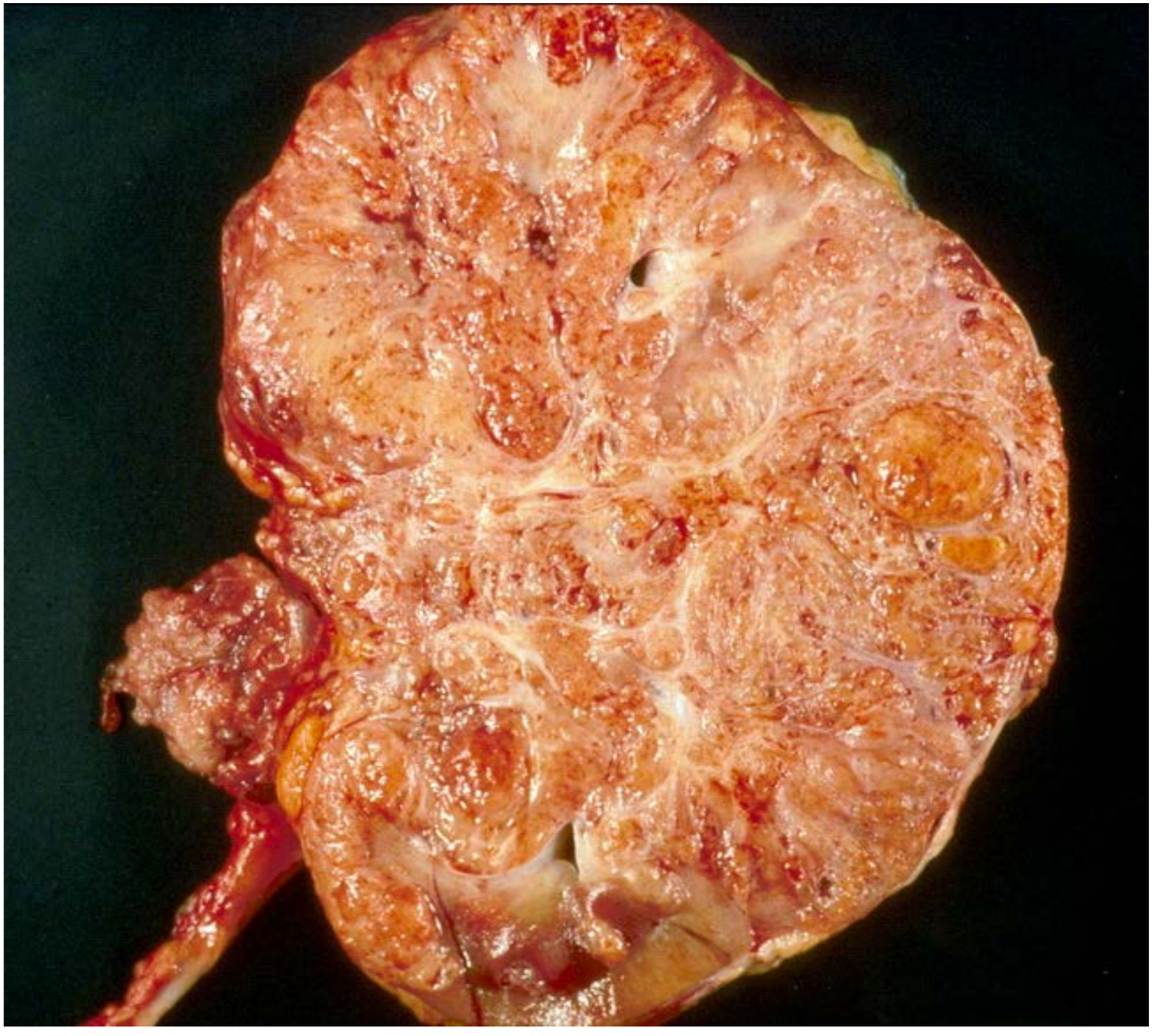
MiT family Translocation renal cell carcinomas:

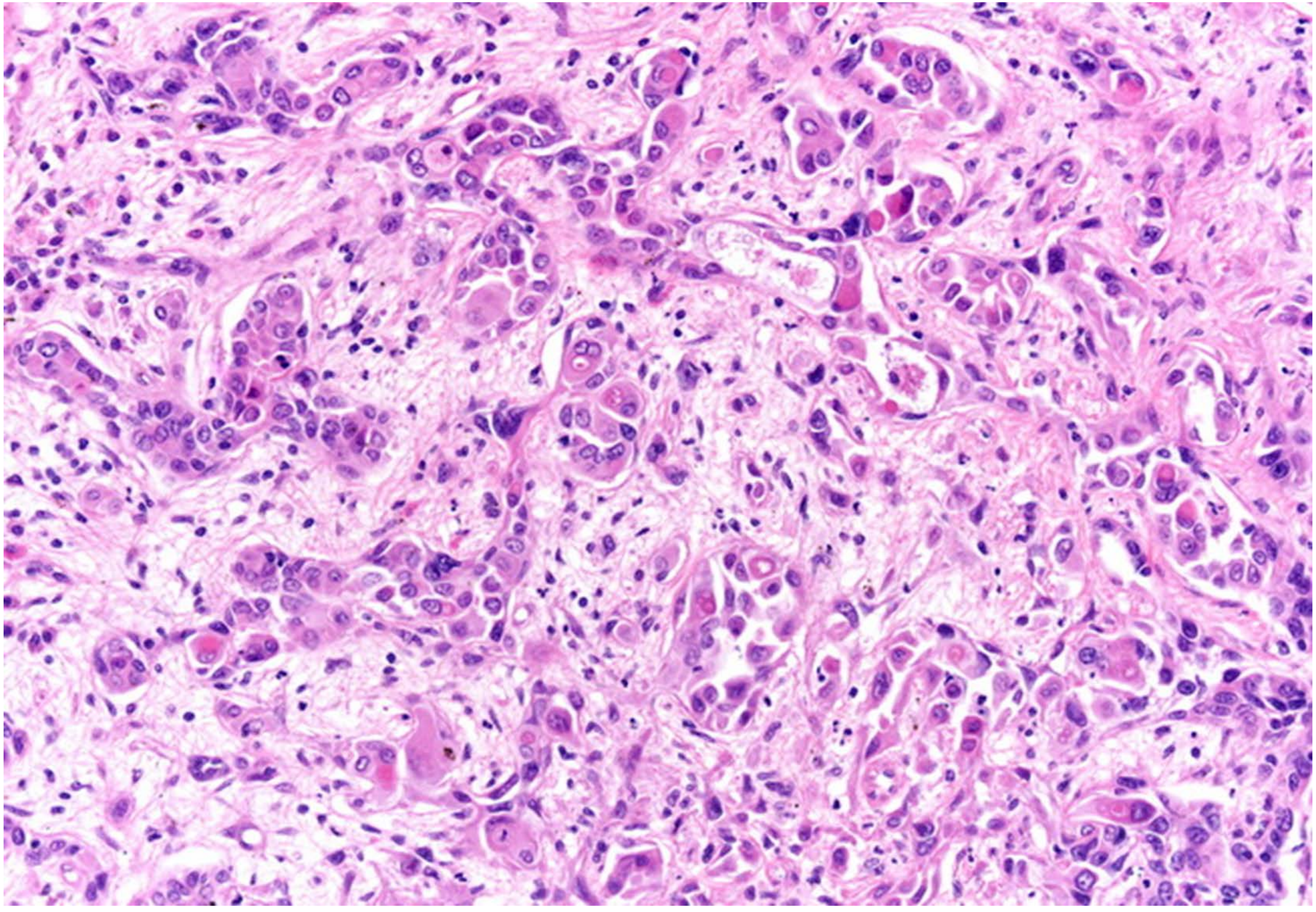
Fusion of the TFE3 gene to a number of other genes, including ASPL and PRCC on chromosome Xp11.2.

Occur in younger age compared with other RCCs. Median age of 24 years, more common in women than men (57:43).

Has been reported in children who have received antecedent chemotherapy for malignancies, autoimmune disorders, or bone marrow transplant conditioning.

Unique gene expression signature as compared with other RCC types, Activation of Microphthalmia-associated transcription factor (MITF)
Transforming growth factor β1
PI3K complex targets.





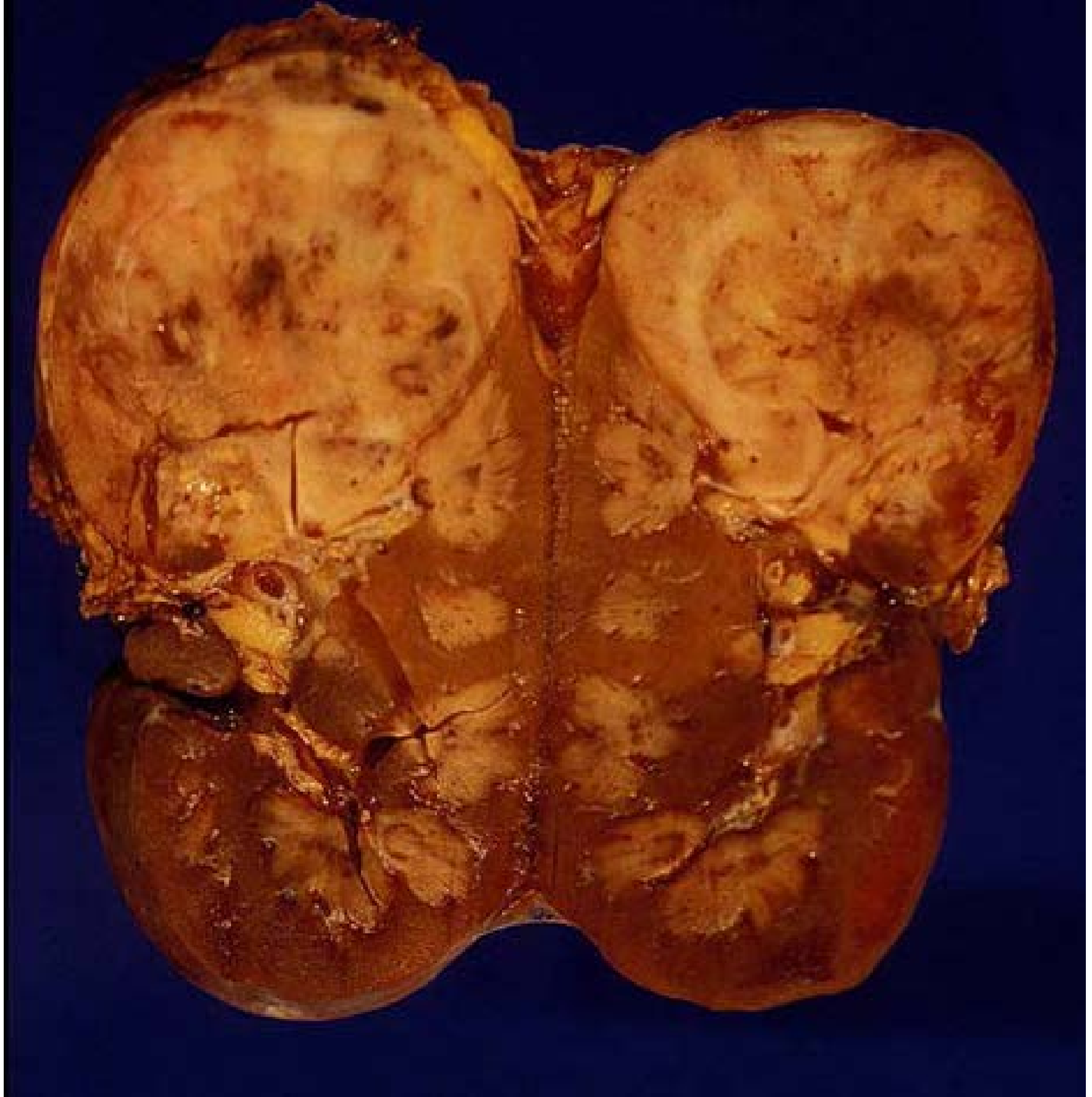
Collecting duct (Bellini's duct) Carcinoma:

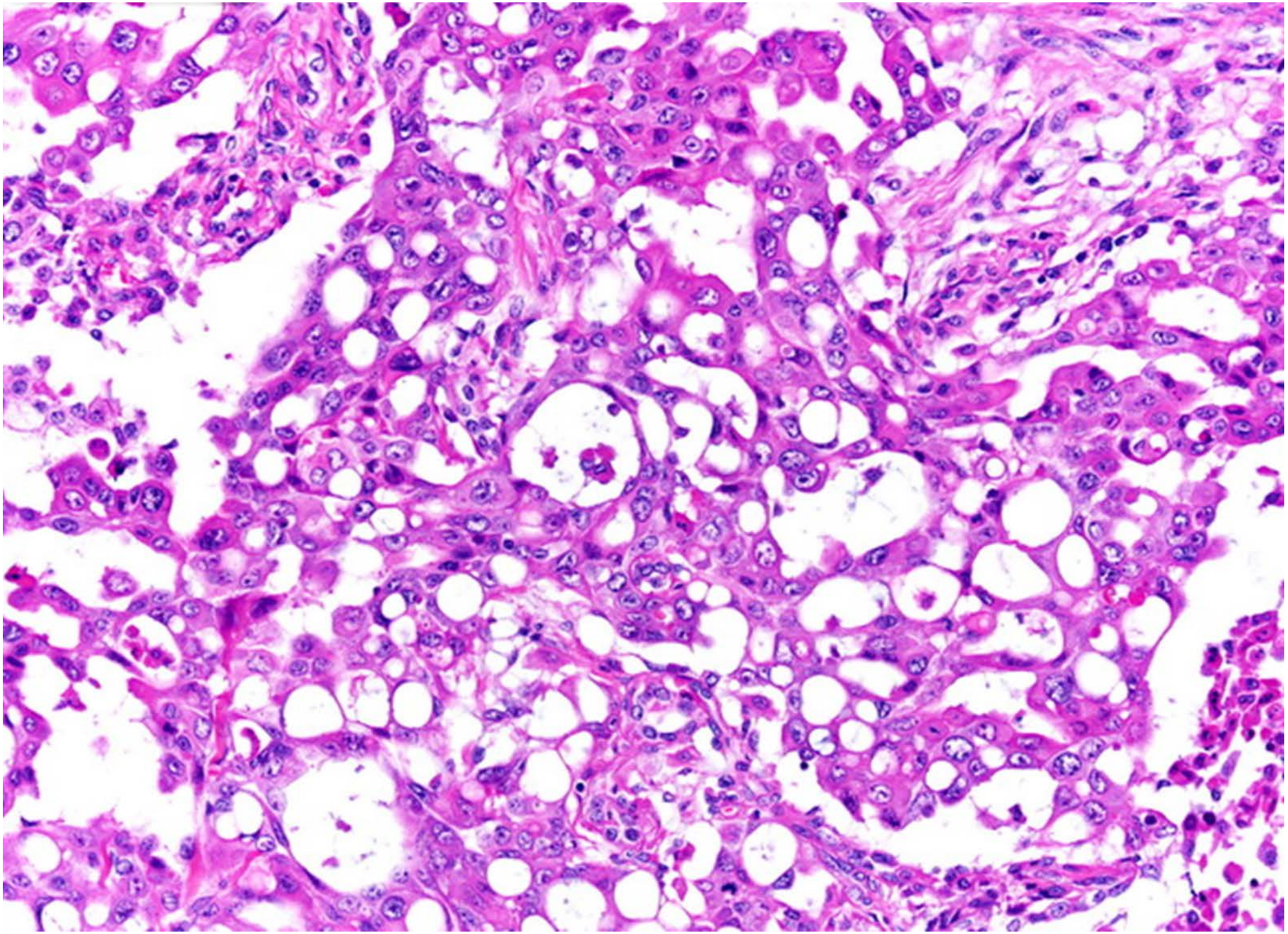
Rare (SEER 160 VS 33,000 ccRCC)
Tend to occur in younger patients and are frequently aggressive.
More frequent in black patients.
Commonly present with gross hematuria.
Presented with advanced (T3/T4) or metastatic disease.

Collecting duct tumors have not been associated with a consistent pattern of genetic abnormalities.

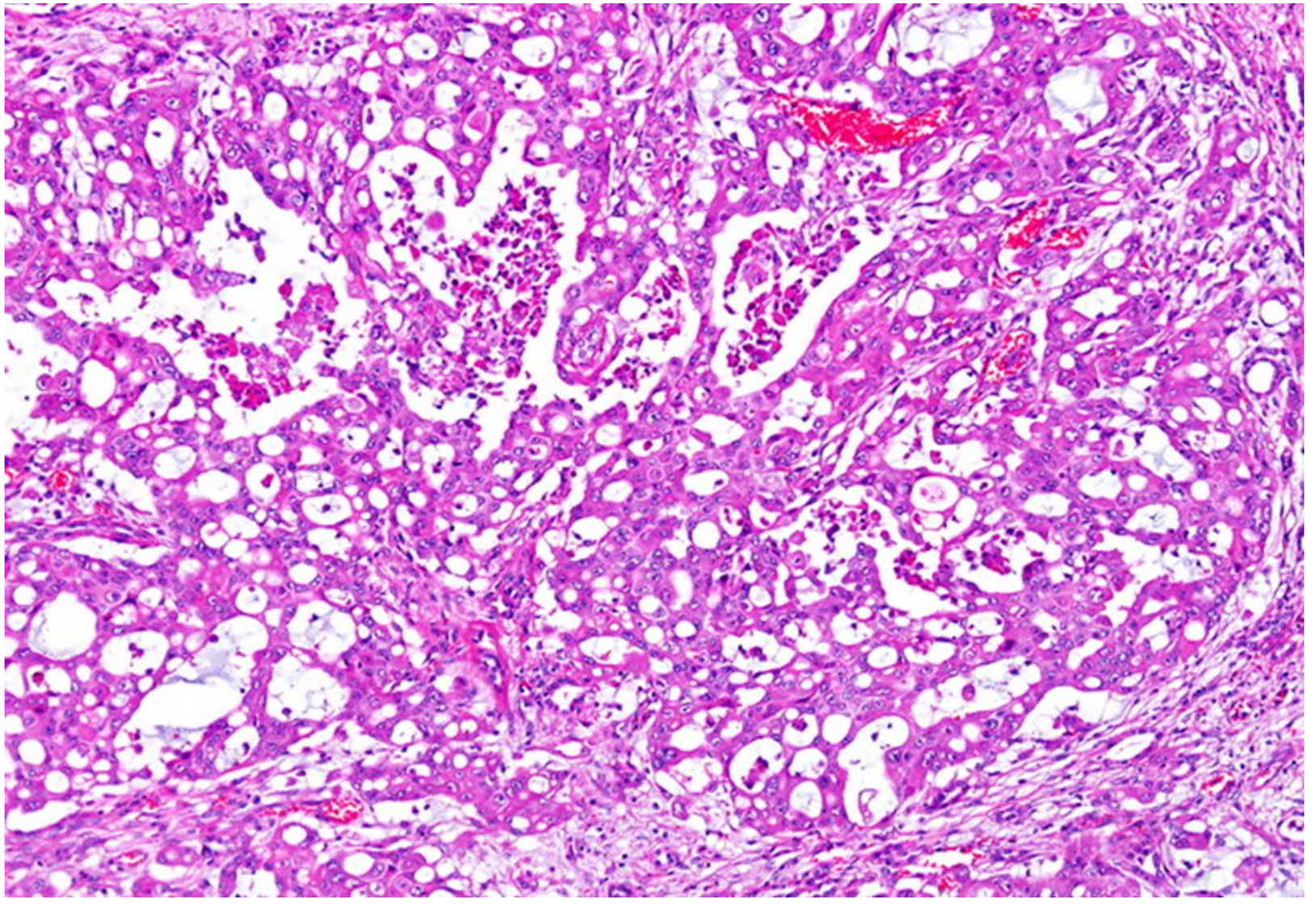
Biologically, these tumors more closely resemble transitional cell than RCCs.

One report of 17 cases assessed by comprehensive genomic profiling showed NF2 and CDKN2A alterations in 29 and 12 percent, respectively.

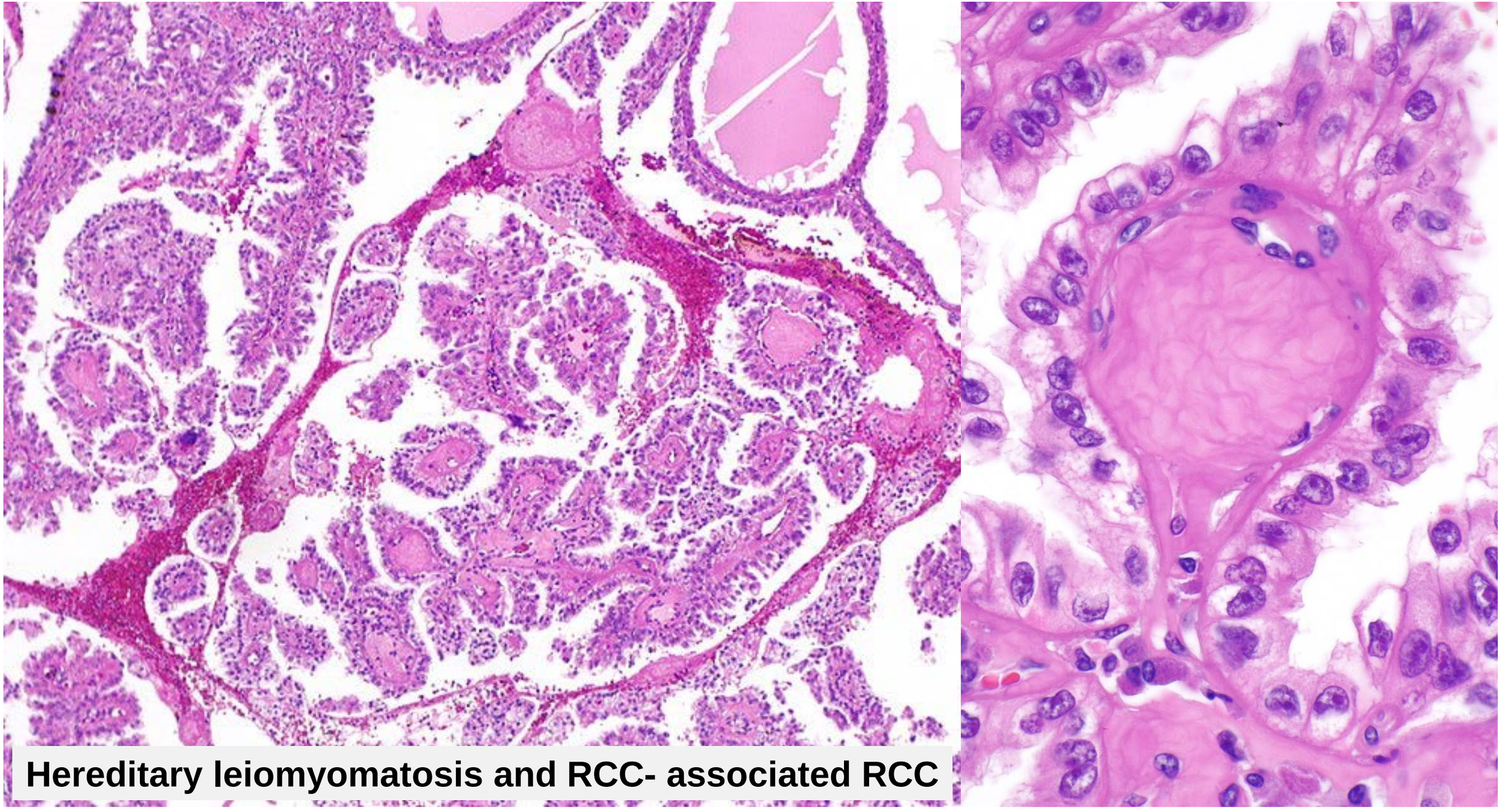




Renal Medullary CA



Medullary carcinoma, which is a highly aggressive variant of collecting duct carcinomas, is associated with the sickle cell trait and develops in young patients.



Hereditary leiomyomatosis and RCC- associated RCC

Hereditary leiomyomatosis and RCC- associated RCC

Clinical

Uncommon
Predominantly younger patients, mean 36 years
May present with multiple cutaneous and uterine leiomyomas (85%)
Cutaneous lesion most common on arms and thorax
Uterine leiomyomas have nuclear features similar to renal tumors
Caused by germline mutation in fumarate hydratase gene (recommend genetic counseling)
Unlike other hereditary tumors, these may be unilateral and single
Poor prognosis
Early widespread dissemination common
Often at least pT3
Often lymph node metastases
Metastases reported even with small tumors

Hereditary leiomyomatosis and RCC- associated RCC

Diagnostic Criteria

Large nuclei with prominent, eosinophilic, inclusion-like nucleoli with perinucleolar clearing

May only be present focally

Papillary architecture most common

Foamy histiocytes uncommon

May show tubular, tubulopapillary tubulocystic, solid, and mixed architecture

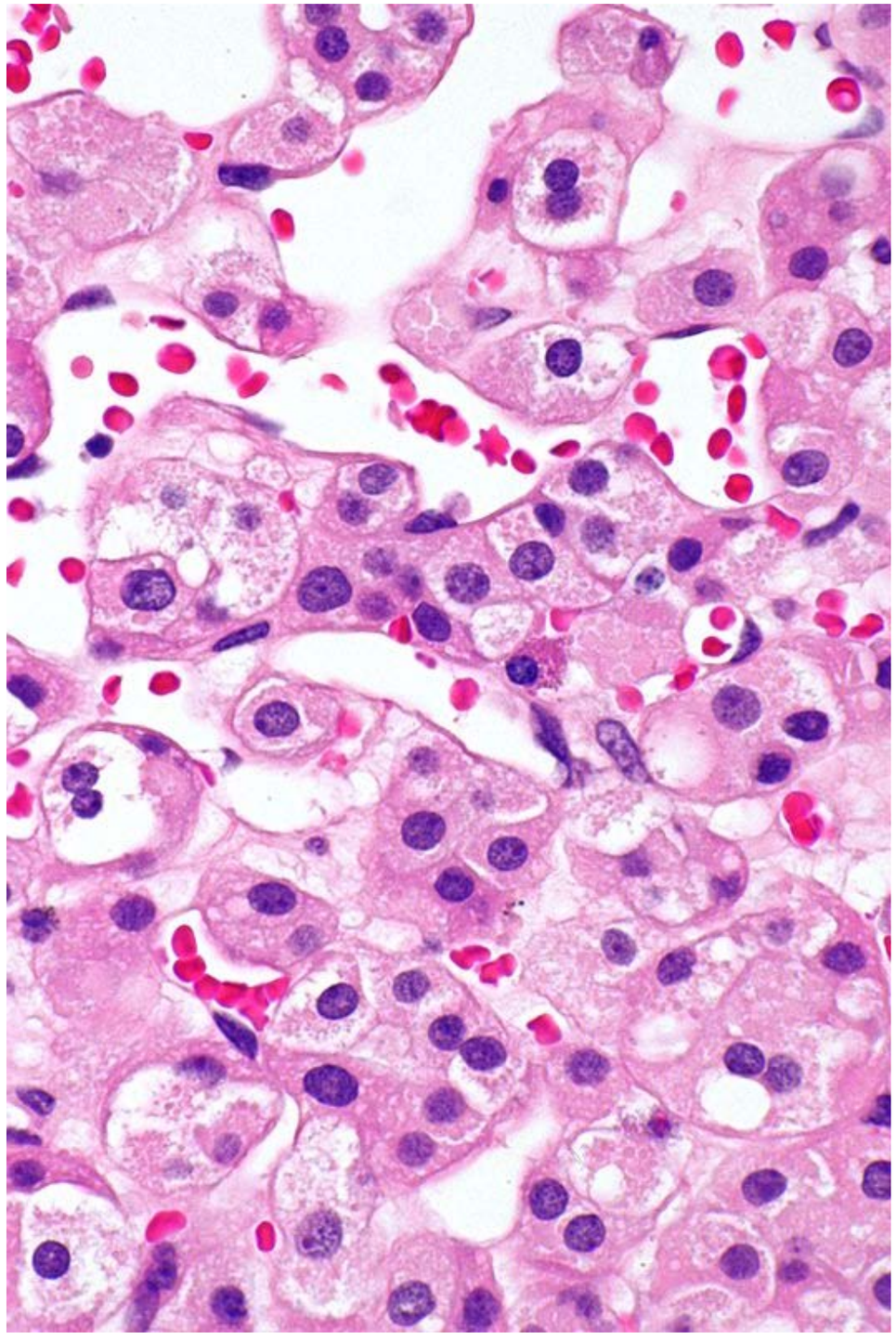
May show collecting duct-like morphology with tubules, solid nests or individual cells infiltrating through desmoplastic stroma

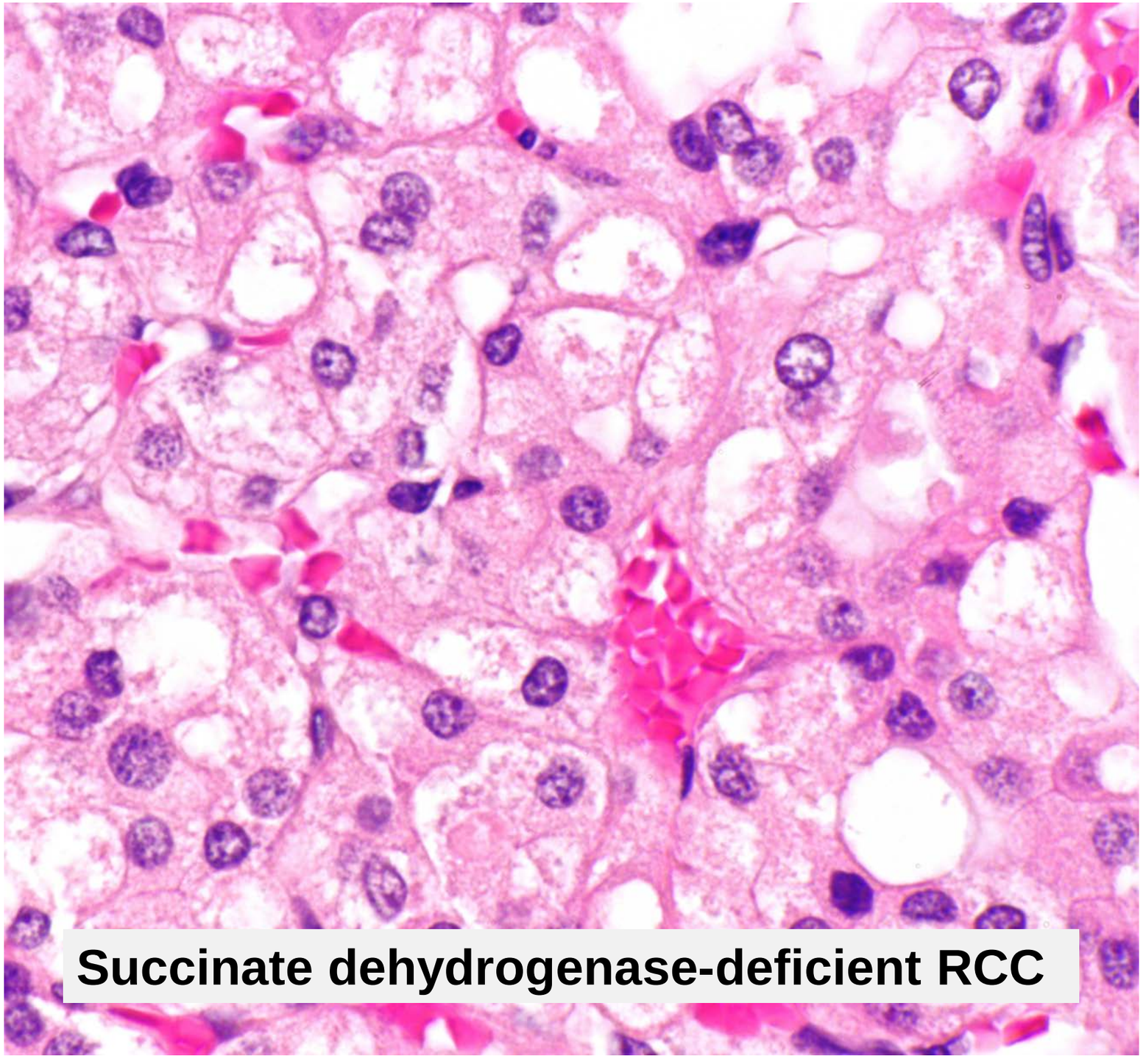
May show sarcomatoid growth

Large cells with abundant eosinophilic cytoplasm

Focal areas may have amphophilic or clear cytoplasm

Loss of fumarate hydratase (FH) expression





Succinate dehydrogenase-deficient RCC

Succinate dehydrogenase–deficient RCC

Clinical

Very rare (0.05 to 0.2% of all renal carcinomas)
Classically presents in young adults (mean age 38)
Slight male predominance
Strong hereditary link
Great majority of patients have germline mutations in SDHB, SDHC, SDHA, or SDHD associated with an autosomal dominant tumor syndrome characterized by SDH-deficient renal cell carcinoma, paraganglioma/pheochromocytoma, or gastrointestinal stromal tumors
All patients with SDH-deficient tumors should be offered genetic testing
Patients need long-term surveillance for other SDH-deficient neoplasms
May be multifocal/bilateral
Relatively good prognosis (metastatic rate of ~10%)
Outcome less favorable with dedifferentiation and necrosis

Succinate dehydrogenase–deficient RCC

Diagnostic Criteria

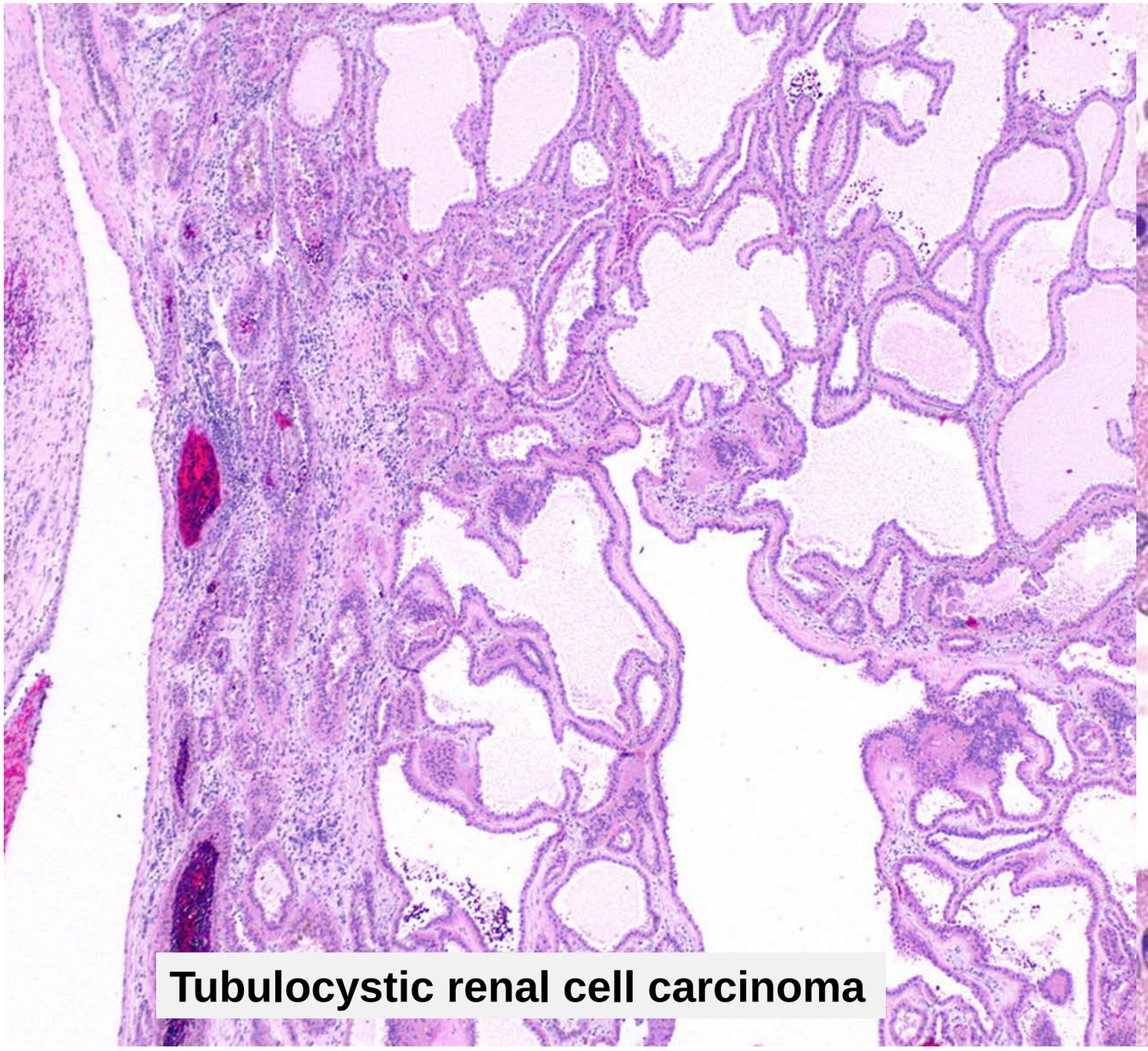
Requirement: Loss of immunohistochemical staining for SDHB

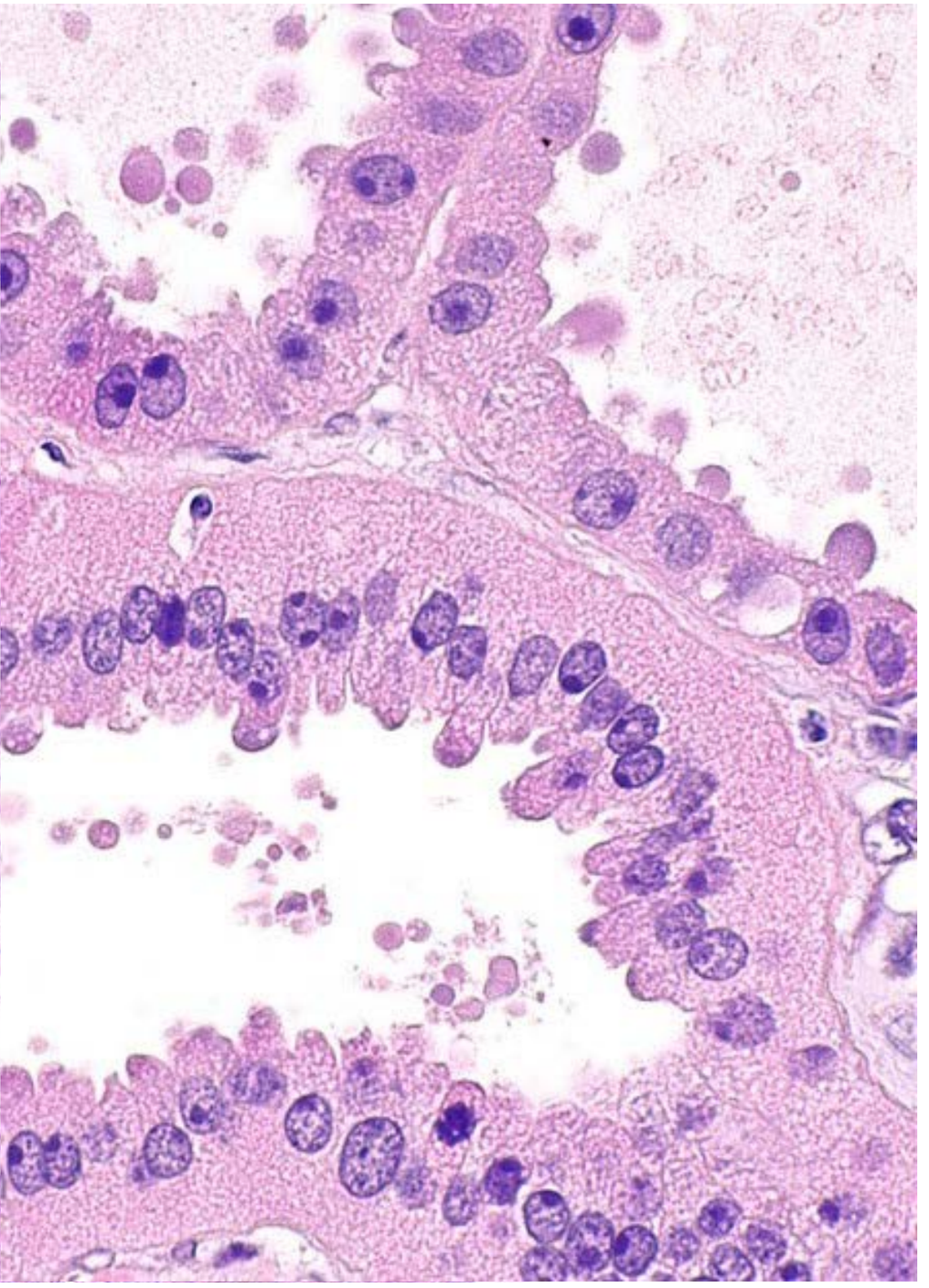
Loss of staining with SDHB signifies a mutation in either SDHA, SDHB, SDHC, or SDHD

Eosinophilic cells with flocculent cytoplasm

Cytoplasmic vacuoles or flocculent inclusions

Neuroendocrine-like nuclei





Tubulocystic renal cell carcinoma

Tubulocystic renal cell carcinoma

Clinical

Mean age about 60 (30-94)
M:F = 7:1
Behavior uncertain
2 of 31 cases reported with metastases

Tubulocystic renal cell carcinoma

Diagnostic criteria

Mixture of closely packed tubules and micro/macro cysts of variable sizes with low grade nuclear features

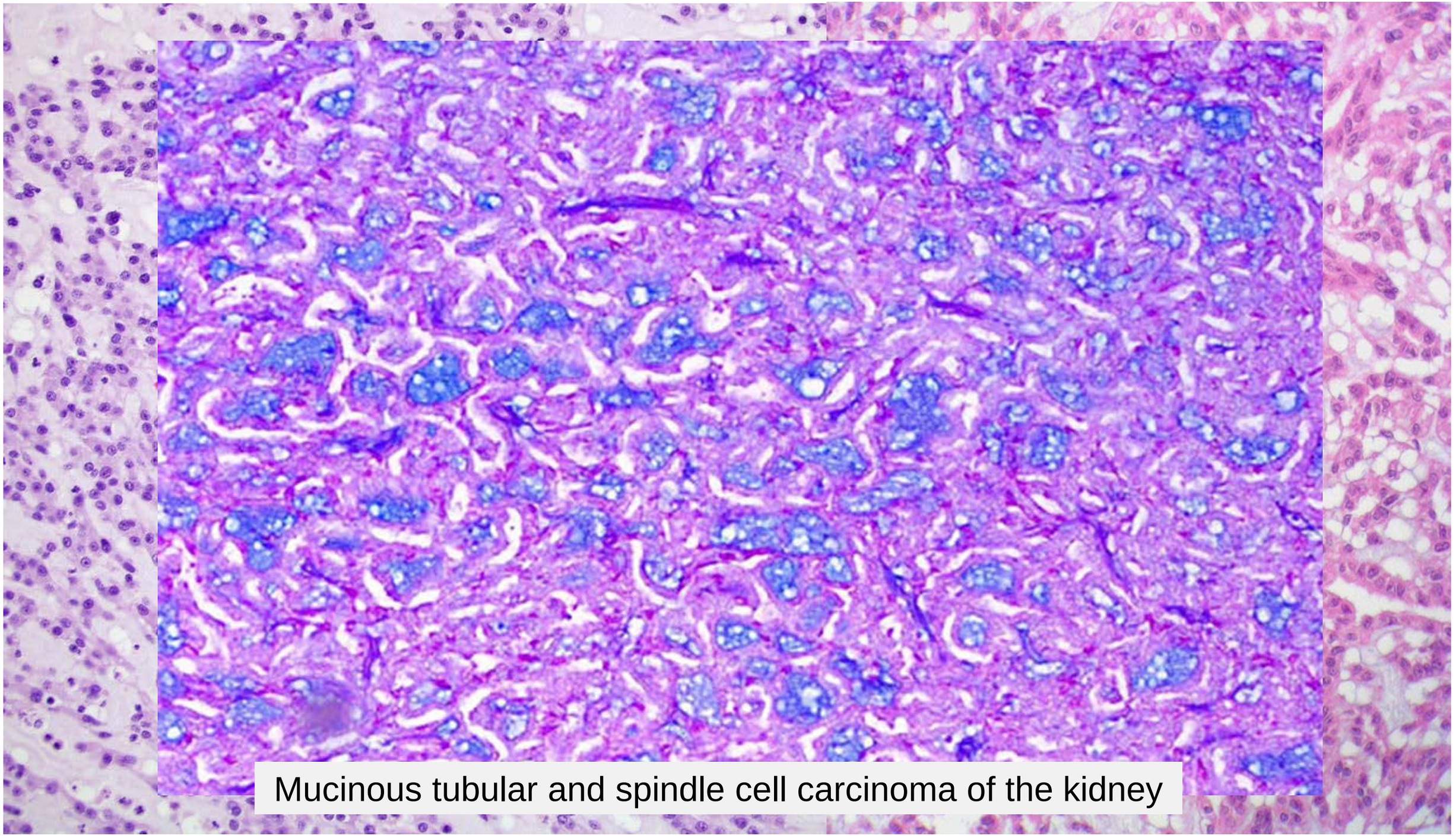
Tubules and cysts are lined by single layer of cuboidal or columnar cells with abundant eosinophilic cytoplasm, uniform nuclei with distinct nucleoli; often have hobnail appearance

Overall low grade nuclear features

Cysts are closely spaced with variable intervening fibrotic stroma

40% coexist with papillary renal cell carcinoma

Minimal mitotic activity, no atypia, no desmoplasia



Mucinous tubular and spindle cell carcinoma of the kidney

Mucinous Tubular and Spindle Cell Carcinoma of the Kidney

Diagnostic Criteria

Composed of elongate tubules, variably packed
Spindle cell population merges with and may represent densely packed collapsed tubules
Mucinous stroma separates the tubules
Epithelial and spindle cells are cytologically bland
Occasional findings
    Collections of foamy macrophages
    Lymphocytic infiltrate
    Psammoma bodies
    Solid foci without detectable stroma
    Clear cell foci
Sarcomatoid change may be seen in rare cases
MTSCC may show morphologic and immunophenotypic overlap with papillary renal cell carcinoma

Mucinous Tubular and Spindle Cell Carcinoma of the Kidney

Clinical

< 1% of all renal neoplasms

Median age 58 years (range 13 - 81)

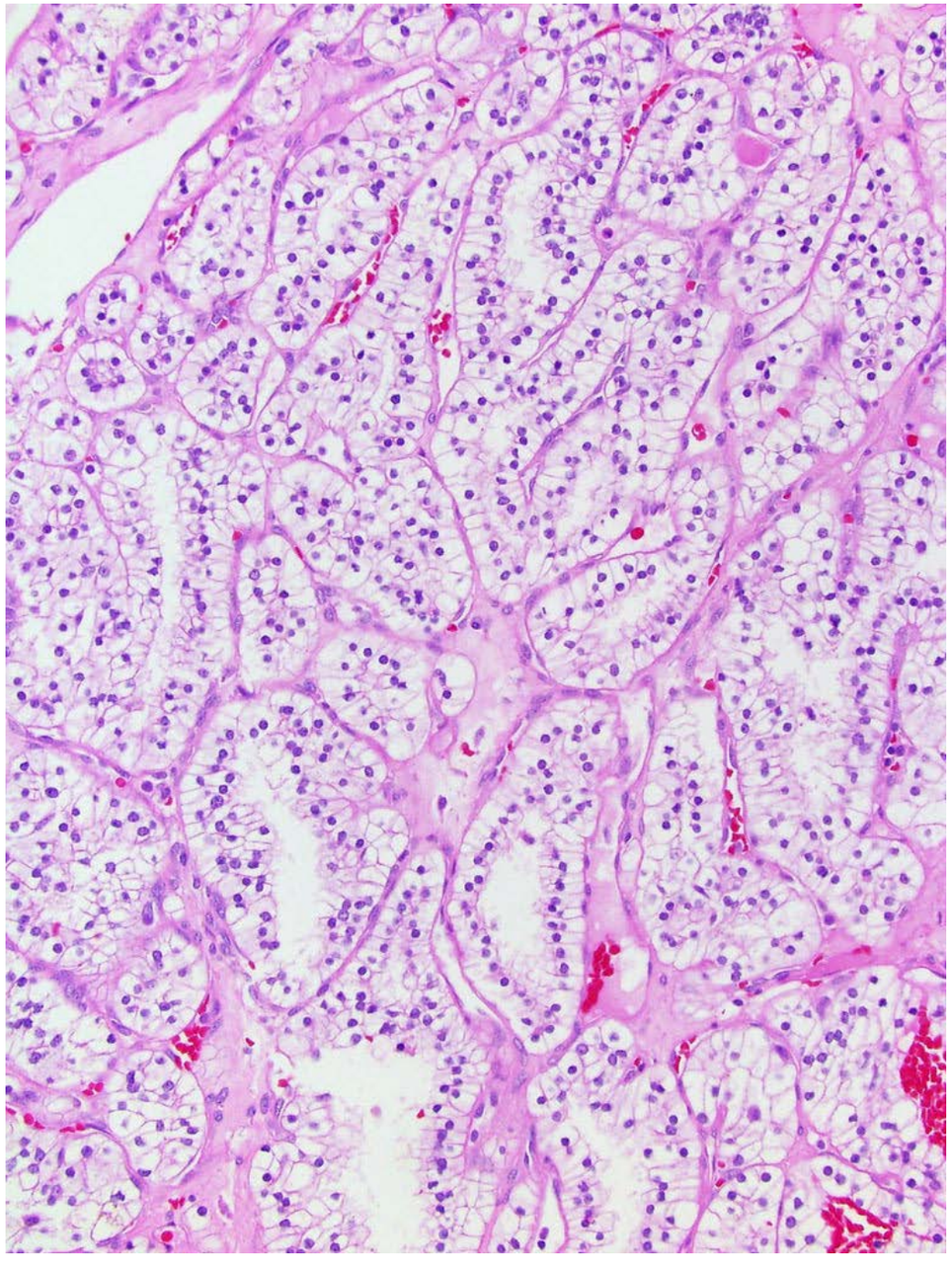
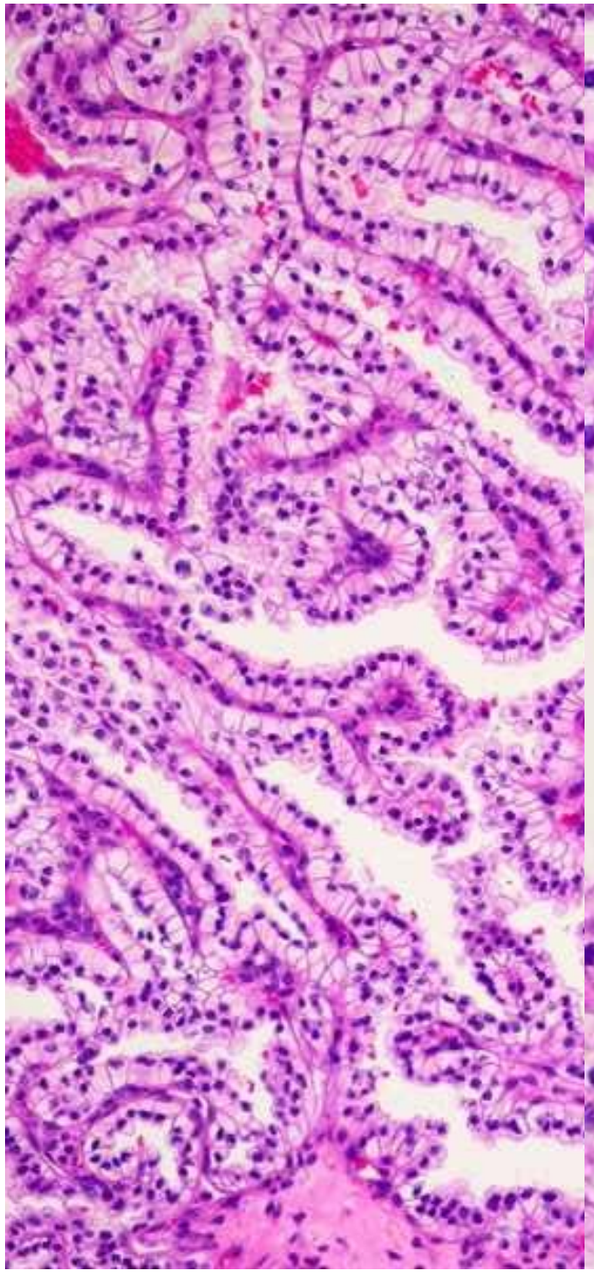
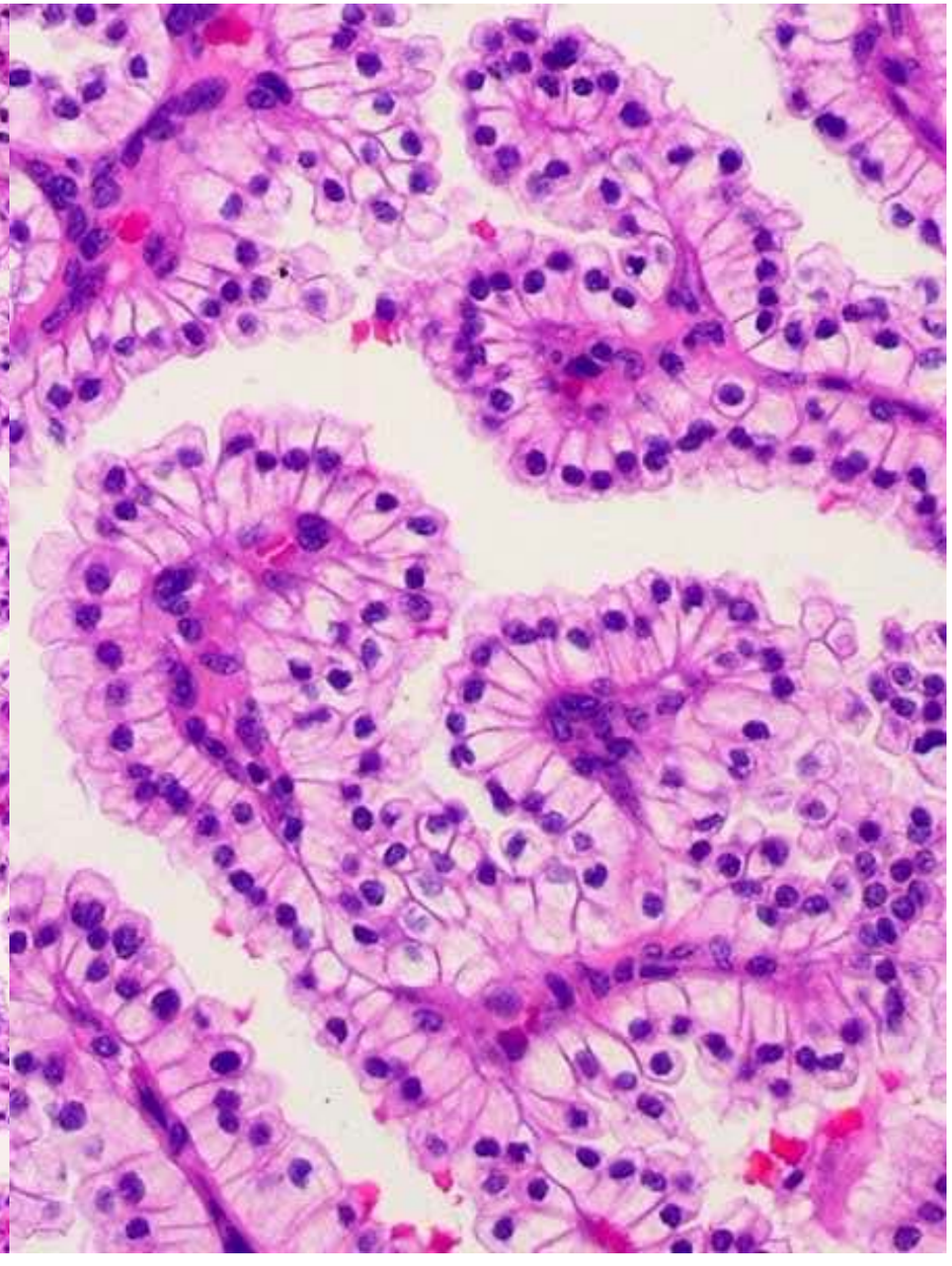
Female:male ratio: 4:1

Usually indolent behavior

Recurrences are uncommon

Metastases are rare, but have been reported with both low grade histology and high grade transformation

Some occur in association with nephrolithiasis

Clear Cell Papillary Renal Cell Carcinoma

Clinical features

Low stage, indolent behavior, no metastases reported

1% - 3% of all renal cell neoplasms, no sex predilection, mean 60 years (18 – 88)

Initially reported in patients with end stage renal disease, but most cases reported subsequently are sporadic, in normal kidneys

Clear Cell Papillary Renal Cell Carcinoma

Diagnostic Criteria

Most tumors exhibit mixtures of tubular, cystic, acinar and papillary patterns

All patterns lined by a single layer of cuboidal to low columnar cells

Nuclei typically uniformly separated from base of cell by clear cytoplasm (pseudoendometrial)

Low grade and stage, WHO/ISUP grade 1 or 2, 95% pT1a, No vascular or renal sinus invasion

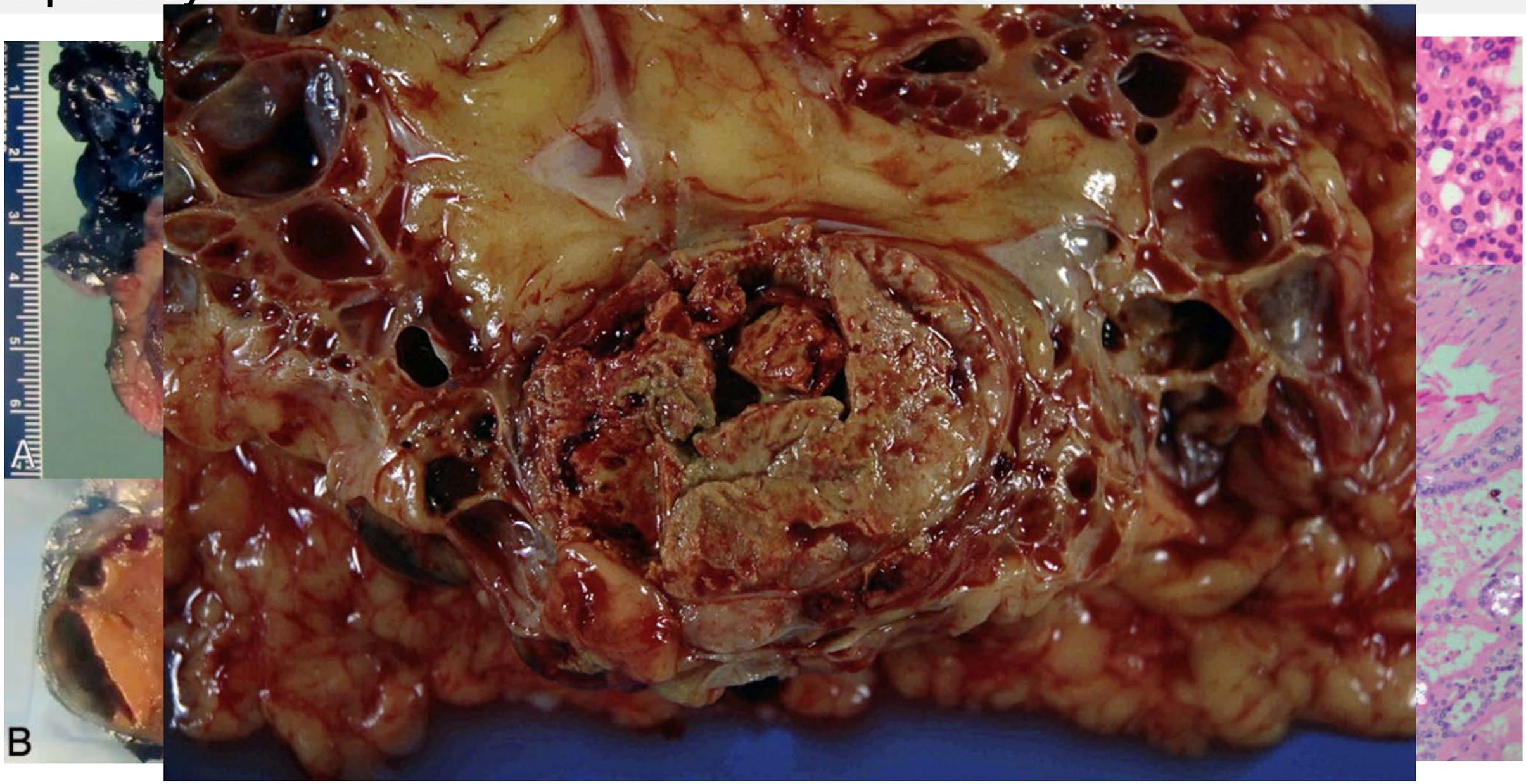
Frequent prominent partial to complete capsule

Immunophenotype CK7 strong +ve, CA9 basal or cup-like, CD10 –ve to focal, Racemase -ve

Small solid foci of clear cells reminiscent of conventional ccRCC may be seen

May be seen in sporadic patients and in those with end stage renal disease

Acquired Cystic Disease–Associated Renal Cell Carcinoma



Arch Pathol Lab Med-Vol 141, April 2017

Acquired Cystic Disease–Associated Renal Cell Carcinoma

Arises in individuals with acquired cystic kidney disease (ACKD) in the setting of ESRD.

Predominantly male sex.

Occur 10 to 20 years after dialysis.

Occurs in 35% of long term dialysis patients; of these, 6% develop RCC

Risk of developing RCC in ACKD is increased by more than 100X (Adv Anat Pathol. 2003;10(3):135-59)

Histopathology

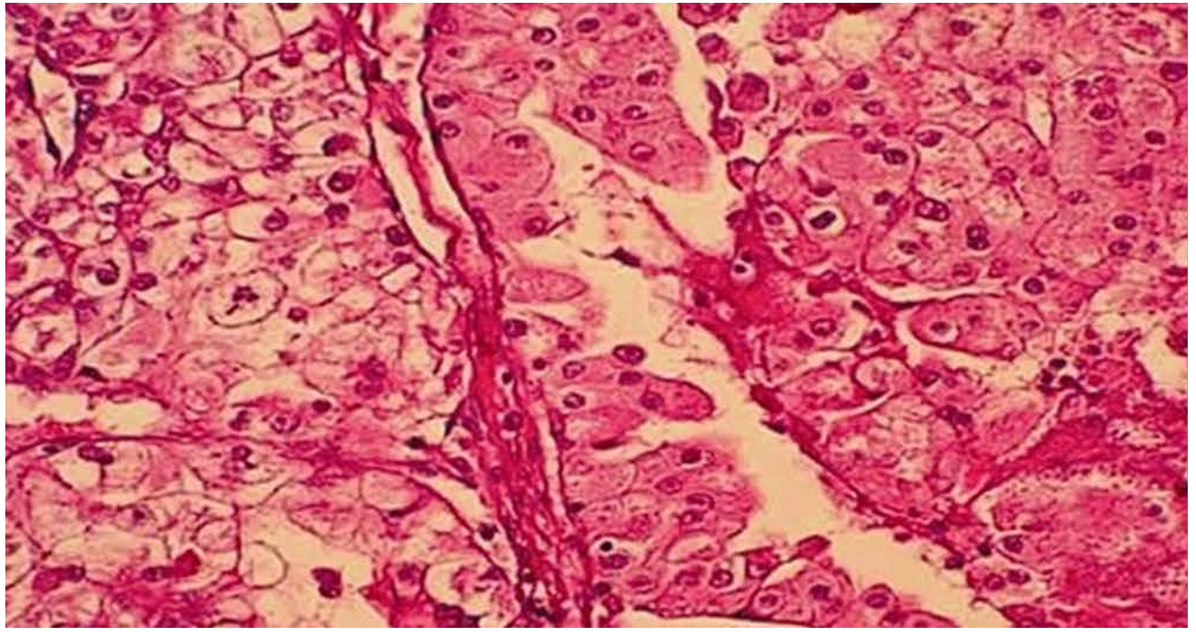
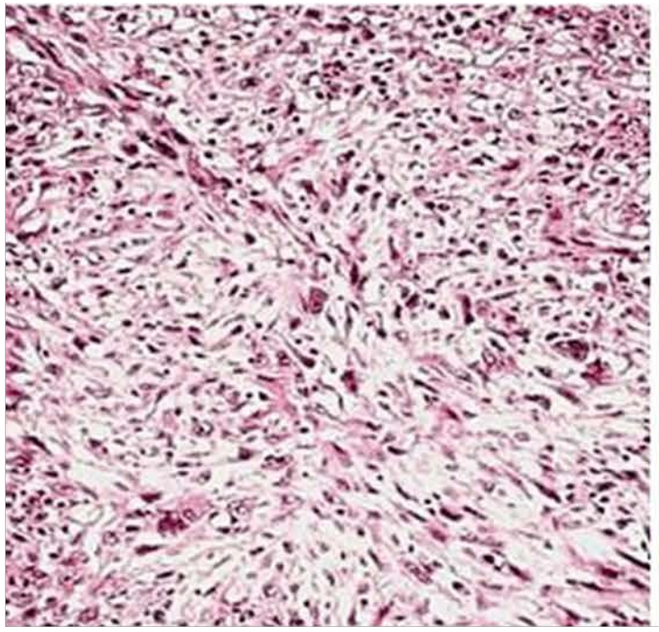
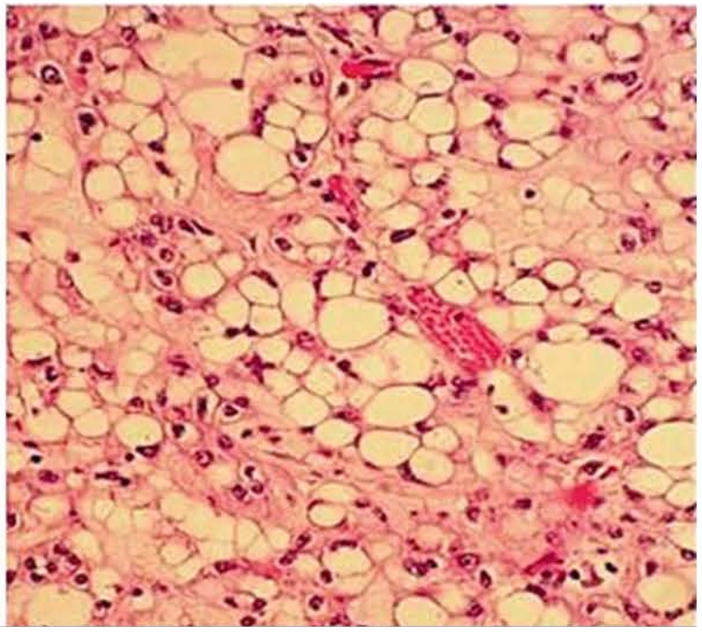
Cribriform / microcystic / sieve-like architecture

Abundant granular eosinophilic cytoplasm with prominent nucleoli

Intratumoral calcium oxalate crystals are very common but not necessary for diagnosis

May be nodules arising from cyst walls or masses separated from cysts

Sometimes prominent clear cell cytology

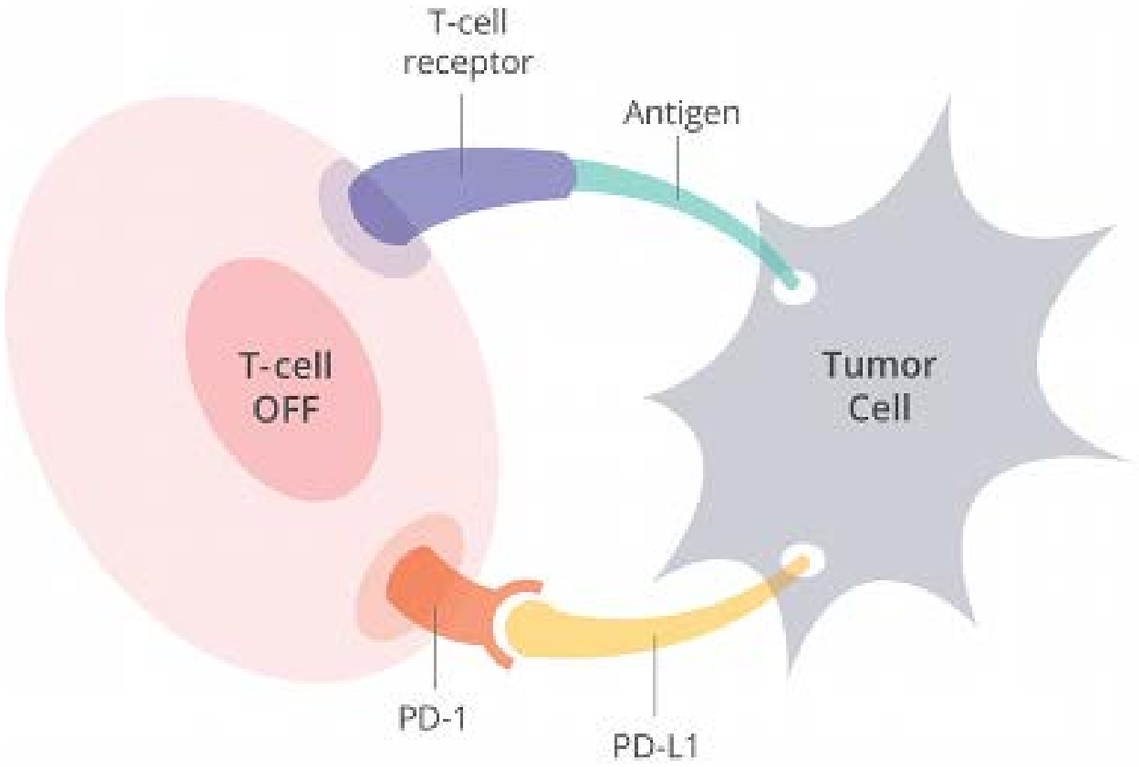
<5% of RCCs are considered unclassified.

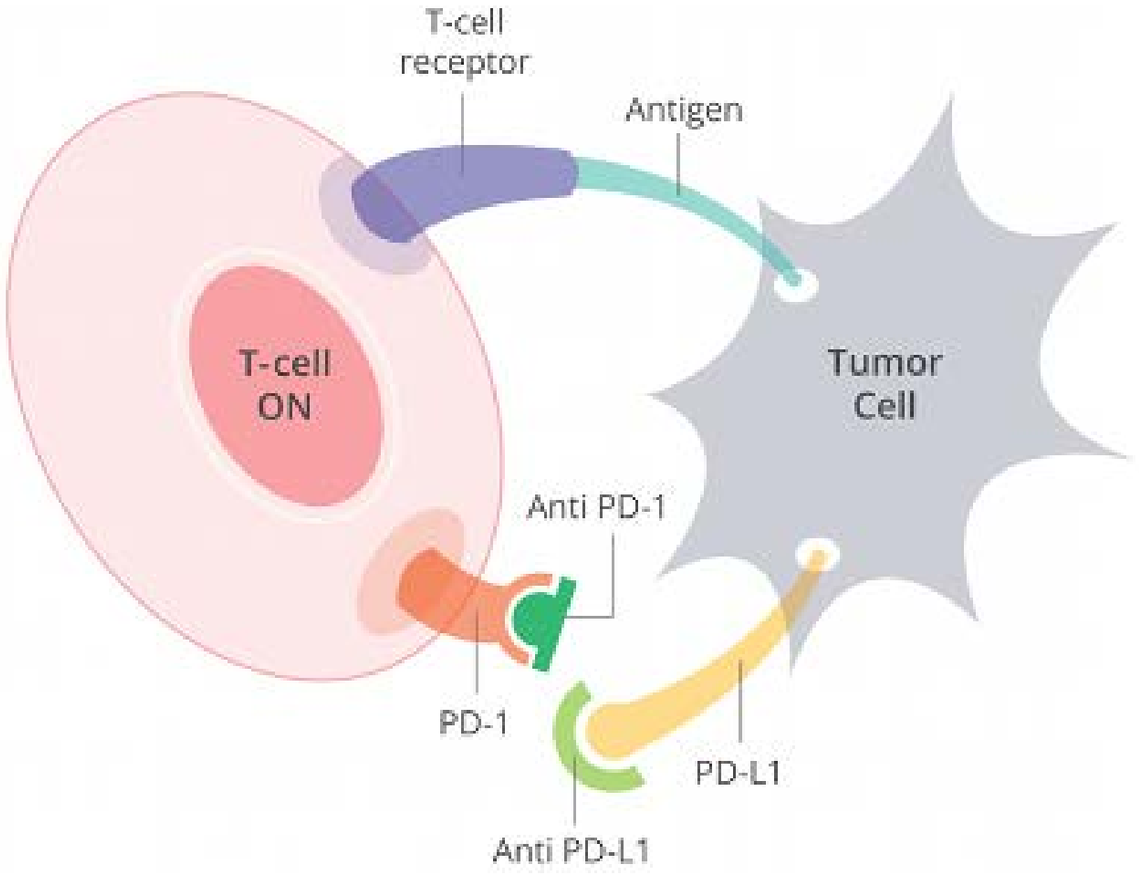
Worse prognosis compared with clear cell cancers.

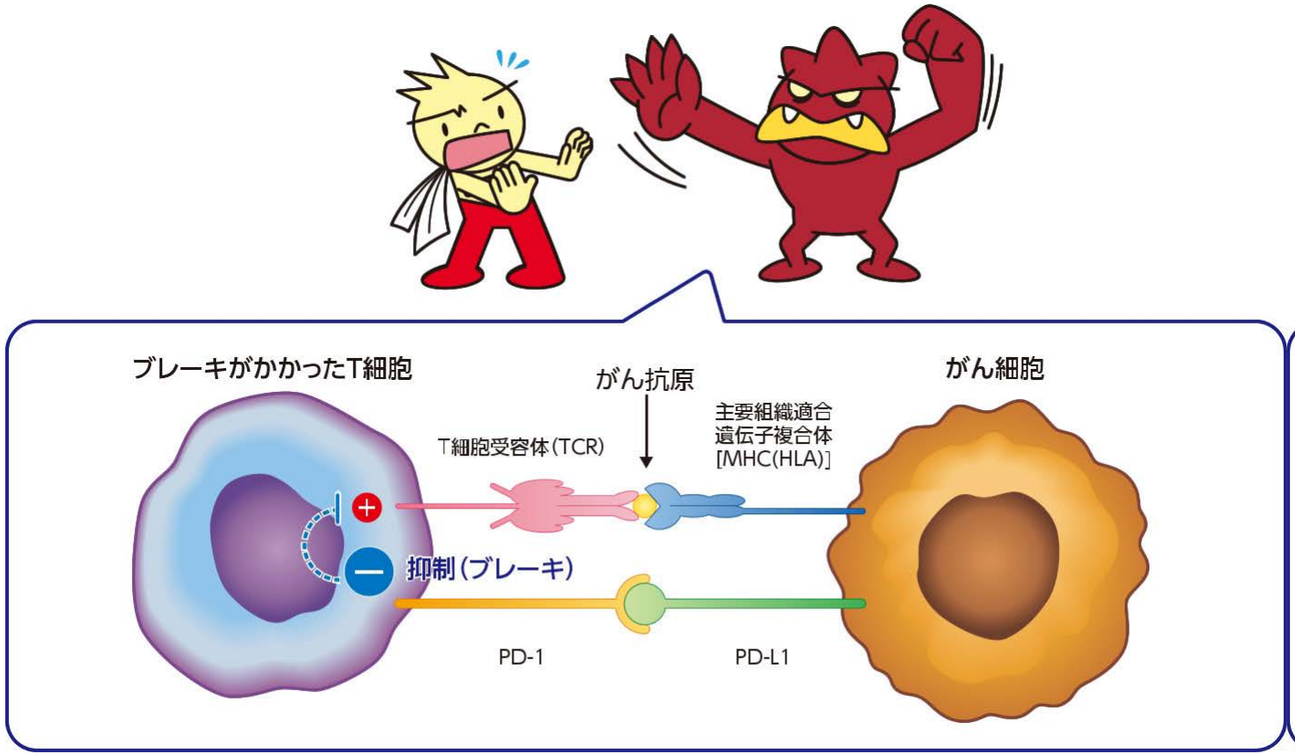
PD-1 is a 288-amino acid cell-surface protein.

PD-1 binds two ligands, PD-L1 and PD-L2, which negatively regulate the immune response.

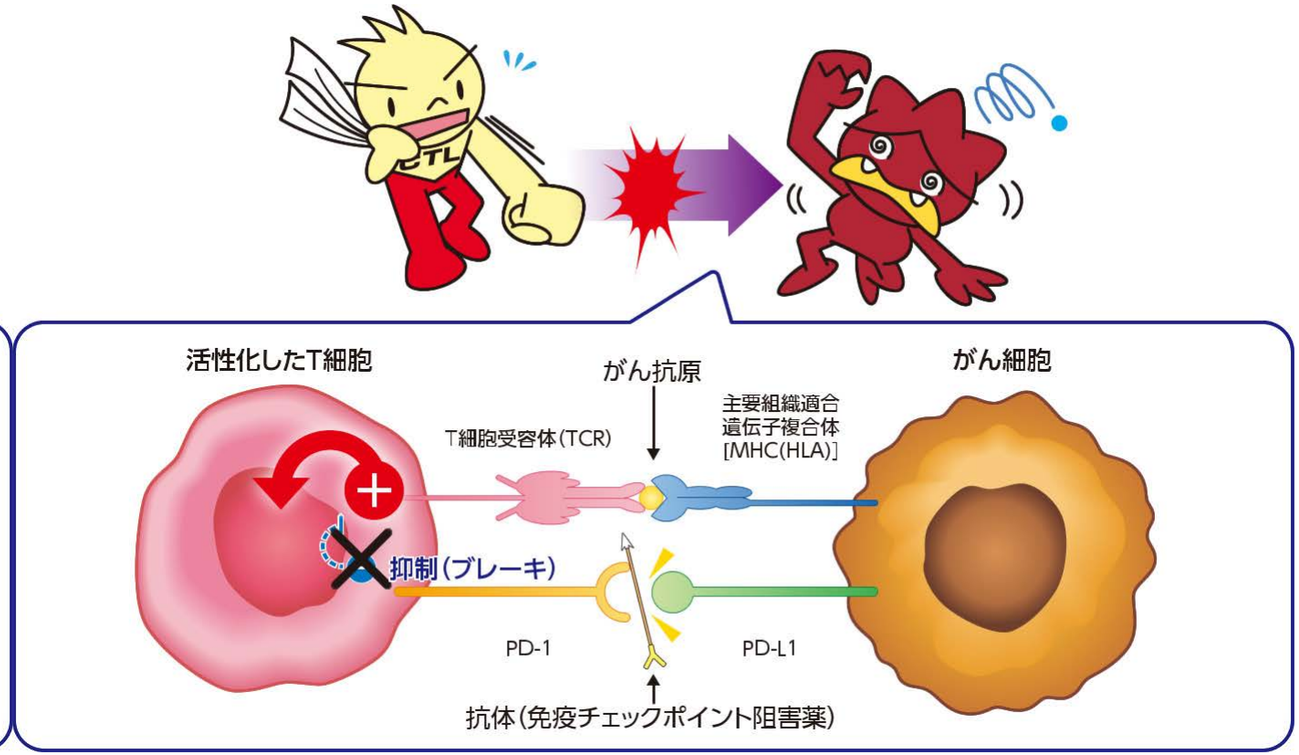
Expression of PD-L1 (B7-H1) on tumor cells leads to the inhibition of the T cell-mediated immune response against cancer, thereby enabling tumor progression and metastasis


T-cell
receptor
Antigen
T-cell
OFF
Tumor
Cell
PD-1
PD-L1


T-cell
receptor
Antigen
T-cell
ON
Tumor
Cell
Anti PD-1
PD-1
PD-L1
Anti PD-L1



Binding of PD-L1 and PD-1 prevents cancer from attacking immune cells by braking against immune cells.



Using an antibody (such as an immunity checkpoint inhibitor: an antibody that inhibits the binding of PD-L1 and PD-1, etc.), the cancer releasing the brake applied to the immune cells, and the T cell whose function is weakened It reactivates again and attacks cancer cells.

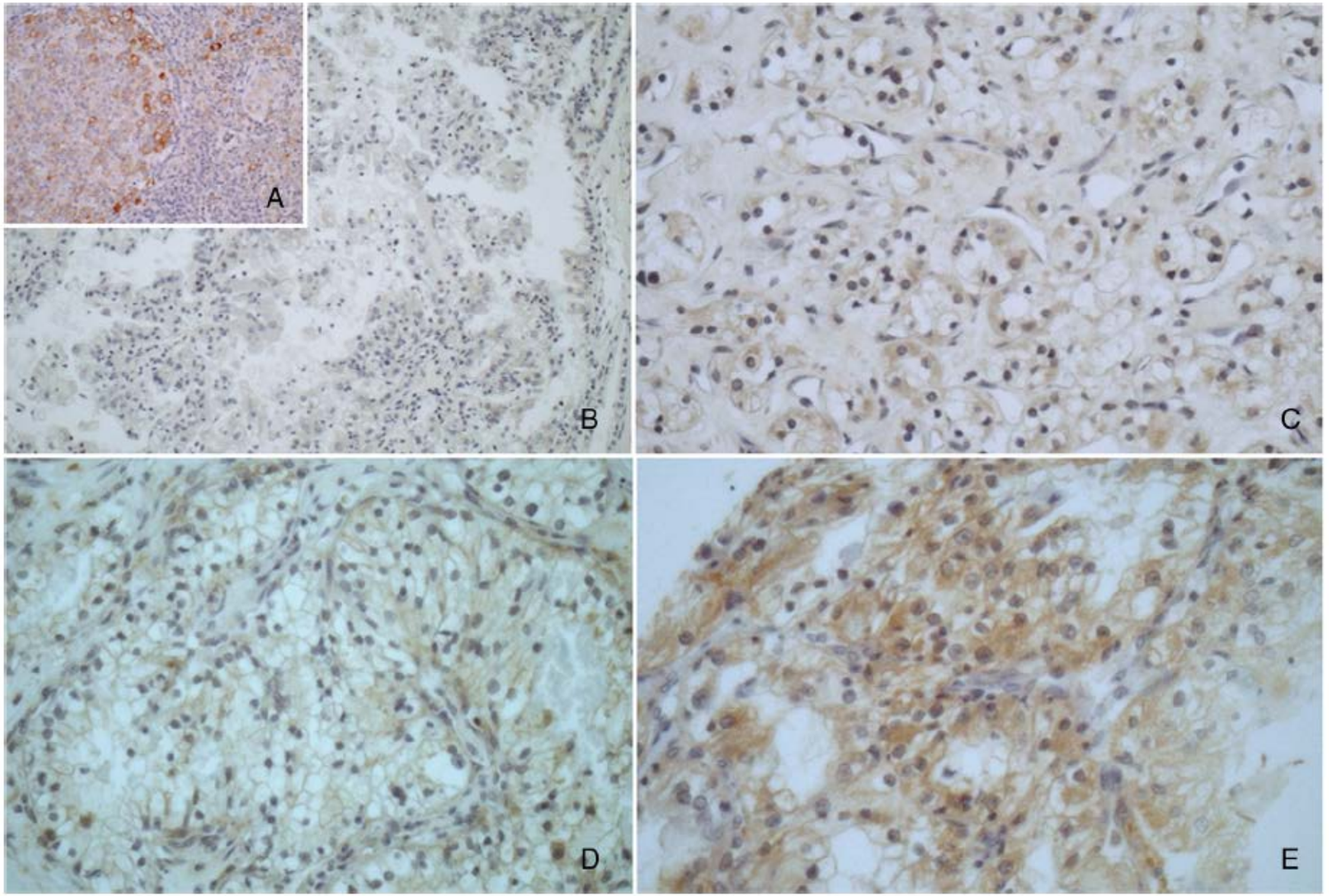
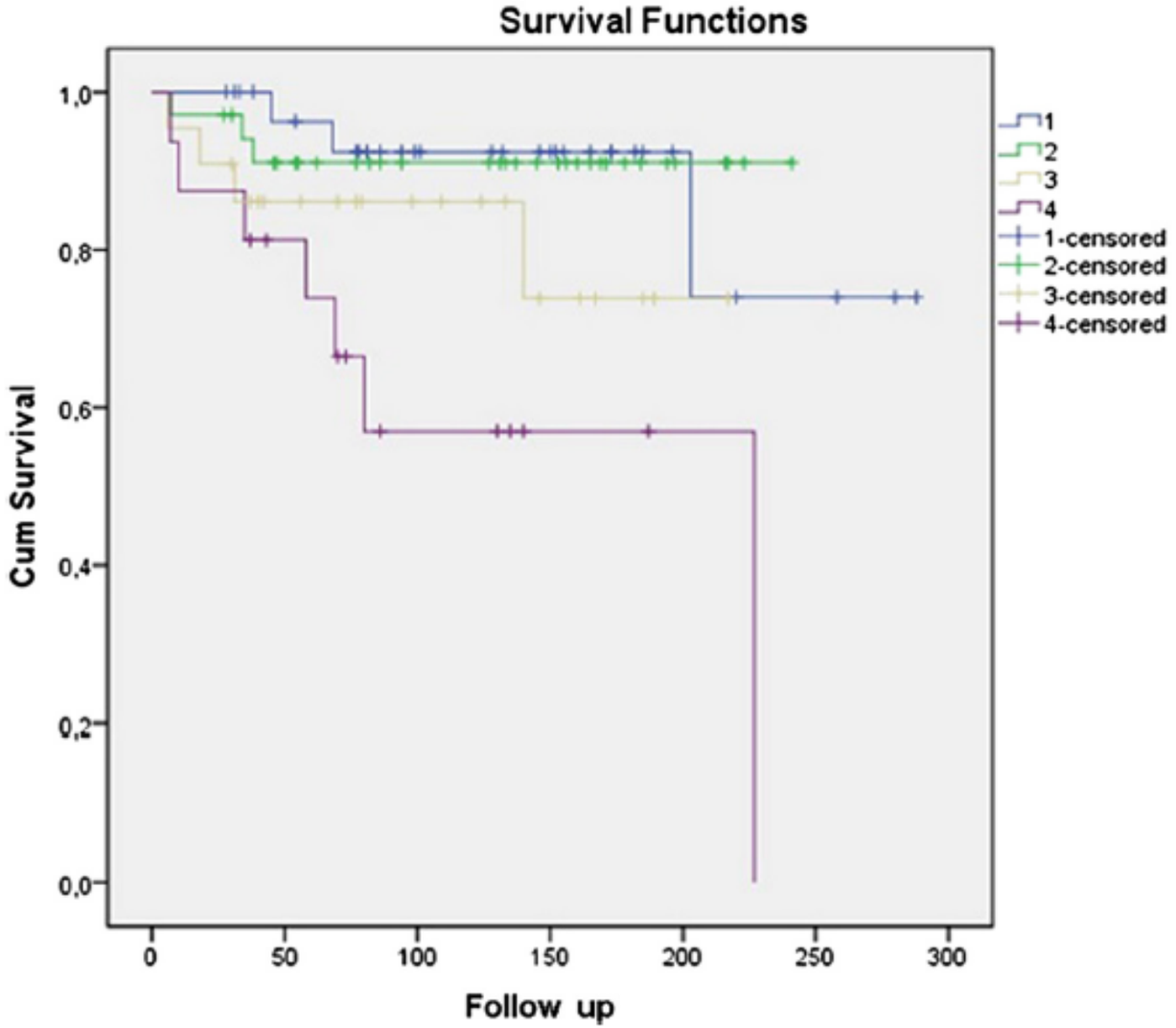


Fig. 1 Photomicrography showing PD-L1 immune-expression in RCC-CC. **a** Positive control, **b** negative control, **c** Positive - score 1, **d** Positive – score 2, **e** Positive – score 3

Leite et al. Diagnostic Pathology (2015) 10:189

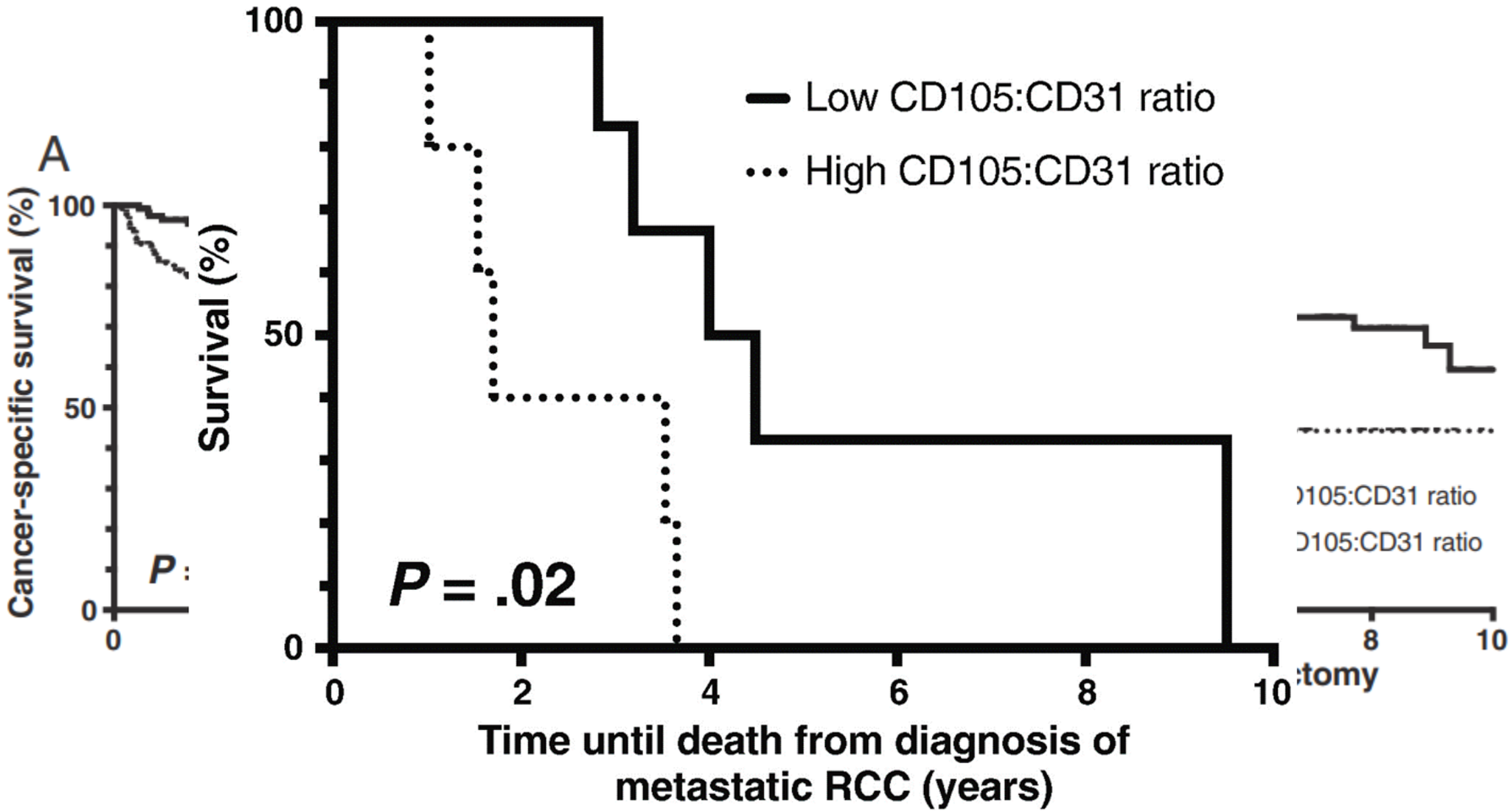


Microvascular invasion
High nuclear grade
PD-L1 +ve

Fig. 2 Kaplan-Meier curve of tumor recurrence. The blue line represents tumors negative for PD-L1 with no microvascular tumor invasion and low nuclear grade. The green line represents tumors with one of the following: PD-L1 expression, microvascular tumor invasion, or high nuclear grade. The yellow line represents tumors with two of these variables, and the purple line represents tumors with all three unfavorable prognostic factors ($p = 0.007$)

Leite et al. Diagnostic Pathology (2015) 10:189

Neovascularity as a prognostic marker in renal cell carcinoma.



TM Bauman, et al. Human Pathol; 57; 98-105;2016.

Prognostic factors:

TMN
Nucl
Histo
Sarc
Tum

Table 2 – Univariate analysis showing mortality in absolute values and percentages according to the pathological variables analyzed

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
	Lower	Upper	Lower	Upper	Lower	Upper	Lower	Upper
pT1,2/pT3,4	1.837	0.432	18.077	1	0	6.277	2.691	14.638
Fuhrman 1,2/3,4	2.03	0.622	10.661	1	0.001	7.616	7.616	25.761
Diameter size <7/≥7	1.832	0.52	38.231	1	0	6.248	2.257	17.296
Necrosis	1.753	0.482	13.224	1	0	5.77	2.243	14.84
Microvascular invasion	1.278	0.445	8.26	1	0.004	3.591	1.502	8.588
Sinus invasion	2.285	0.47	23.606	1	0	9.83	3.91	24.716

	Mortality from renal carcinoma	
	%	p
Stage pT3,4	12/30(40%)	p= 0.000
Fuhrman 3,4	19/69(28%)	p= 0.000
Diameter size ≥7 cm	14/40(35%)	p= 0.000
Necrosis	16/51(31%)	p= 0.000
Microvascular invasion	8/23(35%)	p= 0.006
Sinus invasion	8/16(50%)	p= 0.000

TNM classification system

National Comprehensive Cancer Network®

American Joint Committee on Cancer (AJCC)
TNM Staging System for Kidney Cancer (7th ed., 2010)

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 7 cm or less in greatest dimension, limited to the kidney
T1a	Tumor 4 cm or less in greatest dimension, limited to the kidney
T1b	Tumor more than 4 cm but not more than 7 cm in greatest dimension, limited to the kidney
T2	Tumor more than 7 cm in greatest dimension, limited to the kidney
T2a	Tumor more than 7 cm but less than or equal to 10 cm in greatest dimension, limited to the kidney
T2b	Tumor more than 10 cm, limited to the kidney
T3	Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia
T3a	Tumor grossly extends into the renal vein or its segmental (muscle containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota's fascia
T3b	Tumor grossly extends into the vena cava below the diaphragm
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Anatomic Stage/Prognostic Groups

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1 or T2	N1	M0
	T3	N0 or N1	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

NCCN clinical Practice Guidelines kidney cancer 2016

Table 3. Summary of some important nomograms

Study; nomogram	*n*	Metastatic disease status	Prognostic factors
Yaycioglu et al. (2001) [65]	296	M0	Tumor size, presentation (symptomatic/asymptomatic)
Kattan et al. (2001) [66]	601	M0	Stage, tumor size, symptom classification, histology
Frank et al. (2002) [67]; SSIGN	1,801	M0 (n = 1,516), M1 (n = 285)	TNM stage, tumor size, FNG, necrosis
Motzer et al. (2002) [68]; MSKCC	463	M1	Hgb, LDH, Ca^{2+}, KPS, time from diagnosis to treatment
Zisman et al. (2001) [69]; UISS	477	M0 (n = 211), M1 (n = 266)	TNM stage, FNG, ECOG PS
Kim et al. (2004) [71]	318	M0 (n = 163), M1 (n = 155)	T stage, M stage, ECOG PS, CAIX, p53, vimentin
Mekhail et al. (2005) [70]	353	M1 (n = 353)	MSKCC plus radiotherapy, hepatic, lung, retroperitoneal metastases
Choueiri et al. (2007) [72]	120	M1[a]	ECOG PS, Ca^{2+}, time from diagnosis to treatment, platelets, ANC
Karakiewicz et al. (2007) [73]	2,530	M0 (n = 2,203), M1 (n = 327)	TNM stage, tumor size, FNG, symptom classification
Motzer et al. (2008) [36]	375	M1	Hgb, LDH, Ca^{2+}, KPS, time from diagnosis to treatment, metastatic sites (n), nephrectomy, lung/liver metastases, ECOG PS, ALP, thrombocytosis
Klatte et al. (2009) [74]	170	M0	T stage, ECOG PS, Ki-67, p53, endothelial VEGFR-1, epithelial VEGFR-1, epithelial VEGF-D
Parker et al. (2009) [75]; BioScore	634	M0 (n = 564), M1 (n = 70)	B7-H1, survivin, Ki-67
Heng et al. (2009) [76]	645	M1[a]	Hgb, LDH, Ca^{2+}, KPS, time from diagnosis to treatment, platelets, ANC

Tumor Necrosis

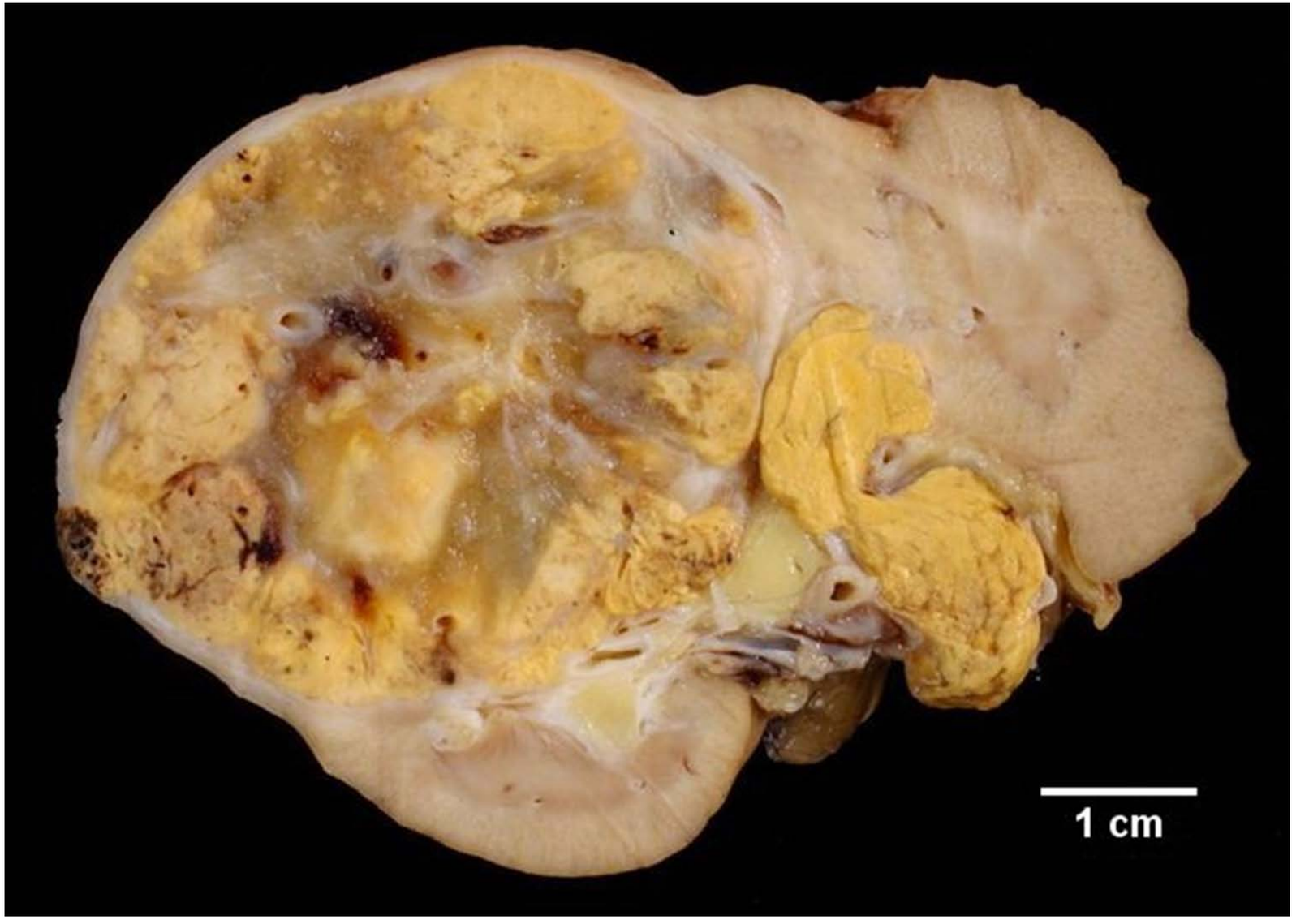
Important prognostic factor in renal cell carcinoma.

Macroscopic and microscopic (coagulative) necrosis

Significance in clear cell and chromophobe renal cell carcinoma.

Necrosis in papillary renal cell carcinoma is controversial.

Cannot be assessed in patients have undergone presurgical arterial embolization.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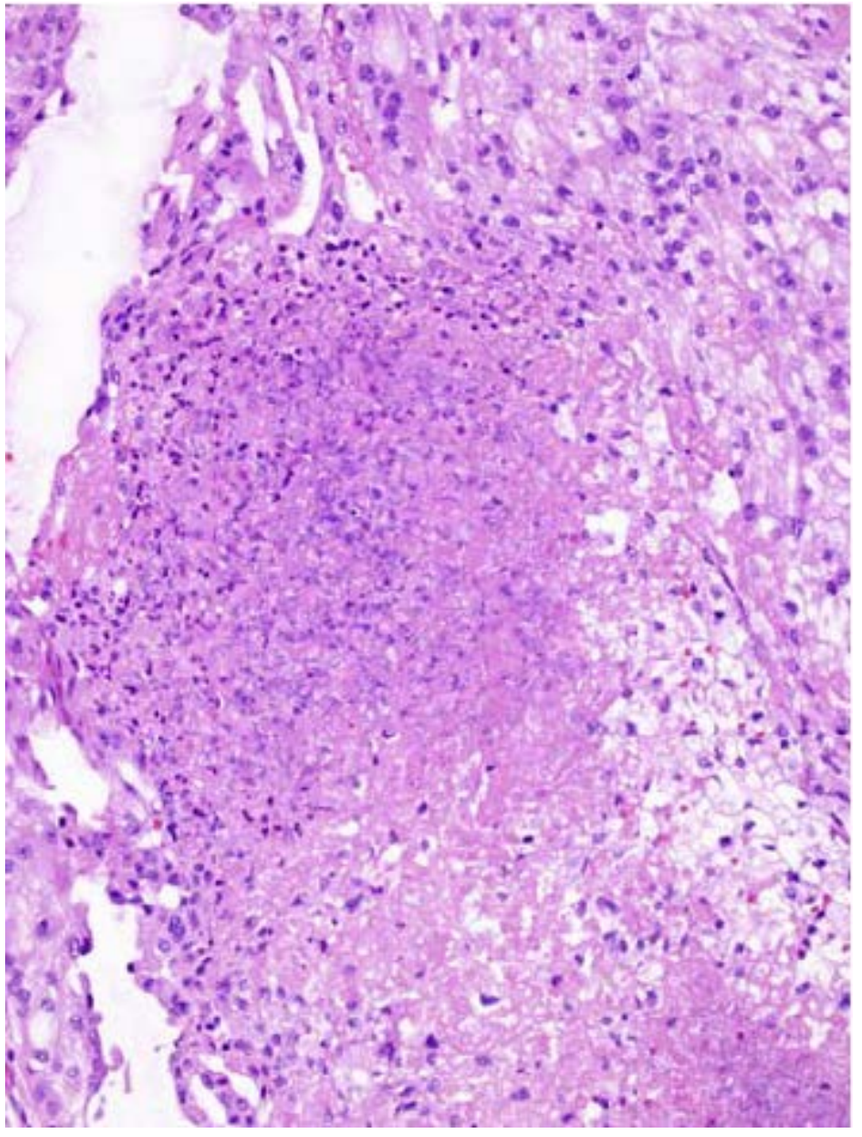

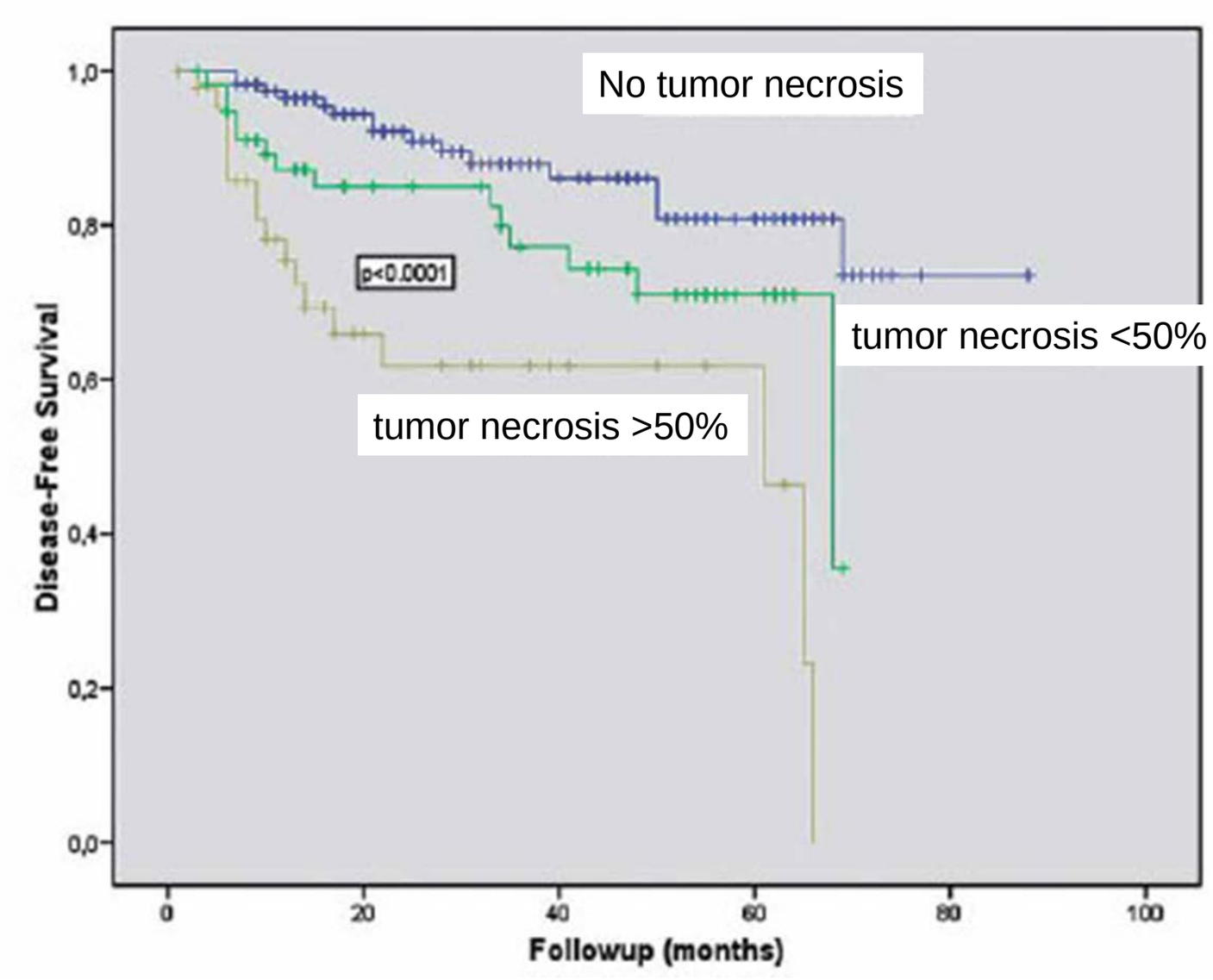

The survival rate at 5 years was 82.5%, 71.6% and 62.5% for patients without tumor necrosis, with less than 50% tumor necrosis and more than 50% tumor necrosis, respectively.

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Table 2 – Common histologic renal cell carcinoma subtypes and their appearance and associated molecular alterations

Tumor type	Subtype*	Gross appearance	Microscopic appearance		Known somatic alterations	Cytogenetic alterations
Clear cell	–	Yellow, well circumscribed, and can possess distinct areas of hemorrhage and necrosis	Abundant clear cytoplasm due to deposition of lipid and glycogen		*VHL, PBRM1, SETD2, BAP1, JARID1A, mTOR, PI3K*	3p (90%), 14q, 8p, and 9p and gains at 5q and 12q
Papillary	1 2	Mixed cystic/solid consistency. Papillary RCC lesions are often reddish-brown and frequently have a well-demarcated pseudocapsule	Papillary or tubulopapillary architecture. Calcifications, necrosis, and foamy macrophage infiltration.	Type 1: thin, basophilic papillae with clear cytoplasm Type 2: heterogenous, thicker papillae and eosinophilic cytoplasm.	*MET* *NRF2, CUL3*	Gains of 7, 8q, 12q, 16p, 17, 20, and loss of 9p. Papillary type 2 with gains of 8q, loss of 1p and 9p.
Chromophobe	Classic Eosinophilic	Large, well-circumscribed, tan-brown tumor with occasional central scar	Distinct cell borders and a voluminous cytoplasm, nuclear morphology with perinuclear halos, binucleation	Classic: pale cytoplasm Eosinophilic: large tumor cells with fine eosinophilic granules	*TP53*	Loss of chromosomes 1, 2, 6, 10, 13, and 17
Oncocytoma	–	Mahogany color, well circumscribed, occasional central scar, and rarely with necrosis	Polygonal cell with abundant eosinophilic cytoplasm and uniform, round nuclei		Mitochondrial complex I genes	Loss of 1 p, loss of Y, often normal karyotype
Collecting duct	–	Partially cystic, white-gray appearance and often exhibit invasion into the renal sinus	Tubulopapillary pattern, often with cells taking columnar pattern with hobnail appearance, presence of mucinous material, desmoplastic stroma		Unknown	Losses at 8p, 16p, 1p, 9p, and gains at 13q
Medullary	–	Tan/white, poorly defined capsule, extensive hemorrhage and necrosis	Poorly differentiated, eosinophilic cells; inflammatory infiltative cells; sheet-like or reticular pattern common		Unknown	Poorly described, but believed normal karyotype
MiT family	–	Yellowish tissue often studded by hemorrhage and necrosis	Papillary or nested architecture, granular and eosinophilic cells with voluminous, cytoplasm		–	Recurrent translocations involving Xp11.2 (TFE3) or 6p21(TFEB)

Table 3 – Listing of known hereditary renal cancer syndromes

Syndrome	Gene(s)	Chromosome location	Histology
Von Hippel-Lindau syndrome	*VHL*	3p25	Clear cell
Hereditary papillary renal cell cancer	*MET*	7q31	Papillary type 1
Hereditary leiomyomatosis and renal cell cancer	*FH*	1p42	Distinct form of papillary type 2
Birt-Hogg-Dubé syndrome	*FLCN*	17p11	Hhybrid oncocytic, chromophobe, oncocytoma
Tuberous sclerosis complex	*TSC1/2*	9q34/16p13	Clear cell, papillary, and chromophobe
Cowden syndrome	*PTEN*	10q23	Clear cell, papillary, and chromophobe
Hereditary pheochromocytoma and paraganglioma	*SDH B/C/D*	1p36/1q23/11q23	Clear cell, unclassified/eosinophilic variant
Chromosome 3 translocation renal cell	–	Translocations (3:6,3:8,3:11)	Clear cell
Unnamed	*MITF*	3p14	Not yet described


Thank
you