KIDNEYS, URETERS, BLADDER CANCER

Kenneth Alonso, MD, FACP

Intravenous pyelogram

- A scout film is obtained before contrast is given.
- On the five minute film, contrast is in the kidney and collecting system.
- Kidneys should be roughly equal in size.
- Calyces should be sharp in outline and symmetrical with equal filling.
- Ureters are just beginning to show.
- Slow filling in hypertension.

Intravenous pyelogram

- On the ten minute film, ureters are completely filled.
- Any calculi (stones) or strictures would be seen here.
- At fifteen minutes, the bladder is filling.
- Any abnormalities in shape or filling voids within would be visible.
- Post void film would show whether bladder is emptying properly.

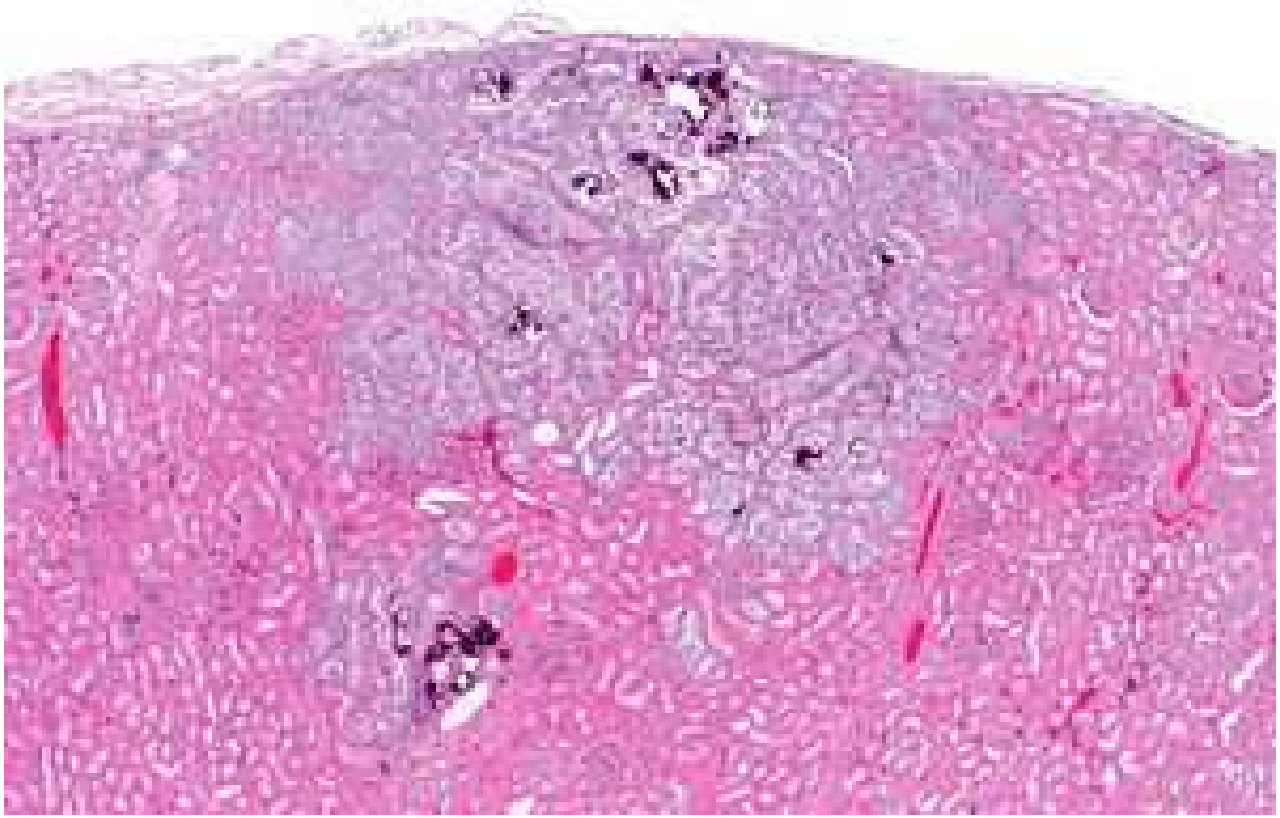
Adenoma

- Arise from renal tubular epithelium
- Usually papillary
- 7-22% of patients
- <1.5 cm in diameter
- Increased risk of metastasis if >3cm in diameter.

Adenoma

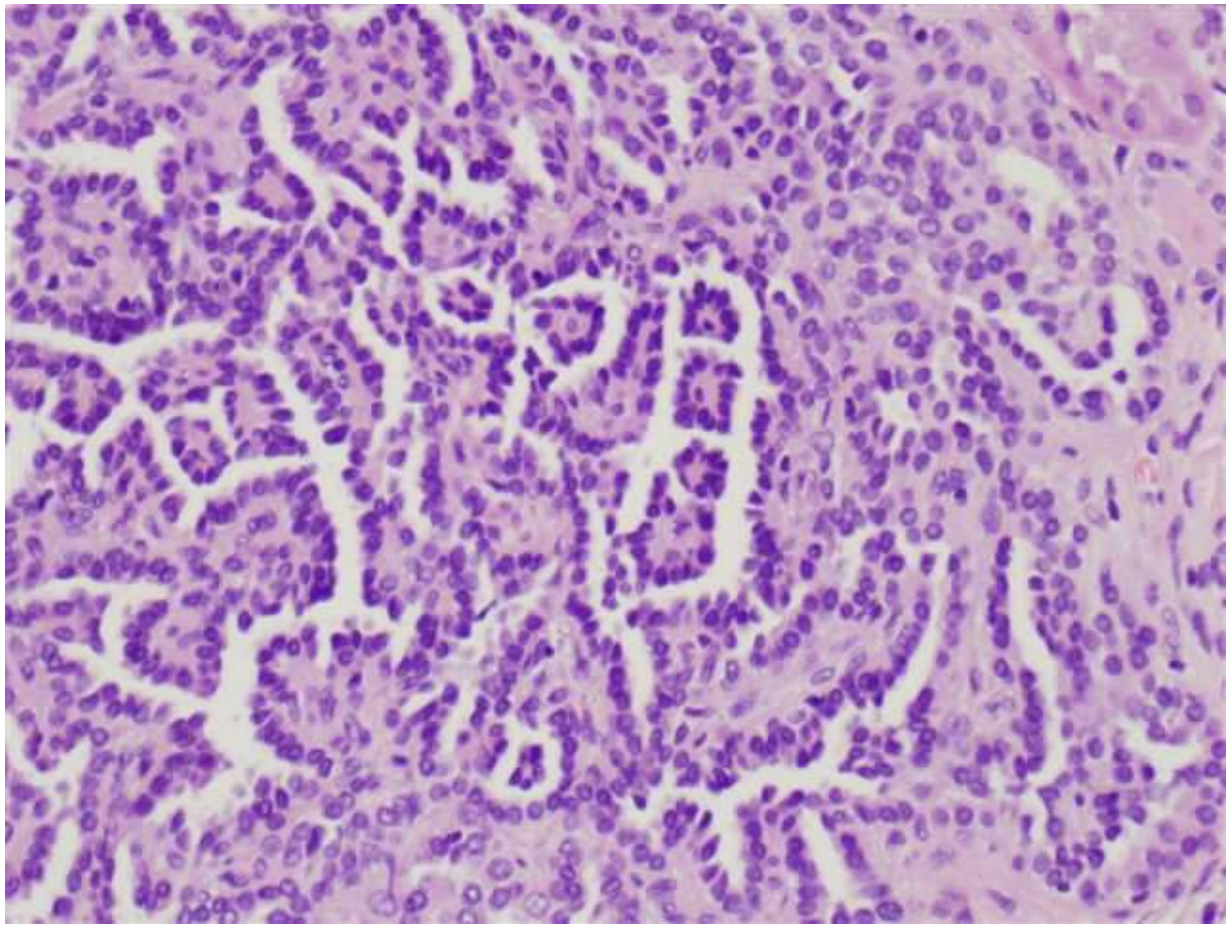
- Pale yellow-gray, discrete, well-circumscribed cortical nodules.
- Composed of complex, branching, papillomatous structures with numerous complex fronds. Cells may also grow as tubules, glands, cords, and sheets of cells.
- The cells are cuboidal to polygonal in shape and have regular, small central nuclei, scanty cytoplasm, and no atypia.

Renal papillary adenoma



https://librepathology.org/w/images/thumb/d/d6/Renal_papillary_adenoma_--_very_low_mag.jpg/300px-Renal_papillary_adenoma_--_very_low_mag.jpg
Accessed 02/20/2020

Renal papillary adenoma

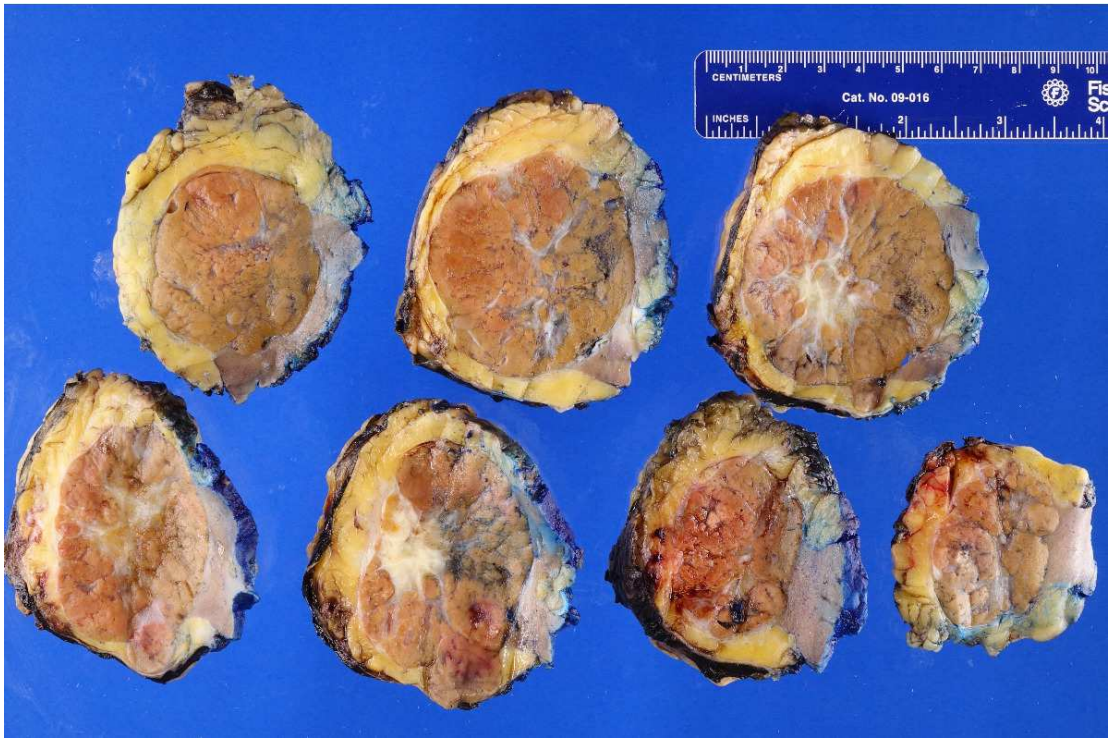


http://www.pathologyoutlines.com/caseofweek/Case200643image2.jpg accessed 02/20/2020

Oncocytoma

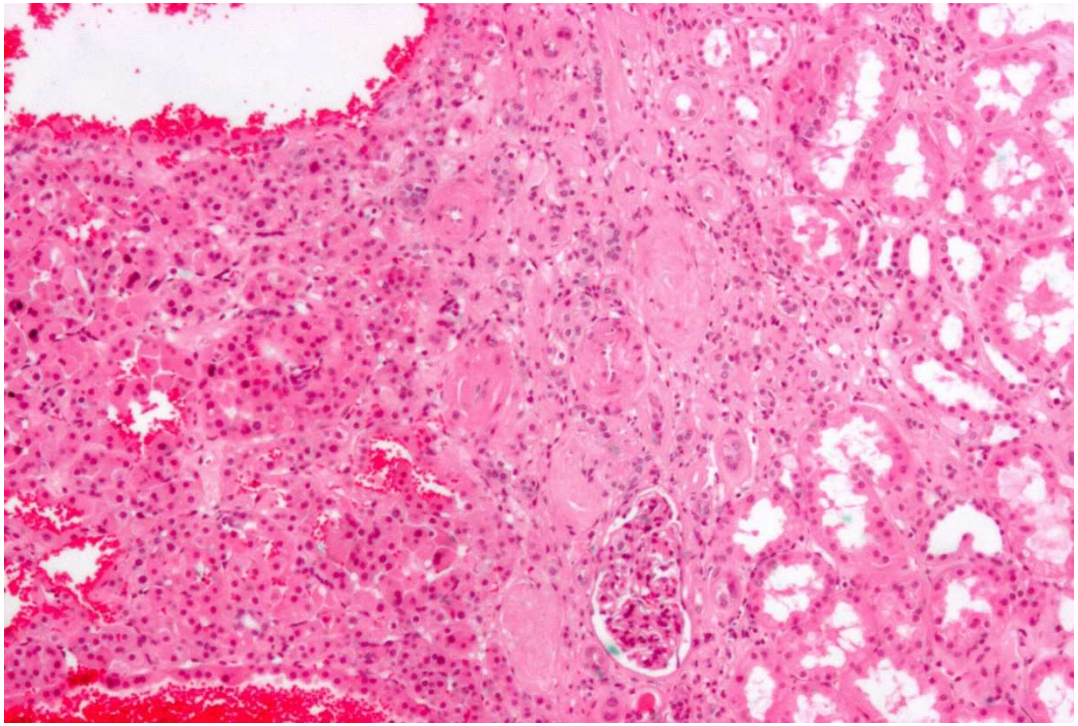
- Composed of large eosinophilic cells having small, round, benign-appearing nuclei that have large nucleoli.
- Arise from the intercalated cells
- Have numerous mitochondria.
- Tan or mahogany brown, relatively homogeneous, and usually well encapsulated with a central scar in one-third of cases.

Renal Oncocytoma



http://www.pathologyoutlines.com/topic/kidneytumoroncocytoma.html Contributed by Debra Zynger, MD
Accessed 02/20/2020

Renal oncocytoma



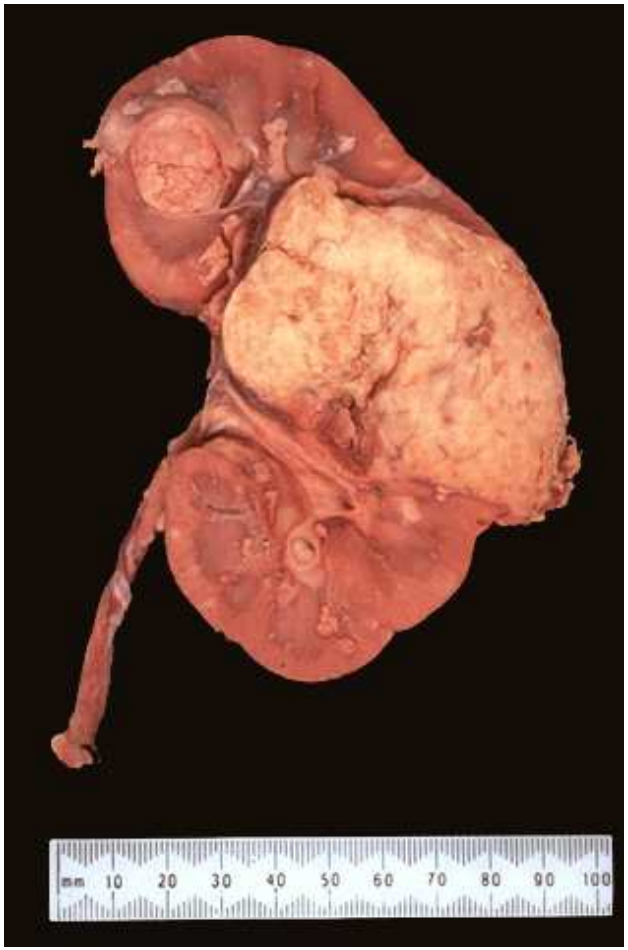
The tumor cells (left of the image) are arranged in nests, have slightly enlarged nuclei and have a more eosinophilic cytoplasm than the normal kidney (right of image). A glomerulus is seen at the bottom-center of the image. Normal renal tubules are seen on the right of the image.

https://upload.wikimedia.org/wikipedia/commons/d/d9/Renal_oncocytoma3.jpg
Accessed 02/20/2020

Angiolipoma

- Vessels, smooth muscle, and fat originating from perivascular epithelioid cells in the cortex
- Up to 50% of patients with tuberous sclerosis
- Loss-of-function mutations in the TSC1 or TSC2 tumor suppressor genes.
- Loss of regulation of mTOR signaling
- Tendency to spontaneous hemorrhage

Angiomyolipoma

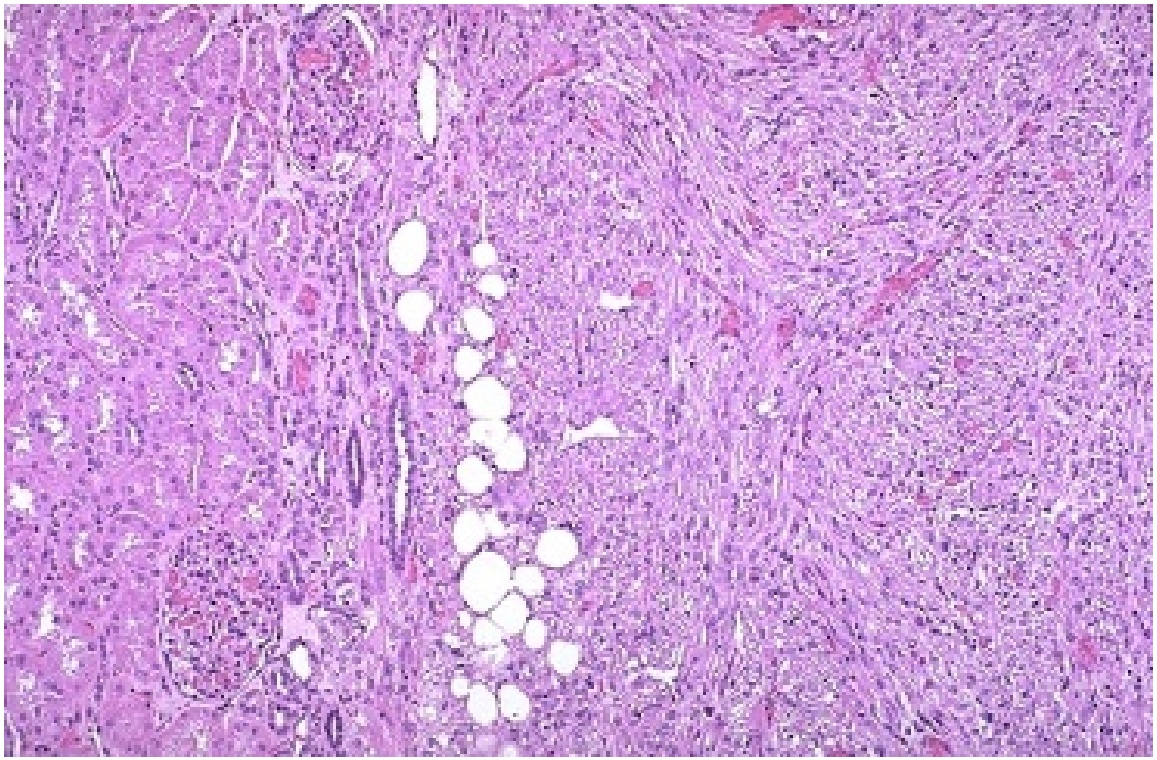


Note that it is solid and has a tan to yellowish-tan cut surface. It is also multifocal. Most of these tumors are incidental findings. Those with tuberous sclerosis often have these tumors. This neoplasm is one form of perivascular epithelioid cell tumor (PEComa) derived from the perivascular epithelioid cell (PEC), and not present in normal tissue.

[Image contributed by John Nicholls, MD, Hong Kong University]

https://webpath.med.utah.edu/RENAHTML/RENAL115.html
Accessed 01/20/2020

Angiomyolipoma



There is normal renal parenchyma at the left. The tumor has a strip of adipose tissue in the center that then blends in with interlacing bundles of smooth muscle in which are scattered vascular spaces.

https://webpath.med.utah.edu/RENAHTML/RENAL106.html
Accessed 01/20/2020

Mesoblastic nephroma

- Most common renal cancer in infancy
- 5% of all pediatric renal cancers
- May present in utero with polyhydramnios
- Classic type presents at 16 days of age
- Mixed type presents at 2 months of age
- Cellular type presents at 5 months of age
- 5-10% recur or metastasize
- Usually by age 1
- Metastases to lung and brain, NOT bone

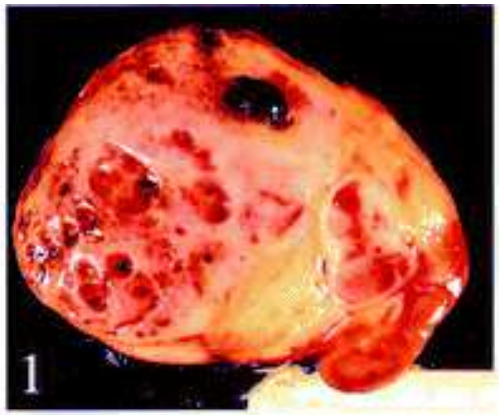
Mesoblastic nephroma

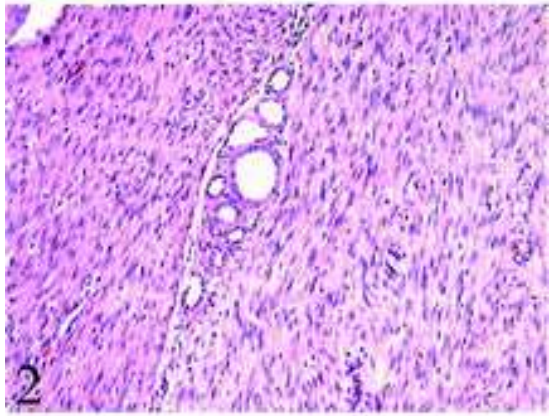
- Classic (25%):
- Resembles infantile fibromatosis or leiomyoma
- Fascicles and whorls of bland spindled myofibroblasts and thin collagen fibers
- No desmoplasia
- Tumor surrounds tubules and glomeruli, has irregular borders
- Chondroid metaplasia or dysplasia of the entrapped tubules is common
- Mitoses are rare
- No recurrent genetic aberration

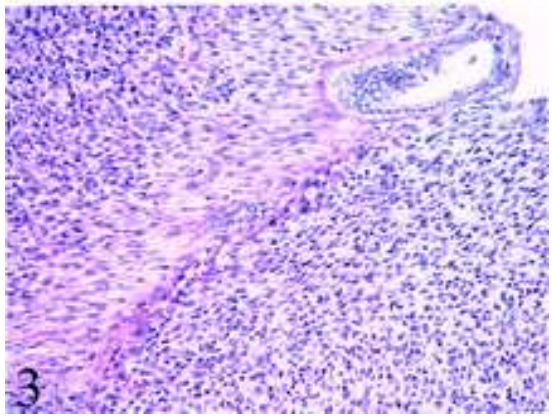
Mesoblastic nephroma

- Cellular (65%):
- Resembles infantile fibrosarcoma
- Sheet-like proliferation of plump, atypical spindle cells with abundant cytoplasm, vesicular nuclei and nucleoli
- Mitoses are common
- Necrosis
- The tumor has a pushing border
- Shares the same translocation with infantile fibrosarcoma: t(12;15) and results in ETV6-NTRK3 fusion protein
- Mixed (10%):
- A combination of classic and cellular features

Mesoblastic Nephroma







Cellular areas have mitotic figures, cystic degeneration, hemorrhage and necrosis.
SMA and Vimentin positive.

https://www.archivesofpathology.org/action/showFullPopup?id=i1543-2165-128-8-929-f01&doi=10.1043%2F1543-2165%282004%29128%3C929%3APQCRMI%3E2.0.CO%3B2

Accessed 02/20/2020

Wilm's tumor (nephroblastoma)

- 6-7% of childhood malignancies.
- Most common pediatric renal tumor.
- 90% diagnosed before age 6
- 90% are sporadic
- 5% present with specific genetic syndromes
- May first present with pain
- Flank or abdominal mass.
- Unilateral in sporadic cases
- Hypertension and hematuria.
- Arises from metanephric blastema.

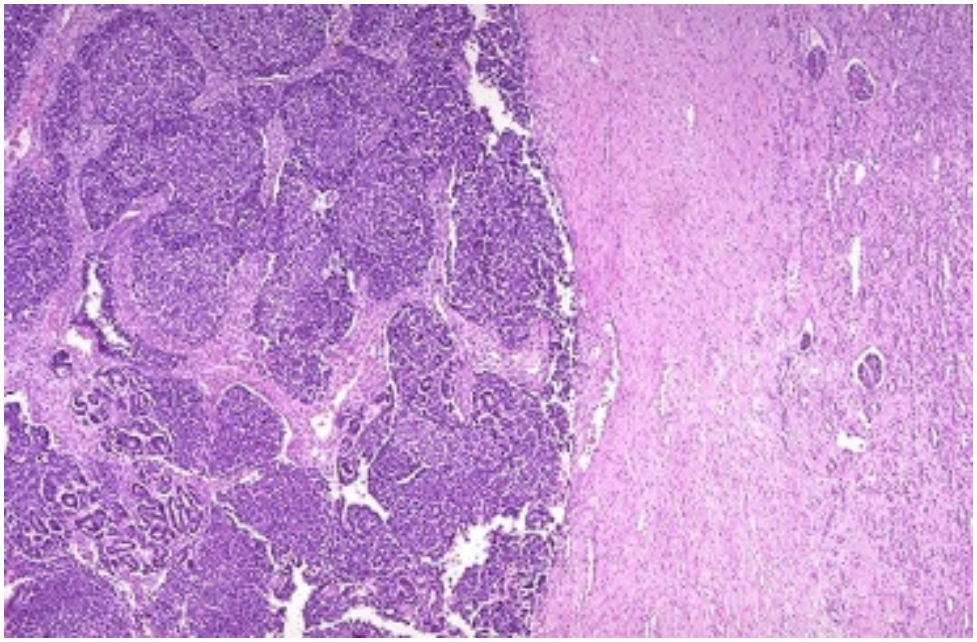
Wilm's tumor

- Triphasic combination of blastemal, stromal, and epithelial cell types
- Sheets of small blue cells with few distinctive features characterize the blastemal component.
- Epithelial differentiation is usually in the form of abortive tubules or glomeruli.
- Stromal cells are usually fibrocytic or myxoid in nature, although skeletal muscle differentiation is not uncommon.
- Rarely, other heterologous elements are identified.
- The presence of nephrogenic rests correlates with high risk of developing contralateral disease

Wilm's tumor

- WT1 gene (zinc finger transcription factor at 11p13) controls blastema development.
- The presence of anaplasia correlates with the presence of p53 mutation and chemotherapy resistance.
- 11q-, 16q-, 1q+ poor prognostic factors.
- Age >2 years poor prognosis
- Liver is most common site of metastasis
- Rarely metastasizes to bone

Wilm's tumor

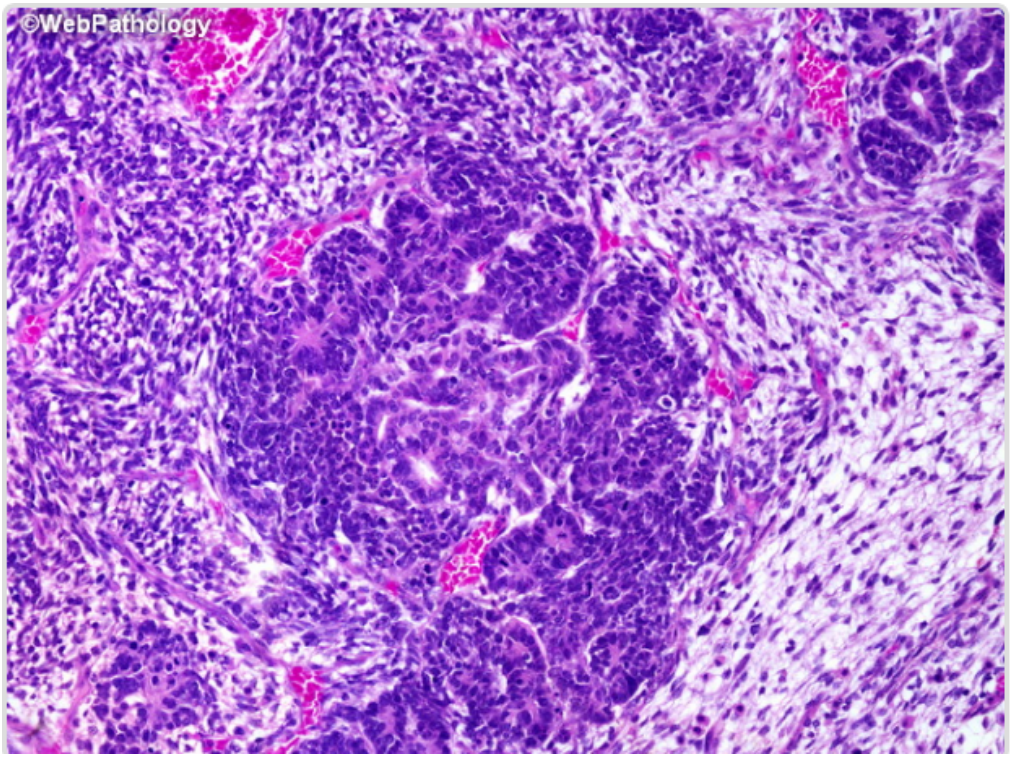


Left. The tumor is a lobulated tan mass. Right: The tumor is comprised of nests and sheets of dark blue cells at the left with compressed normal renal parenchyma at the right.

https://webpath.med.utah.edu/RENAHTML/RENAL057.html and RENAL058.html

Accessed 01/20/2020

Wilm's tumor



http://webpathology.com/image.asp?n=13&Case=73
Accessed 02/20/2020

Classically, Wilms tumor is triphasic and consists of variable proportions of blastema, stroma, and epithelial cells. The blastemal component consists of small poorly differentiated round cells. The epithelial component consists of abortive tubules and glomerular structures. Stroma is usually fibroblastic or myxoid and may contain heterologous elements such as skeletal muscle, smooth muscle, bone, cartilage, adipose tissue, and neuroglial tissue.

CHILDREN'S ONCOLOGY GROUP (COG) STAGING OF WILMS TUMOR[1]

COG Staging of Wilms Tumor	
Stage I	Tumor limited to kidney, completely resected. The renal capsule is intact. The tumor was not ruptured or biopsied prior to removal. The vessels of the renal sinus are not involved. There is no evidence of tumor at or beyond the margins of resection. *Note:* For a tumor to qualify for certain therapeutic protocols as Stage I, regional lymph nodes must be examined microscopically.
Stage II	The tumor is completely resected and there is no evidence of tumor at or beyond the margins of resection. The tumor extends beyond kidney, as is evidenced by any one of the following criteria: • There is regional extension of the tumor (i.e. penetration of the renal capsule, or extensive invasion of the soft tissue of the renal sinus, as discussed below). • Blood vessels within the nephrectomy specimen outside the renal parenchyma, including those of the renal sinus, contain tumor. *Note:* Rupture or spillage confined to the flank, including biopsy of the tumor, is no longer included in Stage II and is now included in Stage III.
Stage III	Residual nonhematogenous tumor present following surgery, and confined to abdomen. Any one of the following may occur: • Lymph nodes within the abdomen or pelvis are involved by tumor. (Lymph node involvement in the thorax, or other extra-abdominal sites is a criterion for Stage IV.) • The tumor has penetrated through the peritoneal surface. • Tumor implants are found on the peritoneal surface. • Gross or microscopic tumor remains postoperatively (e.g., tumor cells are found at the margin of surgical resection on microscopic examination). • The tumor is not completely resectable because of local infiltration into vital structures. • Tumor spillage occurring either before or during surgery. • The tumor was biopsied (whether tru-cut, open or fine needle aspiration) before removal. • Tumor is removed in greater than one piece (e.g. tumor cells are found in a separately excised adrenal gland; a tumor thrombus within the renal vein is removed separately from the nephrectomy specimen). *Note:* Extension of the primary tumor within vena cava into thoracic vena cava and heart is considered Stage III, rather than Stage IV even though outside the abdomen.
Stage IV	Hematogenous metastases (lung, liver, bone, brain, etc.), or lymph node metastases outside the abdominopelvic region are present. (The presence of tumor within the adrenal gland is not interpreted as metastasis and staging depends on all other staging parameters present).
Stage V	Bilateral renal involvement by tumor is present at diagnosis. An attempt should be made to stage each side according to the above criteria on the basis of the extent of disease.

[1] Adapted from Wilms Tumor and Other Childhood Kidney Tumors Treatment (PDQ®)–Health Professional Version. National Cancer Institute. Accessed February 3, 2021. Available at: https://www.cancer.gov/types/kidney/hp/wilms-treatment-pdq#_23_toc

https://www.nccn.org/professionals/physician_gls/pdf/kidney_blocks.pdf
Accessed 03/17/2021

SYNDROMES AND CONGENITAL ANOMALIES ASSOCIATED WITH WILMS TUMOR

- Other Syndromes (cont.)
  - Perlman syndrome[27] (MIM: 614184):
    Inheritance autosomal recessive (AR):
    Gene *DIS3L2*
    Affected children are large at birth, are hypotonic, and show organomegaly, characteristic facial dysmorphisms (inverted V-shaped upper lip, prominent forehead, deep-set eyes, broad and flat nasal bridge, and low-set ears), renal anomalies (nephromegaly and hydronephrosis frequent neurodevelopmental delay, and high neonatal mortality.
  - Bohring-Optiz syndrome[28,29] (MIM: 605039)
    Inheritance AD:
    Gene *ASXL1*
    Malformation syndrome characterized by severe intrauterine growth retardation, poor feeding, profound mental retardation, trigonocephaly, prominent metopic suture, exophthalmos, nevus flammeus of the face, upslanting palpebral fissures, hirsutism, and flexion of the elbow and wrists with deviation of the wrists and metacarpophalangeal joints
  - MULIBREY (MUscle, LIver, BRain, and EYes) Nanism syndrome[30] (MIML 605073, https://omim.org/entry/253250)
    Inheritance AR:
    Gene *TRIM37*
    Growth disorder with prenatal onset, including occasional progressive cardiomyopathy, characteristic facial features, failure of sexual maturation, insulin resistance with type 2 diabetes, and an increased risk for Wilms tumor
- Congenital Anomalies Associated with Predisposition Syndromes
  - Aniridia
  - Cryptorchidism
  - Hemihypertrophy
  - Horseshoe kidney (patients are twice as likely to develop WT)
  - Hypospadias
  - Renal duplication
  - Renal ectopia
  - Renal hypoplasia
  - Mesoblastic nephroma
  - Ureteral duplication
- Surveillance Recommendations for WT Predisposition Syndromes[10,15]
  - The Pediatric Cancer Working Group of the American Association for Cancer Research recommends renal US every 3 mo up to age 8 y

Familial Nephroblastoma

FWT1/FWT2 (Familial WT) gene mutations account for about 1-2% of WT cases. These mutations are autosomal dominant with variable penetrance. They have no association with the *WT1* mutation. *FWT1* is found on chromosome 17q; whereas *FWT2* is found on chromosome 19q.[22,31-33]

References

SYNDROMES AND CONGENITAL ANOMALIES ASSOCIATED WITH WILMS TUMOR

Somatic Genetic Variants

- Most common somatic variants in WT are:
  - *CTNNB1, DROSHA, WT1, WTX, WTX (AMER-1), DGCR8, SIX1, BCORL1, MLLT1, MYCN, SIX2*; TP53 is associated with anaplastic WT[1]
  - *WT1*, a tumor suppressor gene found on chromosome 11p13, is implicated in the development of WT. *WT1* codes a transcription factor crucial for normal kidney/genitourinary function (5%–10% of cases)[2-11]
  - WT2, a tumor suppressor gene found on chromosome 11p15, is also implicated in the development of WT.

- WT predisposition genes by exome sequencing[12-14]
  - *REST, TRIM28, FBXW7, NYNRIN, KDM3B, XPO5, CHEK2, and PALB2*

- Predisposition Syndromes Associated with WT[15]
  - Denys-Drash syndrome[16,17] (MIM: 607102):
    Inheritance Autosomal Dominant (AD):
    Gene *WT1*; locus 11p13
    Disorders of Sexual Development (DSD), mesangial sclerosis, renal failure, usually 46 XY karyotype[18]
  - Frasier syndrome[19] (MIM: 607102)
    Inheritance AD
    Gene *WT1*; locus 11p13
    DSD, progressive glomerular nephropathy, patients present with normal female external genitalia, streak gonads, and XY karyotype, and frequently develop gonadoblastoma
  - Beckwith-Wiedemann syndrome[20,21] (MIM: 616186, 604115, 600856):
    Inheritance complex: AD, Uniparental Disomy, Epimutations involving locus 11p15.5
    Characterized by gigantism, omphalocele, macroglossia, genitourinary abnormalities, ear pits and creases, hypoglycemia, and hemihypertrophy; present in about 5% of children with WT.[22,23]
  - Contiguous Gene Deletion Syndrome or WAGR/WAGR syndrome with obesity (WAGRO)[24] (MIM 194072, 612469)
    Gene *WT1* gene; locus 11p13
    Characterized by aniridia, genitourinary abnormalities, obesity, and hemihypertrophy;
  - Trisomy 18 syndrome[25]

- Other Syndromes
  - Li Fraumeni syndrome[26] (MIM: 191170)
    Inheritance AD:
    Gene *TP53*
    Broad cancer predisposition syndrome associated with anaplastic Wilms tumor in young patients.

General Principles

- The administration of adjuvant, and in some cases neoadjuvant chemotherapy, in combination with surgery ± radiation markedly improves survival for FHWTs.
- Selection of the appropriate chemotherapy regimen is based on tumor histology, stage, tumor weight, the patient's age, response of lung metastases (when present) to chemotherapy, and molecular markers, which together determine the risk group (see Risk Assessment for FHWT [WILMS-F]).
- Adjuvant chemotherapy should be started within 7 to 14 days of up-front nephrectomy and the timing should be coordinated with radiation, if it is required, to avoid co-administration of full doses of dactinomycin or doxorubicin with radiation. Dactinomycin and doxorubicin can be administered at full doses prior to the start of radiation.
- Neoadjuvant chemotherapy is administered for unresectable tumors or tumors for which NSS is indicated (see Principles of Surgery [WILMS-D]) to reduce the size of the tumor(s).
  - Re-image after 6 weeks of neoadjuvant chemotherapy to determine whether the tumor(s) is/are resectable.
  - The postoperative adjuvant chemotherapy regimen is determined by tumor histology, stage, and molecular markers.

Chemotherapy Regimens

- EE4A: 13 doses of vincristine and 7 doses of dactinomycin administered over 18 weeks.[1,2]
- DD4A: 15 doses of vincristine, 5 doses of dactinomycin, and 4 doses of doxorubicin (cumulative dose 150 mg/m²) administered over 24 weeks with alternating doses of dactinomycin and doxorubicin.[1,2]
- VAD: 6–12 doses of vincristine, 2–4 doses of dactinomycin, and 2–4 doses of doxorubicin (cumulative dose 70–140 mg/m²) administered over 6–12 weeks used only in the neoadjuvant setting for patients who are candidates for NSS. In this regimen dactinomycin and doxorubicin are given together.[3]
- Regimen M: 9 doses of vincristine, 5 doses of dactinomycin, 5 doses of doxorubicin (cumulative dose 150 mg/m²), 4 courses of 5 daily doses of cyclophosphamide, and 4 courses of 5 daily doses of etoposide over 24 weeks. Dactinomycin and doxorubicin are given together, and cyclophosphamide and etoposide are given together. This regimen starts at week 7 for tumors requiring augmentation of therapy based on molecular markers or response of lung metastases to 6 weeks of DD4A.[4]
- Regimen I: 9 doses of vincristine, 4 doses of doxorubicin (cumulative dose 180 mg/m²), 7 courses of 3 to 5 daily doses of cyclophosphamide, and 3 courses of 5 daily doses of etoposide. Doxorubicin and 3 daily doses of cyclophosphamide are given together, and 5 daily doses of cyclophosphamide and etoposide are given together. This regimen starts at week 7 for tumors requiring augmentation of therapy based on histology.[3,5,6]

- Initial risk is based on age, clinical, radiographic, surgical. and pathological findings.
- Final risk is based on initial risk plus LOH at 1p and 16q, and response of lung metastases at week 6.

Patient Age	Tumor Weight	Stage	Intital Risk Group	LOH 1p/16q	Lung Metastases Response	Extra-Pulmonary Metastases	Final Risk Group
<2 years	<550 g	I	Very Low	Any	N/A	N/A	Very Low
Any	≥550 g	I	Low	No	N/A	N/A	Low
≥2 years	Any	I	Low	No	N/A	N/A	Low
Any	Any	II	Low	No	N/A	N/A	Low
Any	≥550 g	I	Low	Yes	N/A	N/A	Standard
≥2 years	Any	I	Low	Yes	N/A	N/A	Standard
Any	Any	II	Low	Yes	N/A	N/A	Standard
Any	Any	III	Standard	No	N/A	N/A	Standard
Any	Any	IV	Higher	No	Complete	No	Standard
Any	Any	III	Standard	Yes	N/A	N/A	Higher
Any	Any	IV	Higher	Yes	Any	Any	Higher
Any	Any	IV	Higher	Any	Partial	Any	Higher
Any	Any	IV	Higher	Any	Any	Yes	Higher
Any	Any	V	Bilateral	Any	Any	Any	Bilateral

Prognostic Factors
- Stage (See ST-1)
- Histology (favorable or unfavorable/anaplastic)
- Patient age at diagnosis
- Tumor weight
- Completeness of lung nodule response to therapy at week 6
- LOH of chromosomes 1p, 11p15, and 16q
  - LOI of 11p15
- Chromosome 1q gain[1]

https://www.nccn.org/professionals/physician_gls/pdf/kidney_blocks.pdf
Accessed 03/17/2021

Genetic syndromes

- WAGR Syndrome
- Wilms tumor
- Aniridia (absence of iris)
- Genitourinary abnormalities
- Retardation (mental)
- Germline WT1 gene deletion occurs near PAX6 gene (also at 11p13)
- 33% lifetime risk for Wilm's tumor

Wilm's tumor

- Denys-Drash syndrome
- Gonadal dysgenesis (male pseudohermaphroditism) and early-onset nephropathy leading to renal failure.
- Diffuse glomerular sclerosis
- Dominant-negative missense mutation in the zinc-finger region of the WT1 protein inactivates wild-type allele
- Leads to gonadal dysgenesis
- At risk for developing gonadoblastoma
- Bi-allelic loss of WT1 associated with Wilm's tumor
- 90% of patients

Wilm's tumor

- Beckwith-Wiedemann syndrome
- Exophthalmos
- Microglossia
- Gigantism
- Hemihypertrophy
- WT2 gene at 11p15.
- This chromosomal region usually contains genes that are normally expressed from only one of the two parental alleles
- Transcriptional silencing (imprinting) of the other gene by methylation of the promoter region.
- Higher risk for hepatoblastoma, adrenal cortical and pancreatic tumors, rhabdomyosarcoma

Wilm's tumor

- Predisposition to tumorigenesis
- Overexpression of insulin growth factor (IGF2) also in this region.
- Doubling of paternal IGF2 allele with maternal allele deletion (uniparental paternal disomy) is also a cause.
- CDKNIC mutations (p57) and β-catenin mutations are also associated with tumor expression in Beckwith-Wiedemann syndrome.
- If either aniridia or Beckwith-Wiedemann syndrome is diagnosed in a child, screen for Wilm's tumor.

Therapy

- Primary resection provides necessary biologic information for risk stratification and selection of appropriate therapy.
- Minimize treatment for low-risk patients
- Improve survival in higher risk patients.
- Transabdominal or a thoracoabdominal exposure with transperitoneal approach (preferred surgical approaches) and abdominal exploration, unilateral radical ureteronephrectomy with LN sampling.
- LN sampling MUST be performed for adequate staging; recommend obtaining minimum >5 (nodes) from areas in renal hilum anatomically expected to represent nodes associated with kidney

Therapy

- Contraindications to Primary Resection
- High risk of renal failure for those with germline WT1 mutations (Denys-Drash, WAGR) or bilateral WT.
- Overall risk of long-term renal failure is <1%.
- Unacceptable anesthesia risk due to disease burden
- Massive pulmonary disease
- Very large abdominal tumors causing pulmonary compromise

Therapy

- Contraindications to Primary Resection
- Surgeon judgment:
- Operation would lead to significant morbidity/mortality, tumor spill, or residual tumor
- Solitary kidney
- IVC tumor thrombus above the level of the hepatic veins

Therapy

- Goals of Surgery for Unilateral WT
- Complete clearance of all disease
- Accurate LN staging
- Complete pathologic evaluation
- Resection without rupture of the tumor

Therapy

- Summary of Surgical Approach to Bilateral WT
- Do not biopsy upon presentation of bilateral WT.
- Use of standardized 3-drug neoadjuvant chemotherapy (VAD) followed by bilateral nephron-sparing surgery (NSS) to preserve renal function
- Possible criteria for successful NSS:
- Small tumor size
- Peripheral or polar location of the mass
- Lack of invasion or encasement of renal vessels

Therapy

- Relative contraindications to NSS:
- Central location
- Proximity to the renal vessels

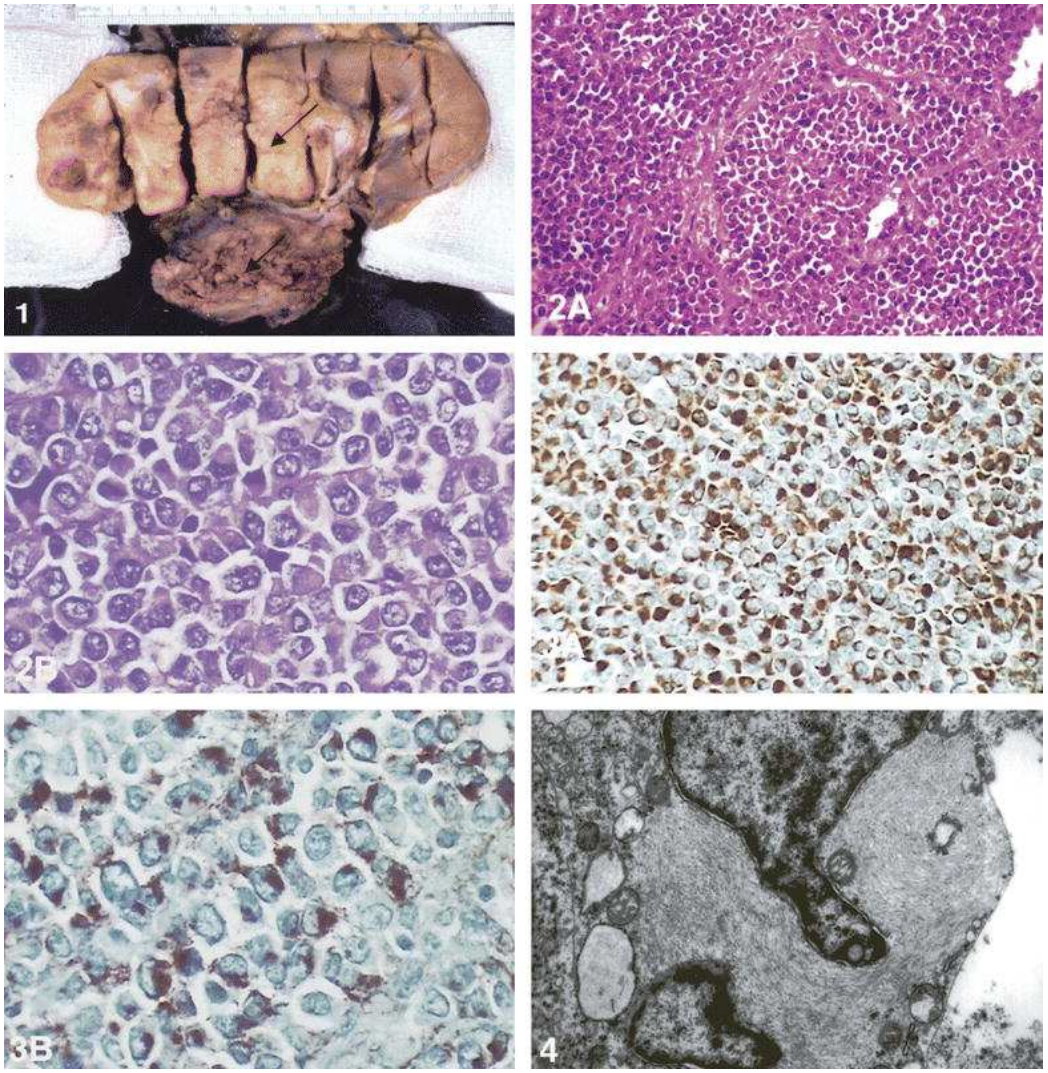
Therapy

- Week 6 re-evaluation
- Perform surgery if bilateral NSS is possible
- For less than a partial response to chemotherapy, consider open biopsy to assess for presence of anaplasia
- Continue chemotherapy if patient has some response but is not a candidate for NSS
- Surgery should be performed within 12 weeks of starting neoadjuvant therapy
- Aim for bilateral NSS, if possible. If operating after chemotherapy, enucleation is safe
- If disease recurrence, repeat NSS

Rhabdoid tumor

- 1-2% of childhood renal tumors
- 60% <1 year old; 30% 1-3 years old
- 15% associated with pineal neuroectodermal tumor in the midline fossa
- 82% present with metastases
- 90% mortality at 2 years
- Gross appearance is that of a fleshy mass.
- Histologically the tumor is composed of small round cells with prominent nuclei and nucleoli, growing in a sheath like pattern separated by thin fibrovascular septa.
- INI1 deletion

Rhabdoid tumor



3A, Most of the cells stain positively for vimentin (original magnification ×125). B, Focally, tumor cells also stain positively for epithelial membrane antigen (original magnification ×500).
4. Large swirls of cytoplasmic intermediate filaments with some entrapped organelles (original magnification ×22400)

https://www.archivesofpathology.org/na101/home/literatum/publisher/pinnacle/journals/content/arpa/2003/15432165-127.9/1543-2165%282003%29127%3Ce371%3Amrtotk%3E2.0.co%3B2/production/images/large/i1543-2165-127-9-e371-f01.jpeg

Renal cell carcinoma

- Usually men
- Usually >40 years old (median age, 60).
- Often in the upper pole of the kidney
- Usually present with hematuria
- Flank mass and pain may also be present
- Invade along renal vein
- Lung is usual metastatic site
- “Cannon ball” appearance on x-ray
- Osteolytic bone metastases
- Hemorrhagic metastatic nodules in skin
- Highly vascular lesion

Renal cell carcinoma

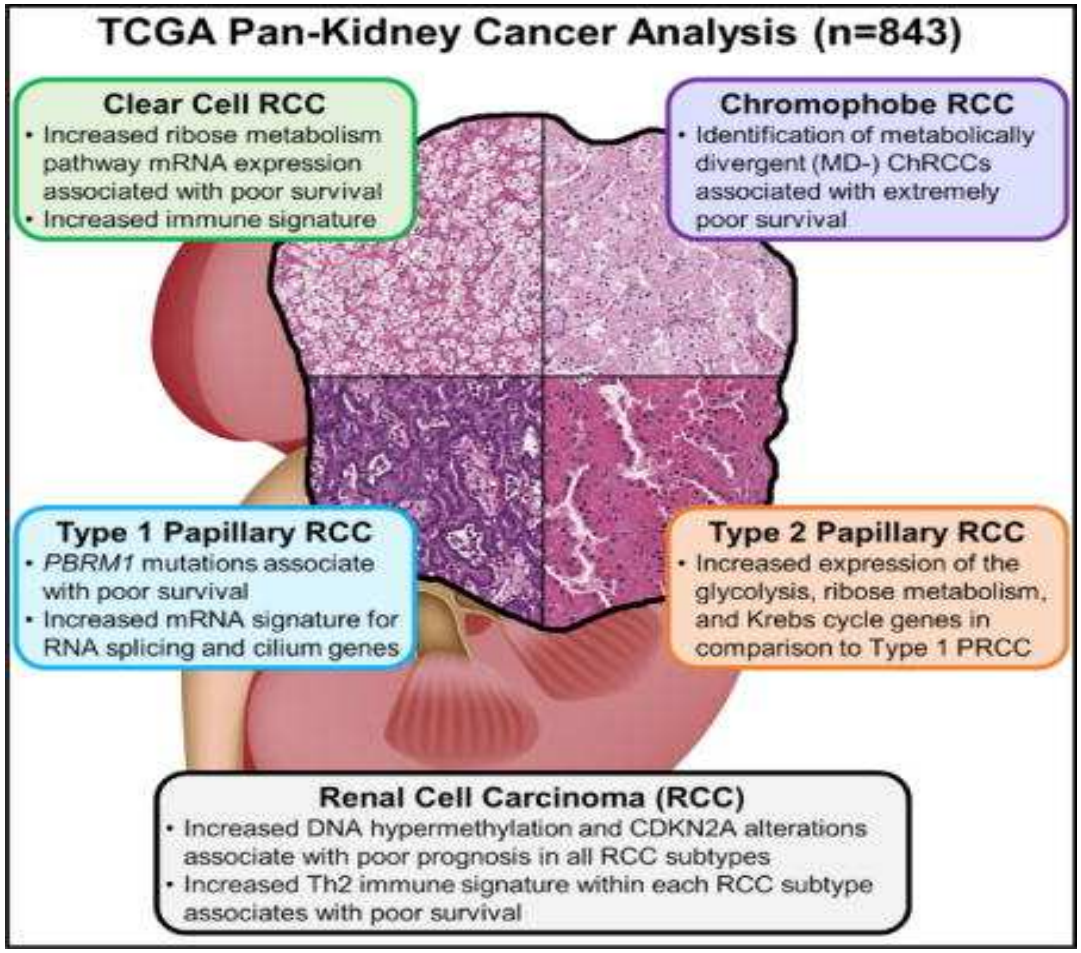
- Left renal kidney involvement may be associated with left varicocele
- Left renal vein involvement blocks drainage of left spermatic vein
- As right spermatic vein drains directly into the inferior vena cava, no development of varicocele in right sided kidney involvement

Renal cell carcinoma

- Ectopic hormone production secondary to abnormalities with Hypoxia induction factor (HIF)
- May produce erythropoietin
- Secondary polycythemia
- May produce parathyroid hormone related peptide
- Hypercalcemia
- Renin overproduction
- Hypertension

Renal cell carcinoma

- Risk factors:
- Tobacco use
- Fried food consumption
- Obesity
- Exposure to asbestos
- Exposure to petroleum products.
- Adult polycystic disease also predisposes (30x greater risk)



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6075733/

Renal cell carcinoma

- Somatic alteration of BAP1 (3p21.1), PBRM1 (3p21.1), and PTEN (10q23.21) and altered metabolic pathways correlate with subtype-specific decreased survival
- BAP1 produces a deubiquinating enzyme
- Inactivating mutations in the BAP1 gene are associated with poor prognosis in clear cell renal cell carcinoma (CC-RCC) and type 1 papillary renal cell carcinoma (PRCC1)
- PBRM1 is an integral component of complexes necessary for ligand-dependent transcriptional activation by nuclear hormone receptors

Renal cell carcinoma

- PTEN is a tumor suppressor in the PI3K/AKT/mTOR pathway
- Inactivation of TP53 or the CDKN2A tumor suppressors or a CpG island hypermethylation phenotype (CIMP) increases in the immune-related Th_2 gene expression signature correlate with decreased survival within all major histologic subtypes.

Renal cell carcinoma

- CpG island methylator phenotype subtype of clear cell renal cell carcinoma (CIMP-RCC) demonstrates an increased immune signature, including the Th_2 gene
- A uniform and distinct metabolic expression pattern identifies a subset of metabolically divergent (MD) chromophobe renal cell carcinoma (ChRCC) that is associated with extremely poor survival.
-

Renal cell carcinoma

- Increased expression of pyruvate dehydrogenase activation genes in and ChRCC
- Oxidative phosphorylation
- Decreased expression of pyruvate dehydrogenase activation genes in and CC-RCC and PRCC2
- Glycolysis dependent energy production

Molecular alterations

- Clear cell renal cell carcinoma demonstrates significant loss of chromosome 3p and gain of 5q
- Type 1 papillary renal cell carcinoma demonstrates gains of chromosomes 7 and 17
- Chromophobe renal cell carcinoma demonstrates a pattern of CIMP-RCC or the type 2 papillary renal cell carcinoma (PRCC2)
- Both demonstrated an increased loss of chromosome 22 that encodes NF2 from the HIPPO pathway and SMARCB1, a fundamental component of the SWI/SNF complex

Molecular alterations

- The CIMP-renal cell carcinoma had loss of chromosome 13q at a similar rate to ChRCC (60% versus 61.3%) that encodes RB1 and BRCA2 chromosomal losses that included 1, 2, 6, 10, 13, and 17
- CA IX abundantly expressed
- Inversely regulated by VHL wt

Molecular alterations

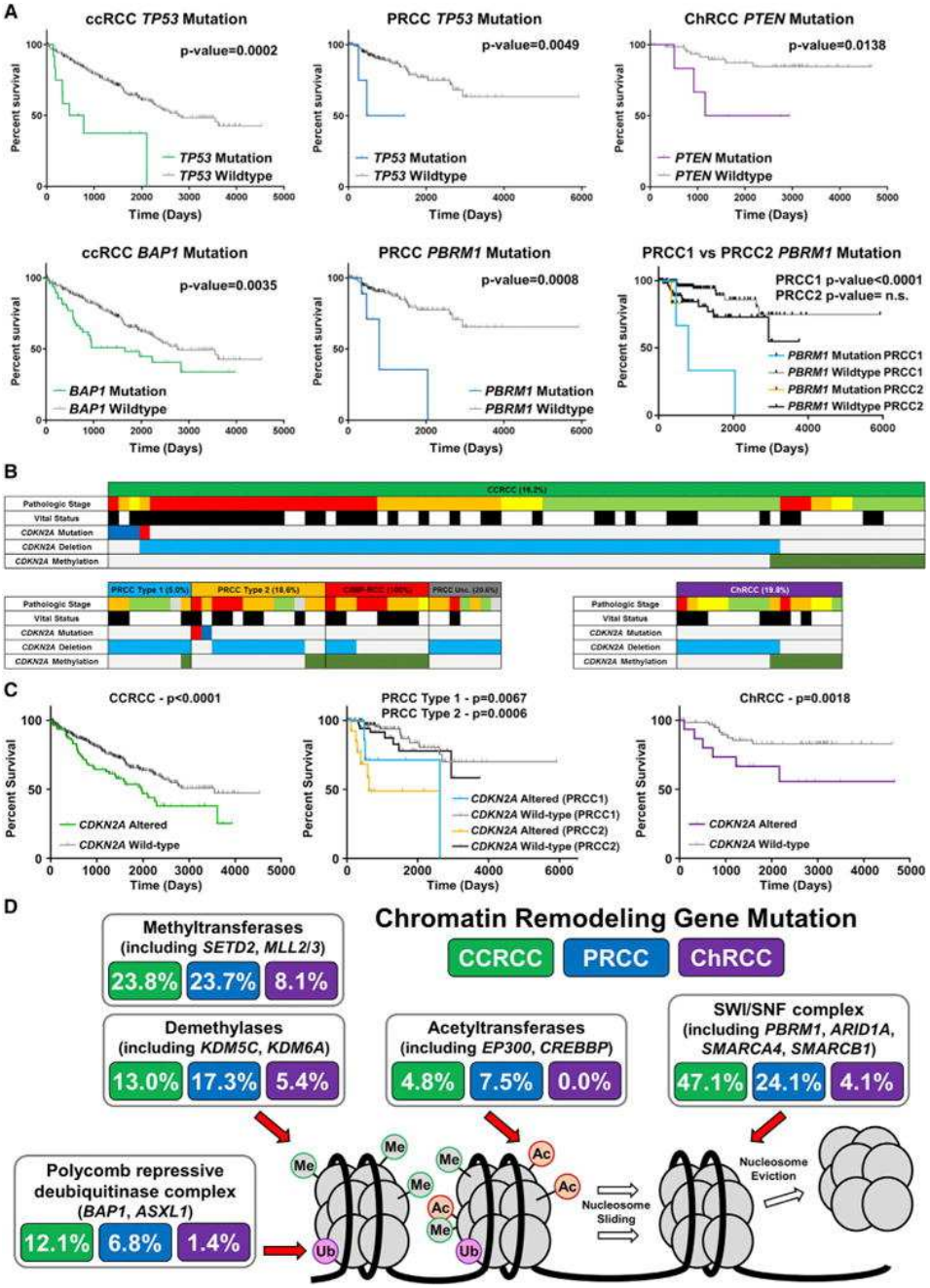
- Sarcomatoid and rhabdoid features may develop in any underlying Renal Cell carcinoma histology (papillary, clear cell, chromophobe) and have distinct molecular features such as BAP1 (3p21) and CDKN2A (9p21) mutations as well as heightened MYC transcriptional programs.
- Resistant to VEGF and mTTOR inhibitors, but respond to nivolumab plus ipilimumab
- Benefit regardless of PDL1 status
- CD8+ PD-1+ TIM3- LAG3-
- TILs stronest predictive biomarker
- Inhibition of PD-1 on Tregs may support immune suppression
- LOF mutation in PBMR1 in VEGF-TKI refractory setting has been linked to enhanced response to nivolumab

Molecular alterations

- 9p and 14q losses are drivers of metastatic spread
- 9p loss poor prognosis in urothelial cancer, not renal cell
- TREM2+ APOE+ C1Q+ macrophages as risk factor for disease recurrence following nephrectomy
- HLA-A*03 carriage respond better to TKI

Molecular alterations

- Genes associated with kidney morphogenesis and angiogenesis respond to nivolumab
- Genes associated with metabolic processes do not respond to nivolumab
- SLAMF7+PD-1+CD8+ population that expresses residency markers (ZNF683/HOBIT and ITGAE/CD103) resistant to nivolumab
- SMP in IL7 intron associated with adverse events in immune therapy



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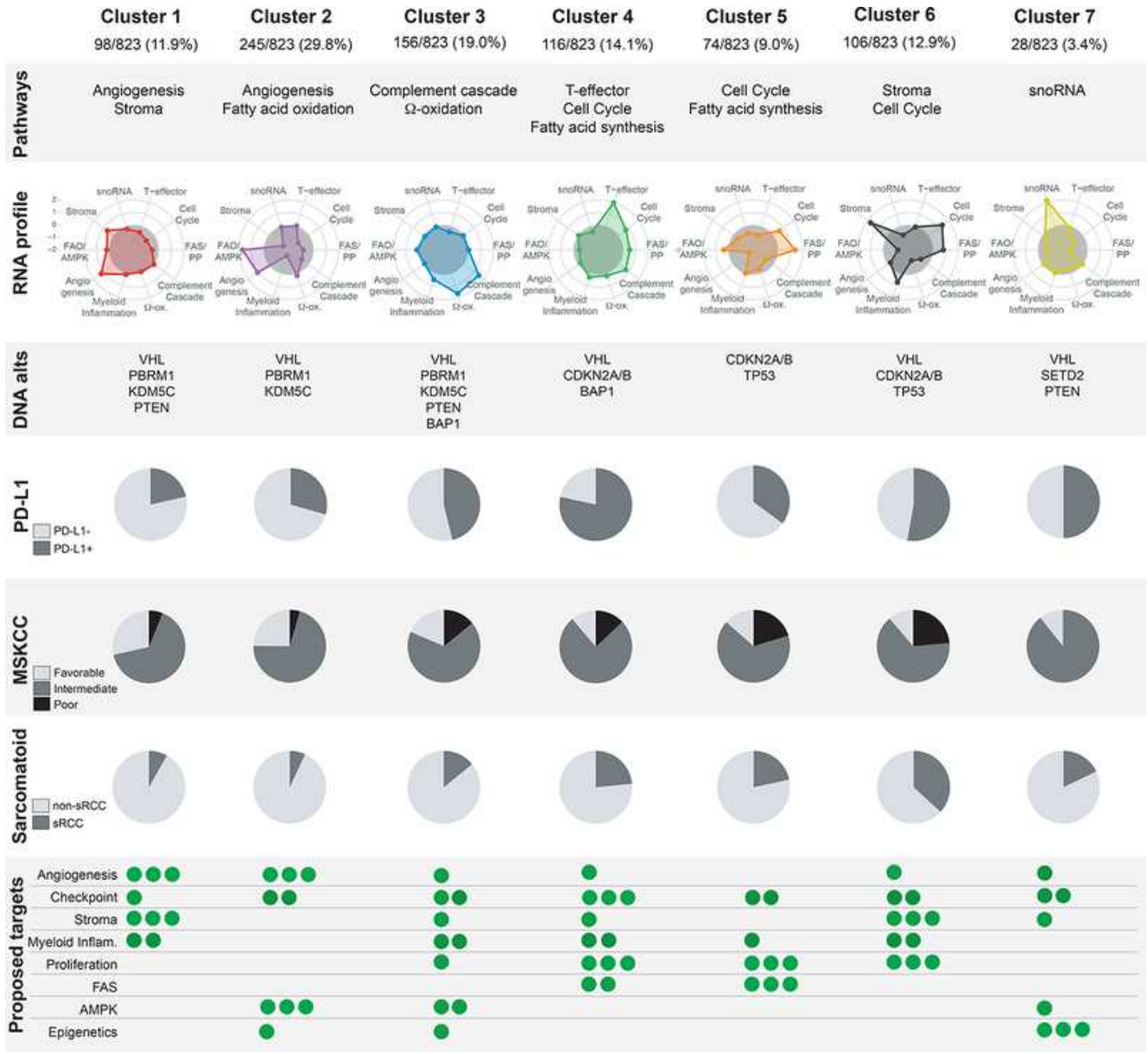
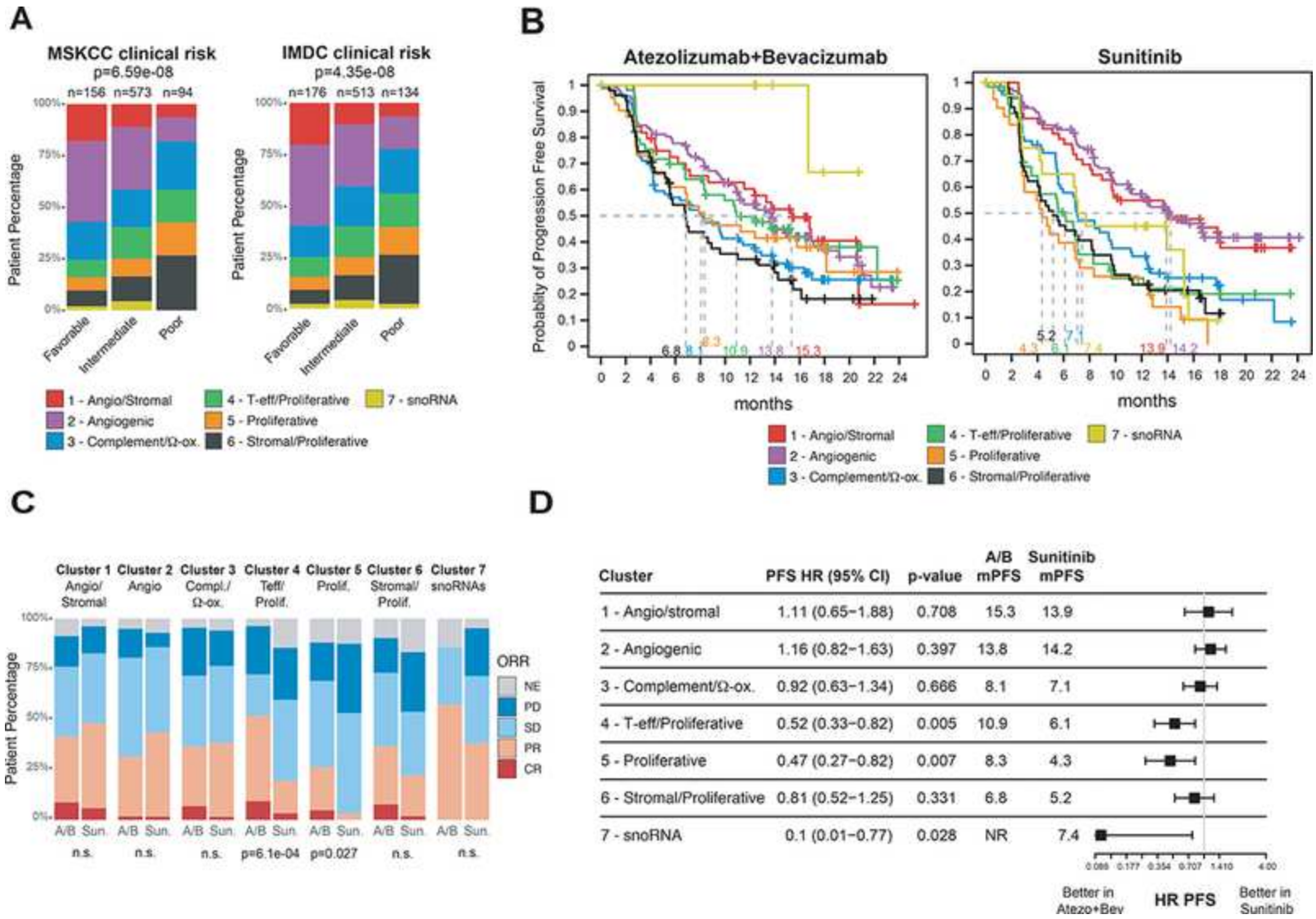


10.1016/j.ccell.2020.10.011



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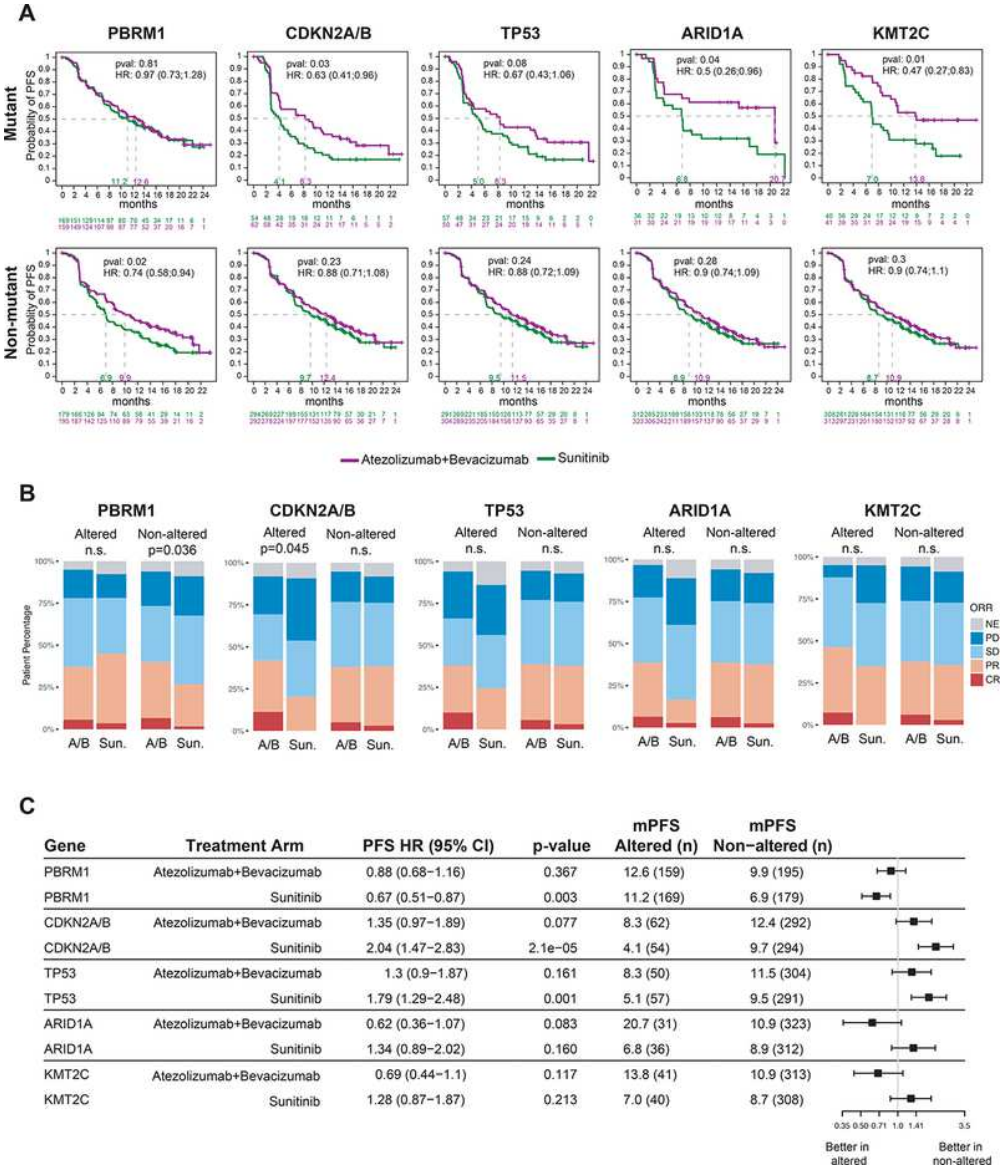


C

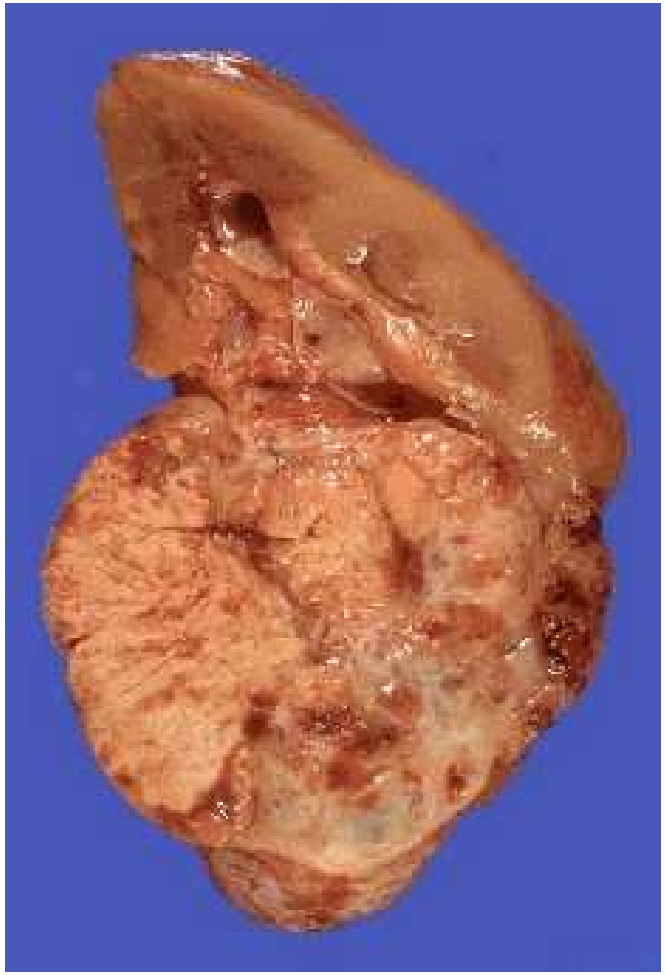
Gene	Treatment Arm	PFS HR (95% CI)	p-value	mPFS Altered (n)	mPFS Non−altered (n)
PBRM1	Atezolizumab+Bevacizumab	0.88 (0.68−1.16)	0.367	12.6 (159)	9.9 (195)
PBRM1	Sunitinib	0.67 (0.51−0.87)	0.003	11.2 (169)	6.9 (179)
CDKN2A/B	Atezolizumab+Bevacizumab	1.35 (0.97−1.89)	0.077	8.3 (62)	12.4 (292)
CDKN2A/B	Sunitinib	2.04 (1.47−2.83)	2.1e−05	4.1 (54)	9.7 (294)
TP53	Atezolizumab+Bevacizumab	1.3 (0.9−1.87)	0.161	8.3 (50)	11.5 (304)
TP53	Sunitinib	1.79 (1.29−2.48)	0.001	5.1 (57)	9.5 (291)
ARID1A	Atezolizumab+Bevacizumab	0.62 (0.36−1.07)	0.083	20.7 (31)	10.9 (323)
ARID1A	Sunitinib	1.34 (0.89−2.02)	0.160	6.8 (36)	8.9 (312)
KMT2C	Atezolizumab+Bevacizumab	0.69 (0.44−1.1)	0.117	13.8 (41)	10.9 (313)
KMT2C	Sunitinib	1.28 (0.87−1.87)	0.213	7.0 (40)	8.7 (308)

10.1016/j.ccell.2020.10.011

Renal cell carcinoma

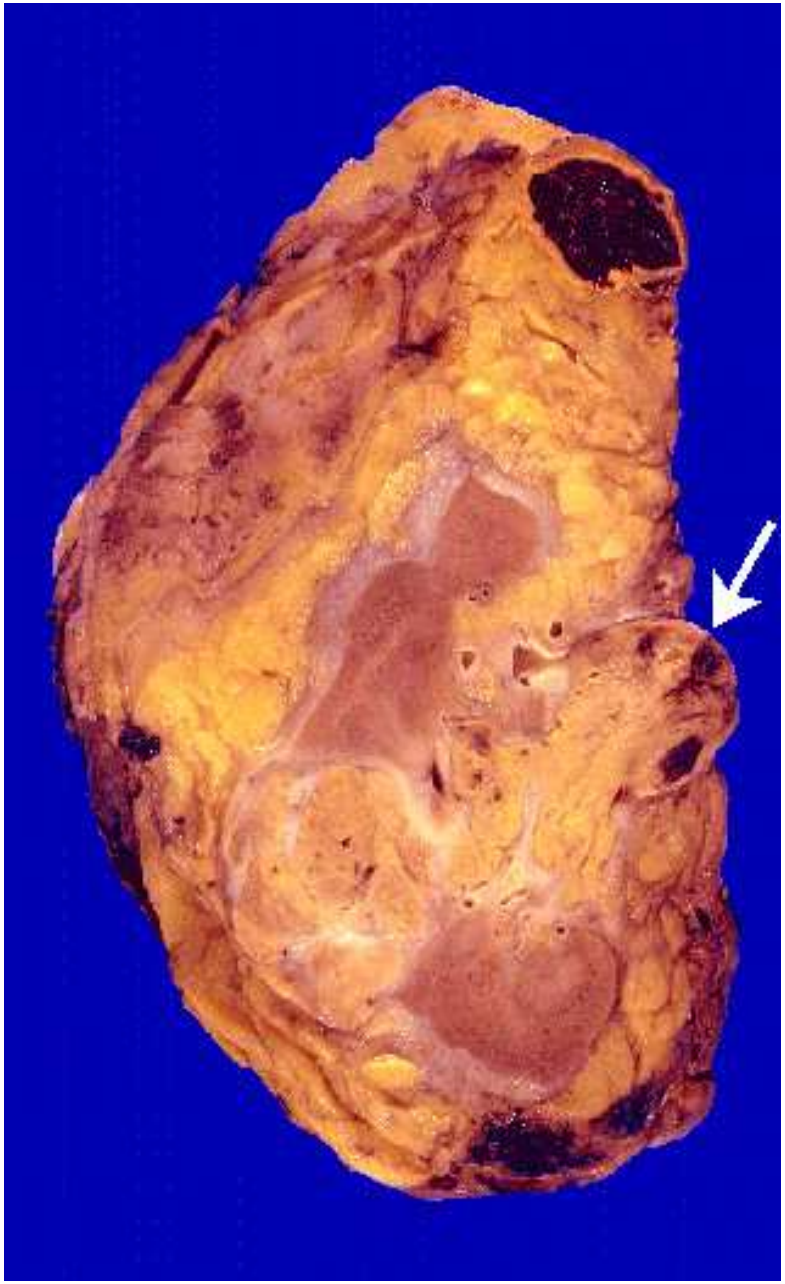
- Tumor is bright yellow as is rich in glycogen and lipids
- Larger tumors have areas of hemorrhage and necrosis
- Histology:
- Principal type is clear cell
- Round or polygonal cells with clear cytoplasm containing glycogen or lipid
- Transitional cell carcinoma 50% of cases in renal pelvis or ureter
- Squamous carcinoma is rare

Renal cell carcinoma



The tumor is fairly circumscribed. The cut surface demonstrates a variegated appearance with yellowish areas.

https://webpath.med.utah.edu/RENAHTML/RENAL062.html
Accessed 01/20/2020



Renal cell carcinoma

Renal vein invasion is shown here at the white arrow in a resected kidney surrounded by adipose tissue. Renal cell carcinomas may invade through the renal capsule. Renal cell carcinomas may metastasize to odd locations, and about a fourth of them first present as metastatic lesions.

https://webpath.med.utah.edu/RENAHTML/RENAL054.html

Accessed 01/20/2020

Renal cell carcinoma

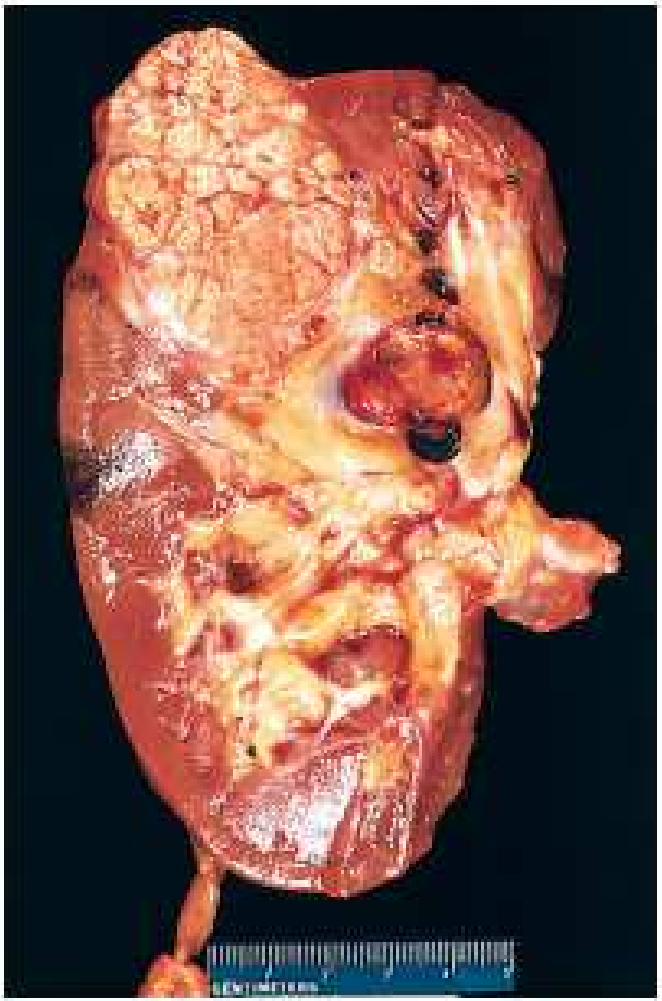


Figure 20.50 Renal cell carcinoma. Typical cross-section of yellowish, spherical neoplasm in one pole of the kidney. Note the tumor in the dilated thrombosed renal vein.

Renal cell carcinoma

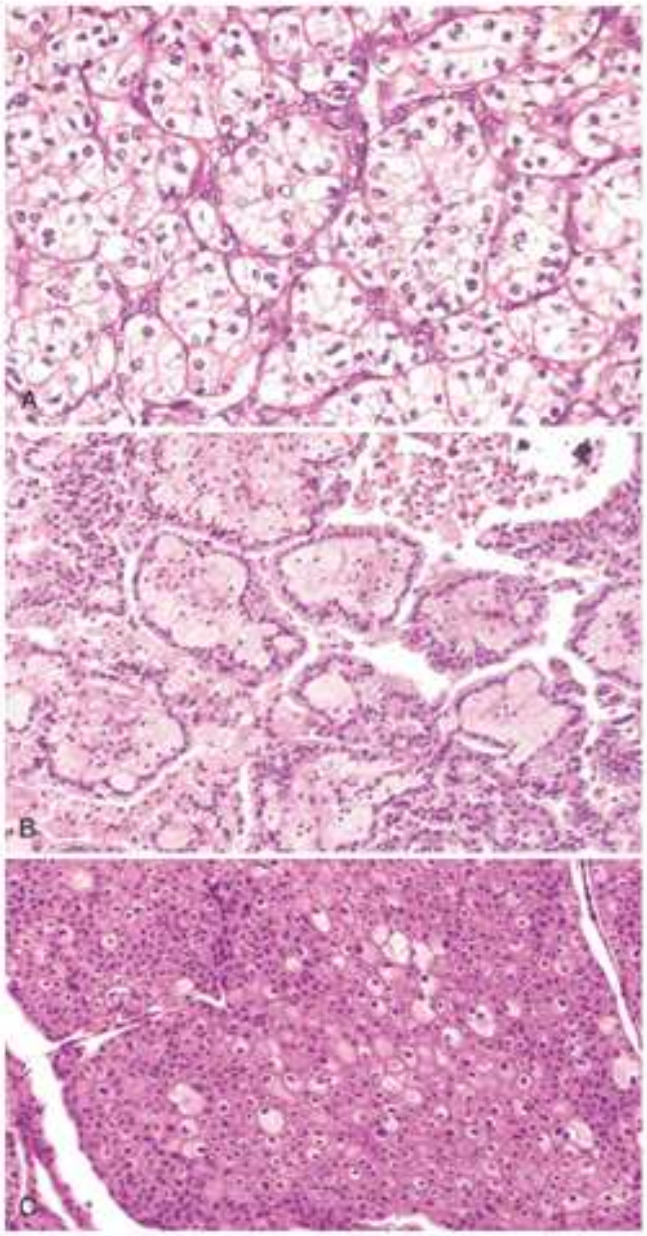
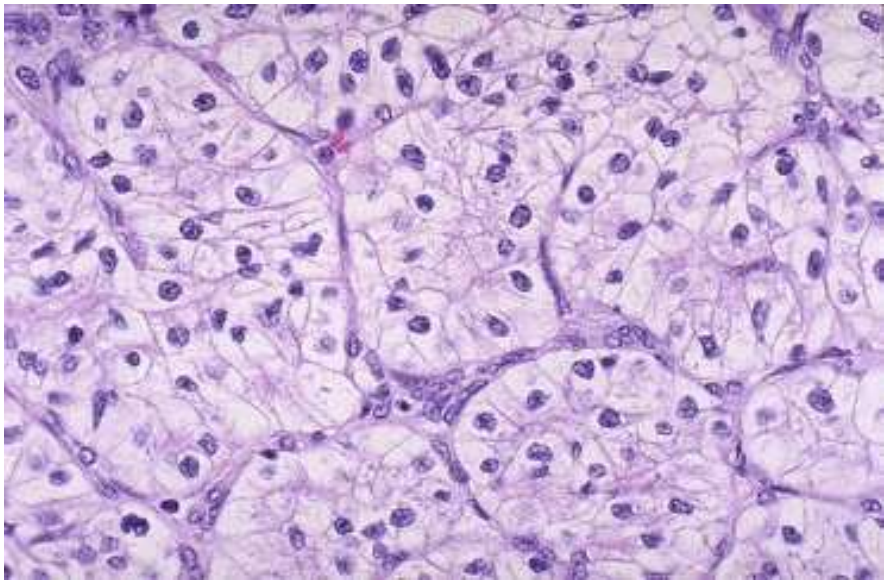
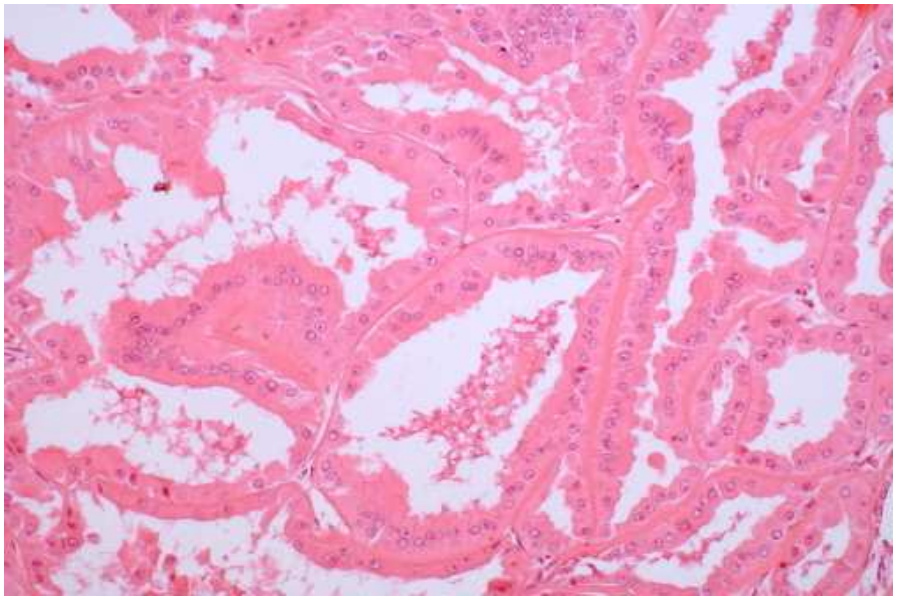


Figure 20.51 Renal cell carcinoma. (A) Clear cell type. (B) Papillary type. Note the papillae and foamy macrophages in the stalk. (C) Chromophobe type. (Courtesy Dr. A. Renshaw, Baptist Hospital, Miami, Fla.)

Renal cell carcinoma





Left: This is the classic clear cell histologic appearance of a renal cell carcinoma (clear cell carcinoma). The neoplastic cells have clear cytoplasm and are arranged in nests with intervening blood vessels. Mutation of the VHL gene may be found. Right: The less common papillary variant of renal cell carcinoma is shown below. Note the eosinophilic cytoplasm. Mutation of the MET gene may be present.
https://webpath.med.utah.edu/RENAHTML/RENAL055.html Accessed 01/20/2020

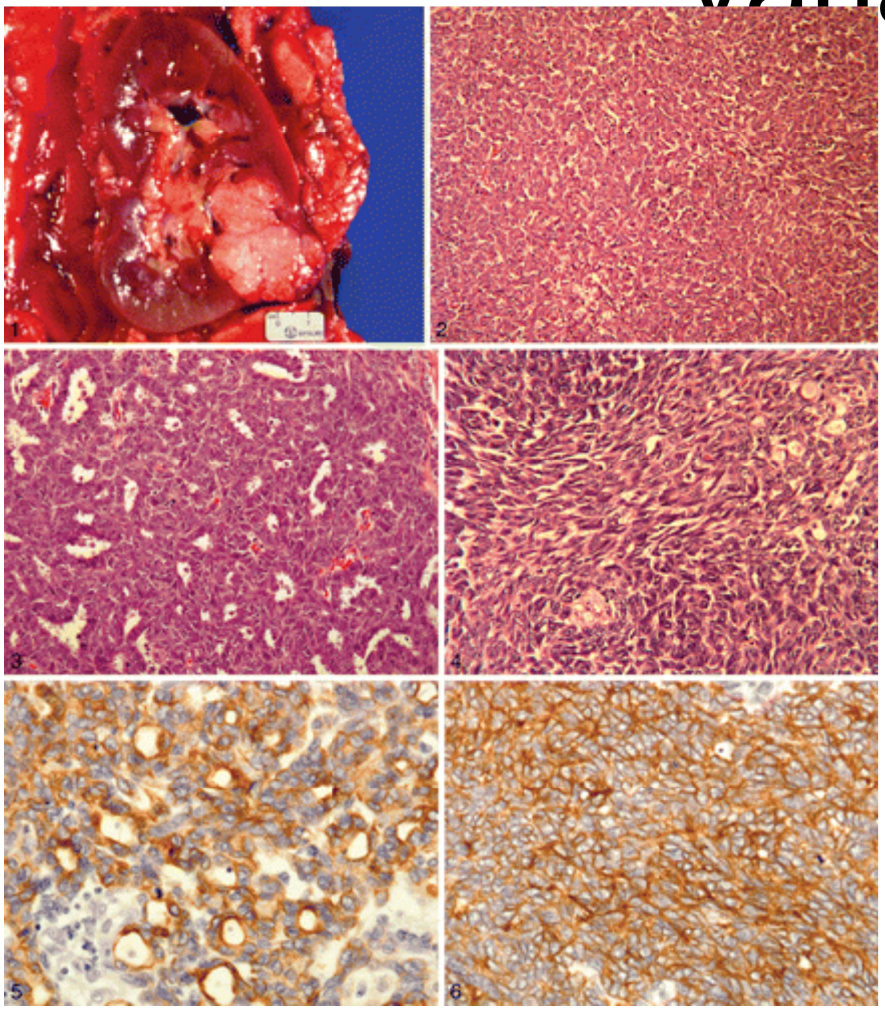
Renal cell carcinoma
solid variant

- 3% of renal cell carcinomas
- Morphologically similar to Type 1 papillary renal carcinoma but lack true papillae containing fibrovascular cores
- Solid sheets of cells, often with distinct micronodules resembling abortive papillae or glomeruloid bodies
- Surrounded by a pseudocapsule

Renal cell carcinoma
solid variant

- Cells have scant to abundant clear, basophilic or eosinophilic cytoplasm
- Nuclei may have nucleoli or nuclear grooves
- May have compact areas of low grade spindle cells lining thin, angulated tubules
- No mucinous stroma
- May have foamy macrophages, psammoma bodies

Renal cell carcinoma solid variant



https://www.archivesofpathology.org/action/showFullPopup?id=i1543-2165-134-8-1210-f01&doi=10.1043%2F2009-0464-CR.1

Accessed 02/20/2020

Figure 1. Gross photograph showing a solid, firm, tan tumor protruding from the renal cortex as a solitary, rounded mass. The tumor interface is well demarcated; the tumor abuts the renal pelvis.

Figure 2. Solid sheets of cells (hematoxylin-eosin, original magnification ×100).

Figure 3. An ill-defined tubular pattern, while in Figure 4, a spindle cell component is seen. (hematoxylin-eosin, original magnification ×400).

Figure 5 and Figure 6. Spindled neoplastic cells are diffusely immunoreactive to cytokeratin 8/18. (original magnification ×400).

Renal cell carcinoma

- Collecting duct neoplasms are rare
- 80% are clear cell carcinomas
- Arise from proximal tubular epithelium
- Sporadic
- LOH 1q, 6p, 13q, 14, 15, 21q, and 22
- del 9 has poor prognosis.
- Consequence of loss of VHL gene (3p25) is disruption of ubiquitin ligase complex.
- Second VHL allele hyper-methylated in 80% of cases of renal carcinoma.

Renal cell carcinoma

- Most common type
- Bright yellow-gray-white masses
- Rounded or polygonal cells with clear or granular cytoplasm which contains glycogen and lipids
- Tend to invade renal vein

Renal cell carcinoma

- Chromophobe tumors account for fewer than 5% of renal neoplasms
- Arise from intercalated cells of collecting ducts
- Composed of cells with prominent cell membranes and pale eosinophilic cytoplasm
- Perinuclear halo common
- Largest cells found arranged about vessels
- Hypodiploid
- 11% bilateral, 22% multifocal

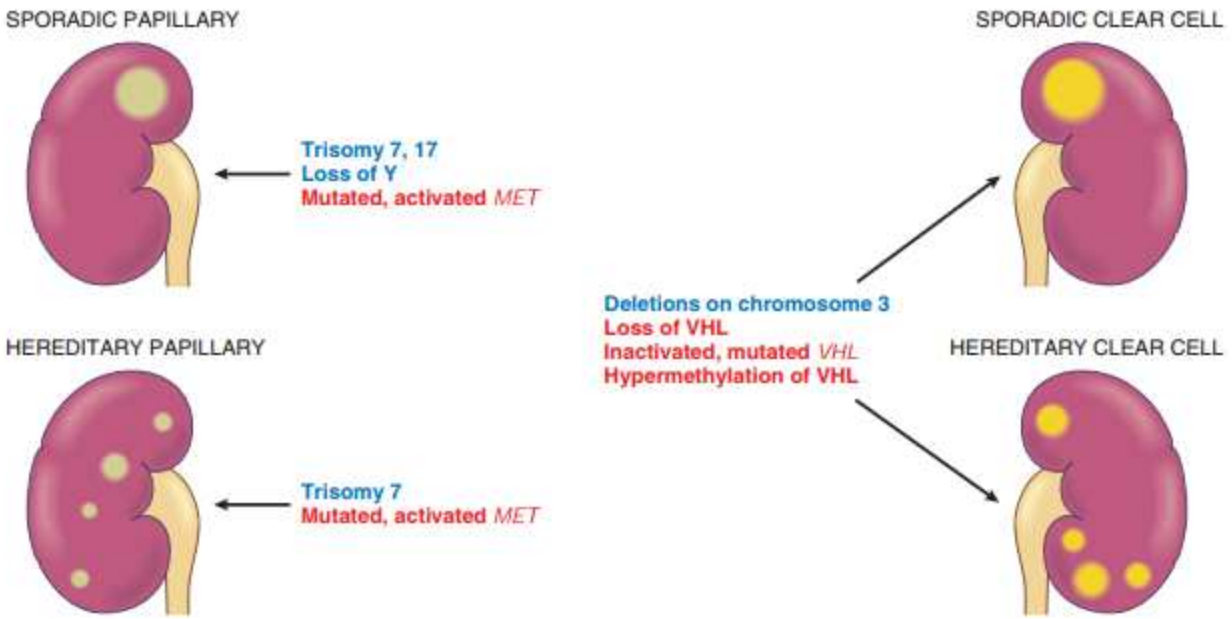


Figure 20.49 Cytogenetics *(blue)* and genetics *(red)* of clear cell versus papillary renal cell carcinoma. (Courtesy Dr. Keith Ligon, Brigham and Women's Hospital, Boston, Mass.)

Other cancers

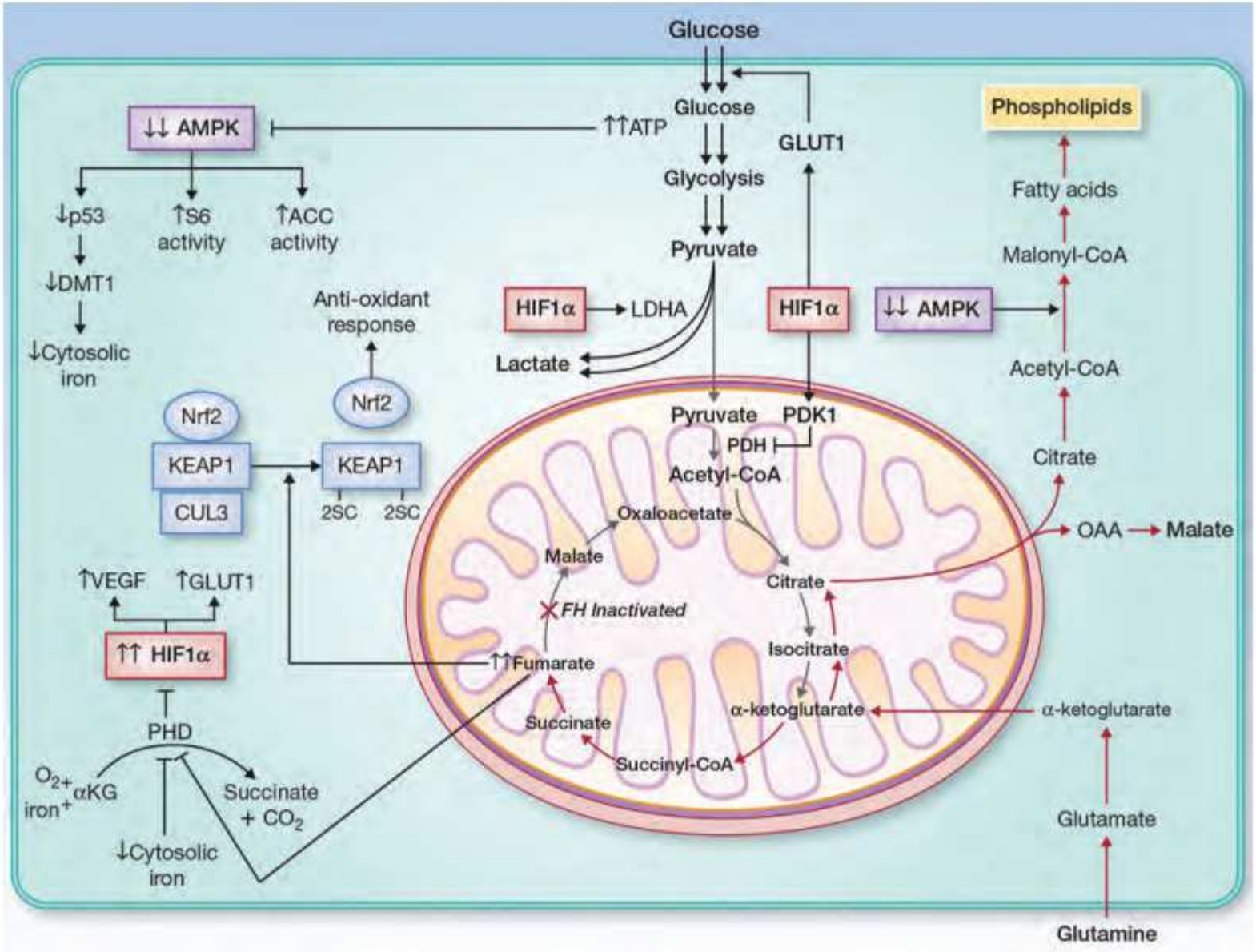
- Xp11 translocation carcinoma
- Young patients
- TFE3 translocations at Xp11.2
- Leucine zipper transcription factor
- Five fusion factors identified
- Clear cytoplasm with a papillary architecture
- Bellini (collecting duct) carcinoma
- 1% of cancers
- Arise from medullary collecting duct cells
- Irregular channels lined by atypical epithelium with hobnail pattern enmeshed in fibrous stroma
- Sarcomatous change is poor prognostic sign

Renal cell carcinoma

- Von Hippel-Lindau disease
- Bilateral
- Younger adults
- Autosomal dominant
- Inactivation of VHL gene
- Increased risk of developing hemangioblastoma
- Increased risk of developing pheochromocytoma
- Not in papillary carcinoma

Renal carcinoma

- HIF accumulates as under normal oxygen conditions.
- The VHL complex targets these factors for ubiquination:
- HIF-1α, poor prognosis
- HIF-2α, more favorable prognosis
- IL-4 and IL-13 share IL-4R chain in their structure.
- Stimulate IgE production
- Mediate antigen stimulated T-cell activity.
- Mutation associated with propensity to renal cancer.


Glucose
Glucose
↓↓ AMPK
↑↑ATP
GLUT1
Glycolysis
Pyruvate
Phospholipids
Fatty acids
Malonyl-CoA
↓p53
↑S6 activity
↑ACC activity
↓DMT1
↓Cytosolic iron
Anti-oxidant response
HIF1α
LDHA
Lactate
HIF1α
↓↓ AMPK
Acetyl-CoA
Nrf2
Nrf2
KEAP1
KEAP1
CUL3
2SC
2SC
Pyruvate
PDK1
PDH
Acetyl-CoA
Citrate
Oxaloacetate
OAA
Malate
Malate
Citrate
FH Inactivated
↑VEGF
↑GLUT1
↑↑ HIF1α
↑↑Fumarate
Isocitrate
α-ketoglutarate
α-ketoglutarate
PHD
Succinate
Succinyl-CoA
O2+ iron+ αKG
Succinate + CO2
↓Cytosolic iron
Glutamate
Glutamine

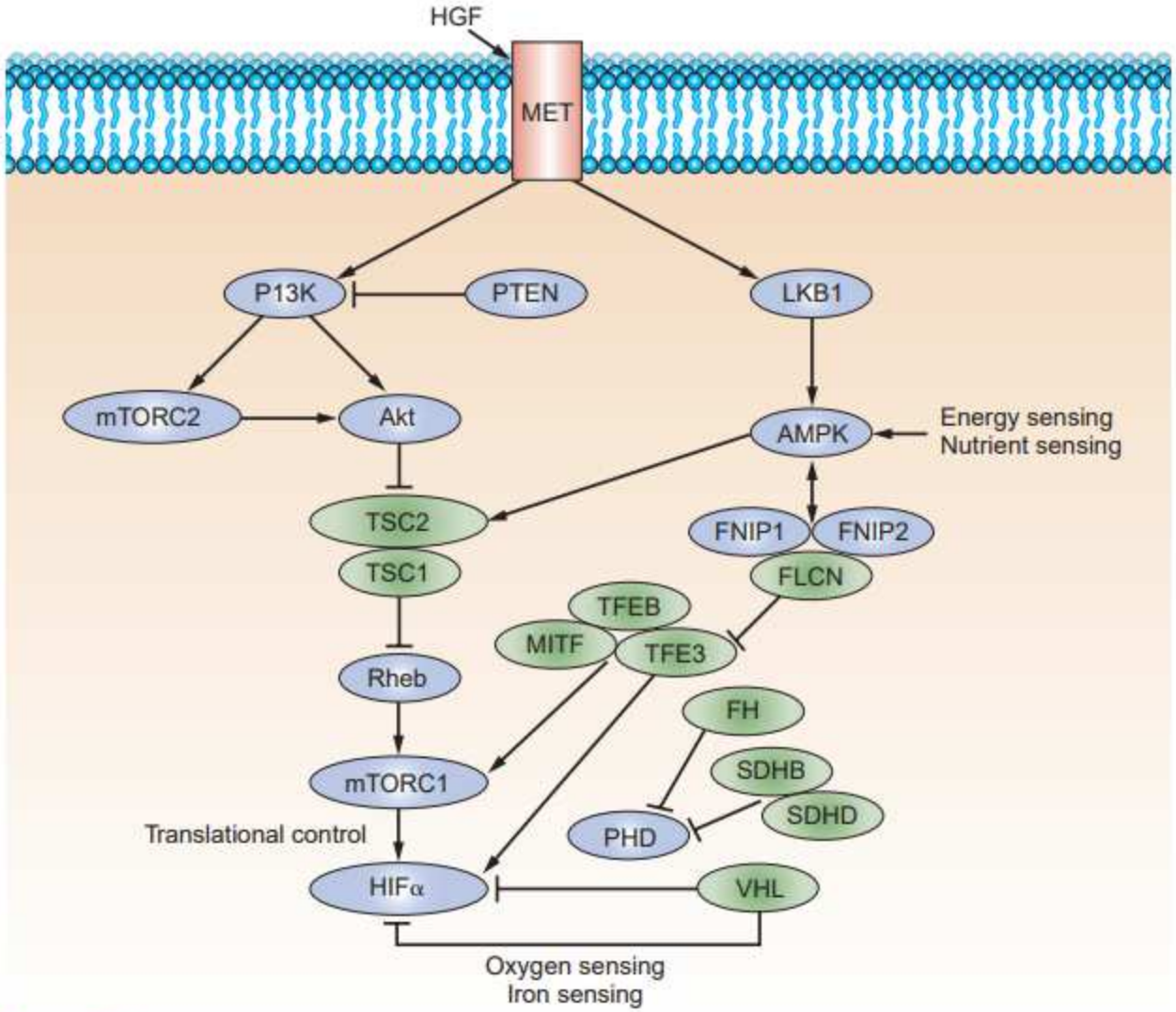


Figure 62.4 The genetic basis of kidney cancer. Twelve renal cancer predisposing genes—*VHL, MET, FLCN, TFE3, TFEB, MITF, TSC1, TSC2, PTEN, FH, SDHB,* and *SDHD*— have been identified mainly through studies of inherited kidney cancer syndromes. These genes interact through common oxygen, iron, nutrient, and energy sensing pathways and demonstrate that kidney cancer is fundamentally a metabolic disease. Our understanding of the molecular mechanisms by which these genes interact in these pathways has enabled the development of targeted therapeutic agents to benefit kidney cancer patients. (From Linehan WM, Ricketts CJ. The metabolic basis of kidney cancer. *Semin Cancer Biol* 2013;23:46–55.)

TABLE 63.1

2004 World Health Organization Classification of Sporadic Renal Cell Carcinoma with Genetic and Clinical Correlates

Type	Genetics	Clinical
ccRCC (70% to 80%)	Deletion, mutation or methylation of 3p25-26 (*VHL*)	Most common variant Prognosis predicted by stage and grade
Multilocular cystic ccRCC (uncommon)	Deletion, mutation, or methylation of 3p25-26 (*VHL*)	Variant of ccRCC Distant metastases uncommon
Papillary RCC (10% to 15%)	Gain of 7 or 17 (trisomy or tetrasomy), loss of Y, deletion of 9p. Mutations of 7q31 when associated with hereditary papillary RCC	10% to 15% of RCC 95%+ 5-year cancer-specific survival in type I papillary RCC Response to tyrosine-kinase inhibitors less robust
Chromophobe RCC (3% to 5%)	Extensive chromosomal loss of Y, 1, 2, 6, 10, 13, 17, 21 Mutations of 17p11.2 when associated with BHD	5% of RCC Affects men and women equally with overall excellent prognosis
Collecting duct carcinoma (Bellini tumor) (<1%)	Highly variable Losses of 1q, 6p, 8p, 9p, 13q, 19q, 21q	Male preponderance (2:1) Mean age 55 Microscopically high grade, may resemble urothelial spectrum of cancers, Overall poor prognosis
Renal medullary carcinoma (rare)	Not defined	Associated with sickle cell trait Aggressive and lethal within 12 mo Mean age 19 y Male>female
Xp11 translocation carcinoma (rare)	Translocation of TFE3 gene on XP11.2	Children and young adults May present at advanced state and act more aggressively in adults
Renal carcinoma associated with neuroblastoma (rare)	Not defined	Morphologically and microscopically similar to ccRCC
Mucinous tubular and spindle cell carcinoma (rare)	Not defined	Female preponderance (4:1) Rarely metastasize
Unclassified RCC (1% to 3%)	Varied	Generally poor prognosis

ccRCC, clear cell renal cell carcinoma; RCC, renal cell carcinoma.

Adapted from Deng FM, Melamed J, Zhou M. Pathology of renal cell carcinoma. In: Libertino JA, ed. In *Renal Cancer: Contemporary Management*. New York: Springer; 2013:51–69.

Renal cell carcinoma

- VEGFα (6p12), PDGFβ (5q33) production stimulated (angiogenesis);
- CAIX (9p12), CAXII (15q22) stimulated (pH regulation through carbonic anhydrase);
- Erythropoietin (7q22), glut-1 (1p34) stimulated;
- TGF-α (2p13), TGF-β (19p13), IGF1 (12q23), EFGR (7p12) stimulated, leading to autocrine growth;
- CXRC4 (2q21) stimulated (associated with metastatic potential).
- All are downstream targets of HIF.

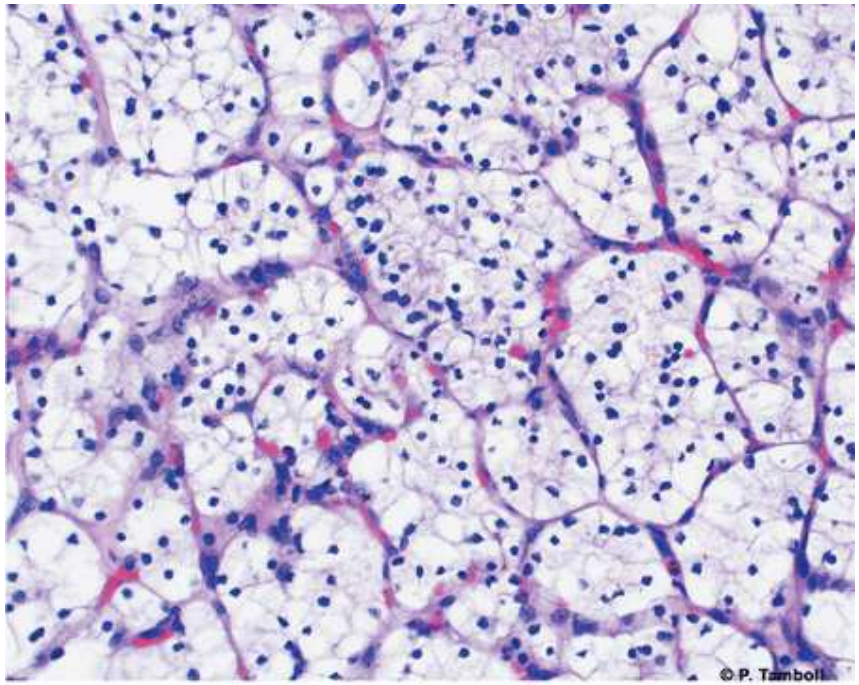
Papillary carcinoma

- 10-15% of renal cancers
- Frequently multifocal in origin
- Arise from distal collecting tubules
- Cuboidal or columnar cells in papillary configuration. Interstitial foam cells common in papillary cores. May find Psammoma bodie.
- Trisomy 7 or 17 or loss of Y chromosome in sporadic cases
- Trisomy 7 in familial cases
- MET activation (Hepatocyte growth factor)

Renal carcinoma

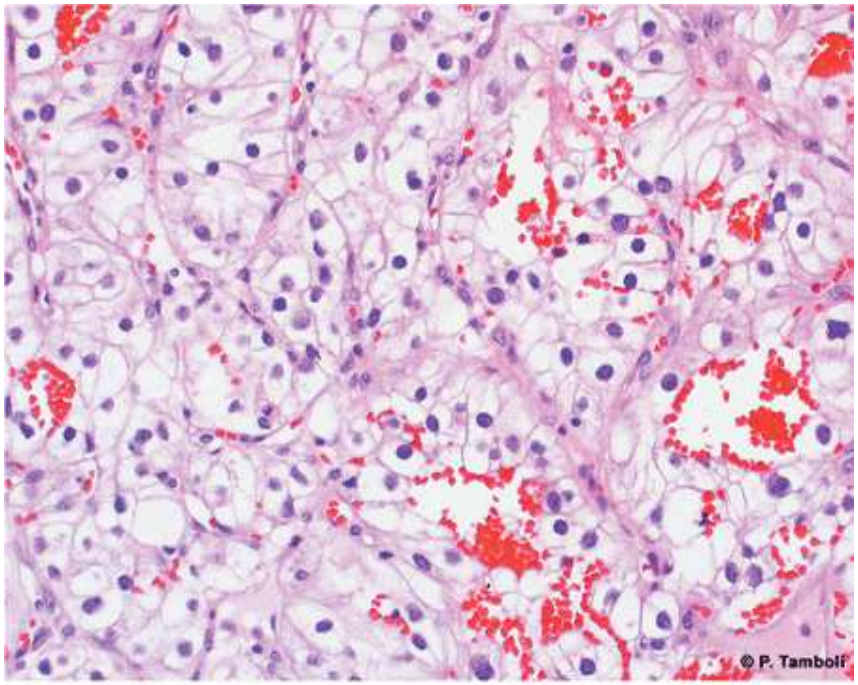
- Papillary adenocarcinomas constitute 10% of renal cancers.
- Arise from intercalated cells of ductal cells.
- Bilateral, multifocal papillary tumors type I
- Associated with:
- Trisomy 7 (familial form)
- C-MET gene (7q31) encodes tyrosine kinase receptor for hepatocyte growth factor.
- (Hypoxia upregulates MET gene normally.)
- del Y (male associated)
- Trisomy 16
- Trisomy 17.

Renal cell papillary carcinoma Type 1



A

Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com



B

Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Photomicrographs of clear cell (conventional) RCC with low-grade nuclear features (A) and high-grade nuclear features (B).

(Reprinted by permission from Pheroze Tamboli, MD.)

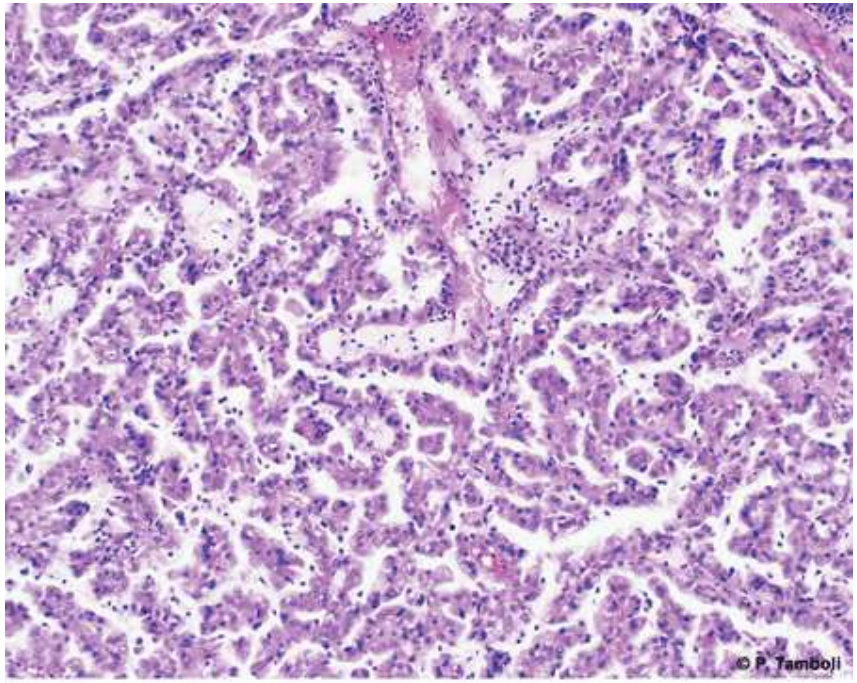
Fig. 29-1 Accessed 08/01/2010

Renal carcinoma

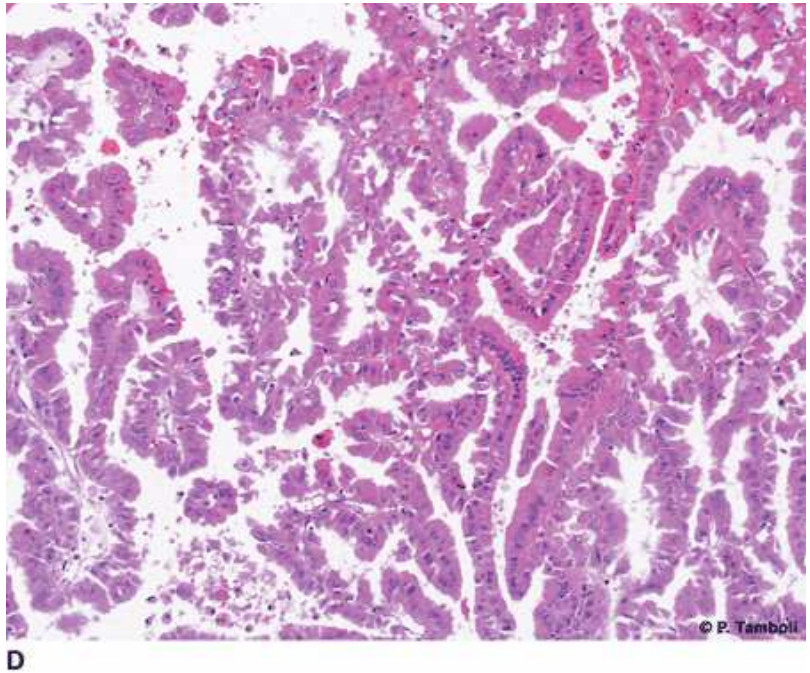
- Bilateral, multifocal papillary tumors type II
- Mutation in fumarate hydratase gene (1q42)
- Deranges mitochondrial conversion of fumarate to malate.
- Hypoxia results (HIF upregulated).
- Papillae lined by tall columnar cells found in tumor.

- Spindle cell renal cell carcinoma is not associated with leiomyoma, rhabdomyoma, or squamous differentiation.

Renal cell carcinoma



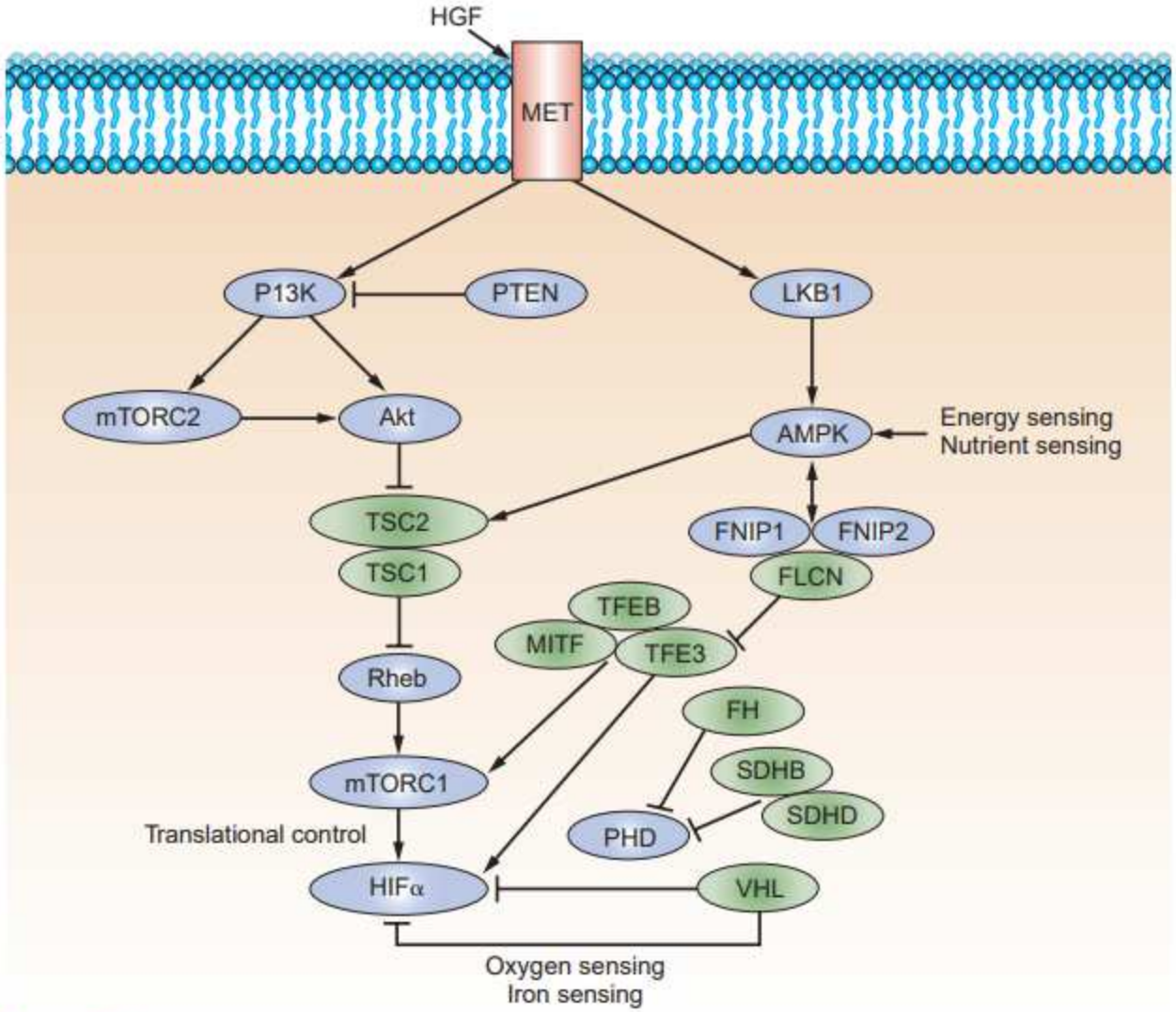
C



D

Photomicrographs of clear cell (conventional) RCC showing papillae lined by short cuboidal cells (C), and type 2 papillary RCC showing papillae lined by tall columnar cells, with eosinophilic cytoplasm and high grade nuclear features (D).

(Reprinted by permission from Pheroze Tamboli, MD.) Fig. 29-1 Accessed 08/01/2010



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Mucinous tubular and spindle cell carcinoma (rare)	Not defined	Female preponderance (4:1) Rarely metastasize
Unclassified RCC (1% to 3%)	Varied	Generally poor prognosis

ccRCC, clear cell renal cell carcinoma; RCC, renal cell carcinoma.

Adapted from Deng FM, Melamed J, Zhou M. Pathology of renal cell carcinoma. In: Libertino JA, ed. In *Renal Cancer: Contemporary Management.* New York: Springer; 2013:51–69.

- An individual with a close blood relative[b] with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene

- An individual with RCC with any of the following criteria:
  - Diagnosed at age ≤46 y
  - Bilateral or multifocal tumors
  - ≥1 first- or second-degree relative[b] with RCC

- An individual whose tumors have the following histologic characteristics:
  - Multifocal papillary histology
  - Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)-associated RCC, RCC with fumarate hydratase (FH) deficiency or other histologic features associated with HLRCC
  - Birt-Hogg-Dubé syndrome (BHDS)-related histology (multiple chromophobe, oncocytoma, or oncocytic hybrid)
  - Angiomyolipomas of the kidney and one additional tuberous sclerosis complex criterion in the same person (See Table 1)
  - Succinate dehydrogenase (SDH)-deficient RCC histology[c]

https://www.nccn.org/professionals/physician_gls/pdf/kidney_blocks.pdf
Accessed 03/17/2021

TABLE 62.1

Hereditary Renal Cancer Syndromes

Syndrome	Chromosome Location	Predisposing Gene	Histology	Frequency of Gene Mutations	
				Germ Line	Sporadic RCC
Von Hippel-Lindau (VHL) disease	3p25	*VHL*	Clear cell	100%[14]	92%[22]
Hereditary papillary renal carcinoma type 1 (HPRC)	7q31	*MET*	Type 1 papillary	100%[6,41,42]	13%[45]
Birt-Hogg-Dubé syndrome (BHD)	17p11.2	*FLCN*	Chromophobe, hybrid	90%[65]	11%[76]
Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)	1q42–43	*FH*	Type 2 papillary	93%[105]	TBD
Succinate dehydrogenase (SDH)–associated familial renal cancer	1p35–36 1q23.3 11q23	*SDHB* *SDHC* *SDHD*	Clear cell, chromophobe, oncocytic neoplasm	TBD	TBD
Tuberous sclerosis complex (TSC)	9q34 16p13.3	*TSC1* *TSC2*	Angiomyolipoma, all histologies	80%–90%	TBD

TBD, to be determined.

TABLE 63.3

Familial Renal Cell Carcinoma Syndromes

Syndrome	Gene (Chromosome)	Major Clinical Manifestations
von Hippel-Lindau	*VHL* gene (3p25-26)	Clear cell RCC Retinal angiomas Central nervous system hemangioblastomas Pheochromocytoma Other tumors
Hereditary papillary RCC	*c-met* proto-oncogene (7q31)	Multiple, bilateral type 1 papillary RCCs
Familial leiomyomatosis and RCC	*Fumarate hydratase* (1q42-43)	Type 2 papillary RCC Collecting duct RCC Leiomyomas of skin or uterus Uterine leiomyosarcomas
Birt-Hogg-Dubé	*Folliculin* (17p11)	Multiple chromophobe RCC, hybrid oncocytic tumor, oncocytomas Occasional clear cell (occasionally) Papillary RCC (occasionally) Facial fibrofolliculomas Lung cysts Spontaneous pneumothorax
Succinate dehydrogenase RCC	Succinate dehydrogenase complex subunits: *SDHB* (1p36.1-35) or *SDHD* (11q23)	Chromophobe, clear cell, type 2 papillary RCC, oncocytoma Paragangliomas (benign and malignant) Papillary thyroid carcinoma
Tuberous sclerosis	*TSC1* (9q34) or *TSC2* (16p13)	Multiple renal angiomyolipomas Clear cell RCC (occasionally) Renal cysts/polycystic kidney disease Cutaneous angiofibromas Pulmonary lymphangiomyomatosis
PTEN hamartoma tumor syndrome (Cowden syndrome)	*PTEN* (10q23)	Breast tumors (malignant and benign) Epithelial thyroid carcinoma Papillary RCC or other histology

PTEN, phosphatase and tensin homolog; RCC, renal cell carcinoma.
Adapted from Linehan WM, Walther MM, Zbar B. The genetic basis of cancer of the kidney. *J Urol* 2003; 170(6 Pt 1):2163-2172. and Linehan WM, Ricketts CJ. The metabolic basis of kidney cancer. *Semin Cancer Biol* 2013;23:46–55.

HEREDITARY RCC SYNDROMES OVERVIEW

Syndrome/Gene	Histology	Inheritance Pattern Major Clinical Manifestations
von Hippel-Lindau (VHL)/ *VHL* gene	Clear cell	• Autosomal dominant • See Table 2
Hereditary papillary renal carcinoma (HPRC)/*MET* gene	Type 1 papillary	• Autosomal dominant • Multifocal, bilateral renal cell tumors
Birt-Hogg-Dubé syndrome (BHDS)/*FLCN* gene[d,e]	Chromophobe, hybrid oncocytoma	• Autosomal dominant • Cutaneous fibrofolliculoma or trichodiscoma, pulmonary cysts, and spontaneous pneumothorax
Tuberous sclerosis complex (TSC)/*TSC1*, *TSC2* genes	Angiomyolipoma, clear cell	• Autosomal dominant • See Table 1
Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)/*FH* gene	HLRCC or FH-associated RCC/ type 2 papillary	• Autosomal dominant • Leiomyomas of skin and uterus, unilateral, solitary, and aggressive renal cell tumors. PET-positive adrenal adenomas
BAP1 tumor predisposition syndrome (TPDS)/*BAP1* gene[f,g]	Clear cell, chromophobe	• Autosomal dominant • Melanoma (uveal and cutaneous), kidney cancer, mesothelioma
Hereditary paraganglioma/ pheochromocytoma (PGL/ PCC) syndrome/*SDHA/B/ C/D* genes	Clear cell (not usually *SDHB*), chromophobe, papillary type 2, renal oncocytoma, oncocytic neoplasm	• Autosomal dominant • Head and neck paraganglioma and adrenal or extra-adrenal pheochromocytomas, benign lung lesions, GIST tumors

https://www.nccn.org/professionals/physician_gls/pdf/kidney_blocks.pdf
Accessed 03/17/2021

Table 1: Features of Tuberous Sclerosis (TSC)

Major Features	Minor Features
• Renal angiomyolipoma (AML)[1,2] • Cardiac rhabdomyoma • Cortical dysplasias, including tubers and cerebral white matter migration lines • Angiofibromas (≥3) or fibrous cephalic plaque • Hypomelanotic macules (3 to >5 mm in diameter) • Lymphangioleiomyomatosis (LAM)[1] • Multiple retinal nodular hamartomas • Shagreen patch • Subependymal giant cell astrocytoma (SEGA) • Subependymal nodules (SENs) • Ungual fibromas (≥2)	• Multiple renal cysts • "Confetti" skin lesions (numerous 1- to 3-mm hypopigmented macules scattered over regions of the body such as the arms and legs) • Dental enamel pits (>3) • Intraoral fibromas (≥2) • Nonrenal hamartomas • Retinal achromic patch

Table 2: Features of Von Hippel-Lindau (VHL) Disease

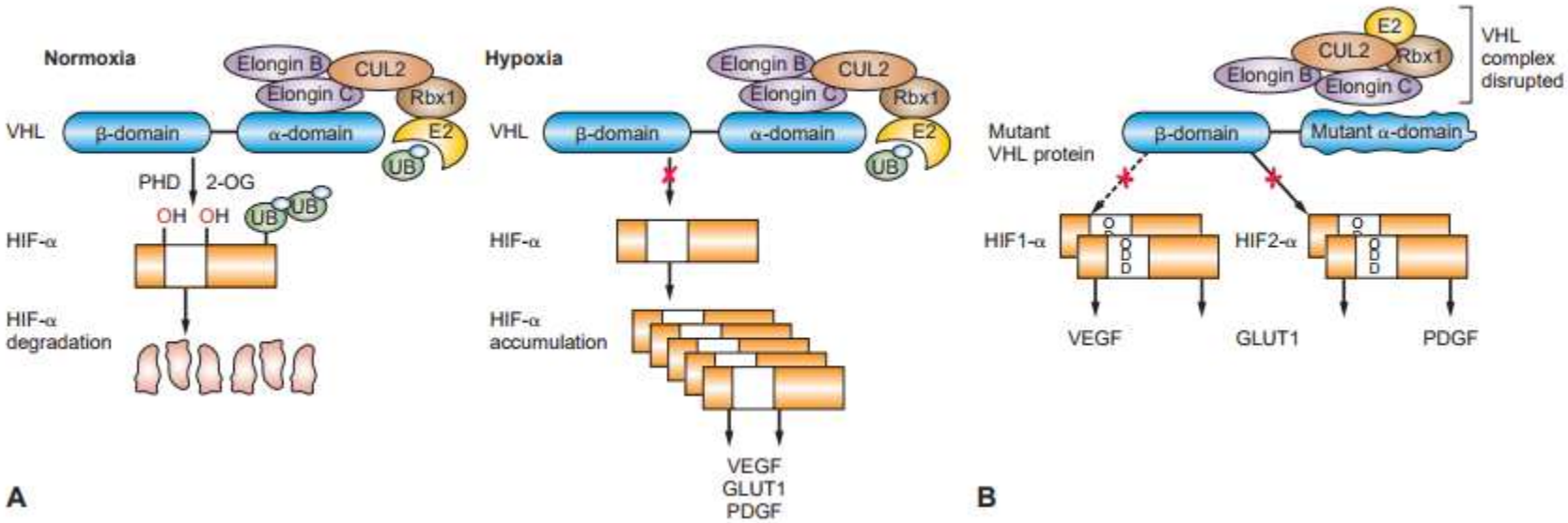
Major Features	Minor Features
• Hemangioblastomas of the retina, spine, or brain • Clear cell RCC (ccRCC) diagnosed <40 years of age or multiple/bilateral ccRCC tumors diagnosed at any age • Adrenal or paraganglioma • Paraganglioma of abdomen, thorax, or neck • Retinal angiomas	• Endolymphatic sac tumors • Papillary cystadenomas of the epididymis or broad ligament • Pancreatic serous cystadenoma (>1) • Pancreatic neuroendocrine tumor or multiple pancreatic cysts (>1)

[1] The combination of AML and LAM does not meet criteria for definite diagnosis.
[2] Multiple AMLs are a major feature.

https://www.nccn.org/professionals/physician_gls/pdf/kidney_blocks.pdf
Accessed 03/17/2021

Familial variants

- Von-Hippel Lindau syndrome
- VHL gene at 3p25.3 is lost
- Encodes E3 ubiquitin ligase
- HIF elevated in normoxic conditions
- Promotes angiogenesis
- With MYC, promotes cell growth
- Renal cysts and multiple renal cell carcinomas
- Nearly all will develop carcinomas over time


Normoxia
Elongin B
CUL2
Elongin C
Rbx1
VHL
β-domain
α-domain
E2
UB
PHD
2-OG
OH
OH
UB
UB
HIF-α
HIF-α
degradation
Hypoxia
Elongin B
CUL2
Elongin C
Rbx1
VHL
β-domain
α-domain
E2
UB
HIF-α
HIF-α
accumulation
VEGF
GLUT1
PDGF
A
E2
CUL2
Rbx1
Elongin B
Elongin C
VHL
complex
disrupted
Mutant
VHL protein
β-domain
Mutant α-domain
HIF1-α
HIF2-α
O
D
D
VEGF
GLUT1
PDGF
B

Familial variants

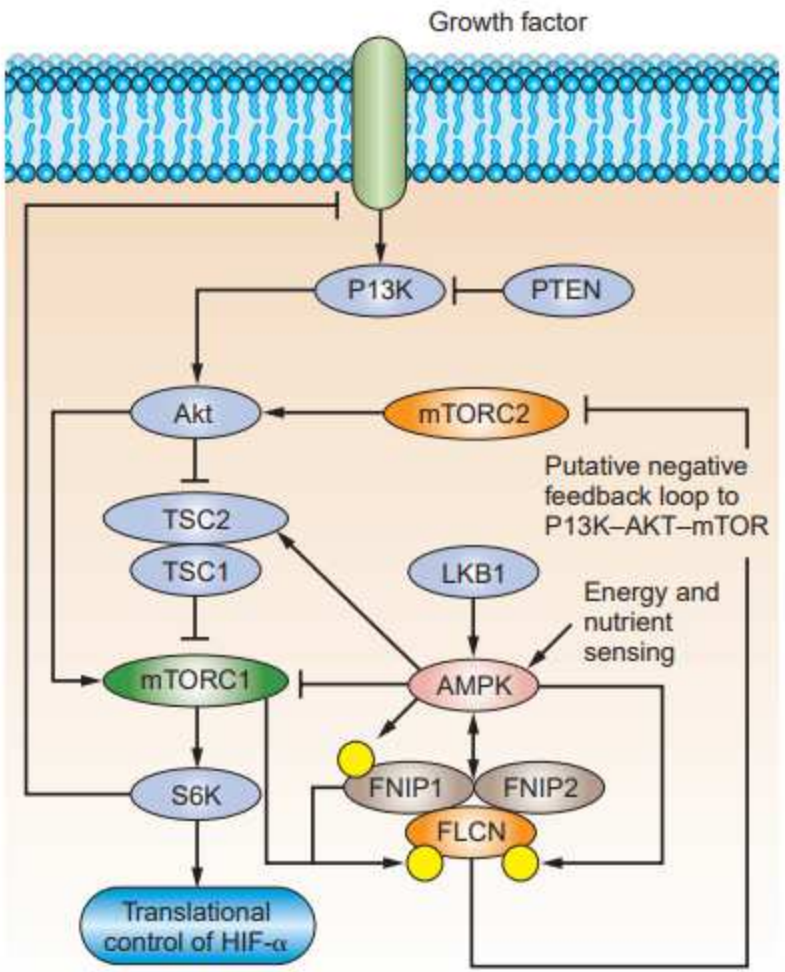
- Hereditary leiomyomatosis and renal cancer syndrome
- Fumarate hydrase (FH) gene at 1q42-43
- Accumulation of fumarate and succinate lead to HIF activation
- Cutaneous and uterine leiomyomata and papillary carcinoma
- High metastatic potential
- Rare to survive 5 years
- Succinate dehydrogenase B and D mutations also lead to accumulation of succinate and HIF activation

Familial variants

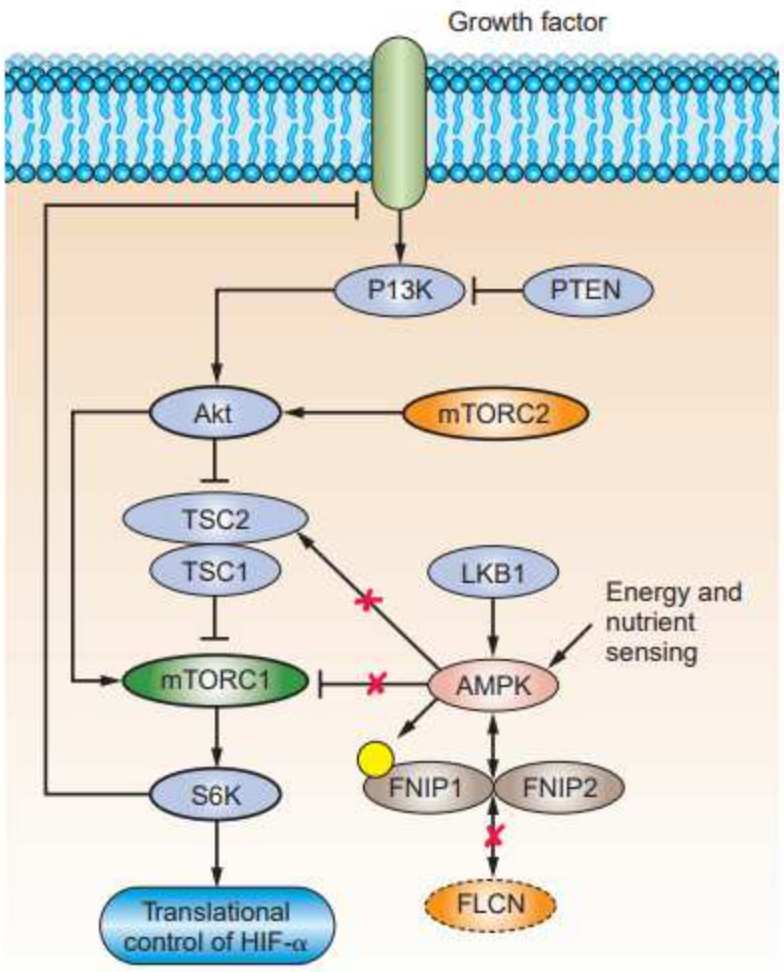
- Hereditary papillary carcinoma
- Bilateral tumors
- Autosomal dominant
- Trisomy 7
- MET gene at 7q31 activated

Familial variants

- Birt-Hogg-Dubé syndrome
- Fibrofolliculomas and lung cysts in 85% of patients
- Autosomal dominant
- FLCN gene at 7q (expresses folliculin)
- LOH mutations in both alleles
- Negative feedback on PI3K-AKT-mTOR
- Translational control of HIF


Growth factor
P13K
PTEN
Akt
mTORC2
Putative negative
feedback loop to
P13K–AKT–mTOR
TSC2
TSC1
LKB1
Energy and
nutrient
sensing
mTORC1
AMPK
FNIP1
FNIP2
S6K
FLCN
Translational
control of HIF-α

A


Growth factor
P13K
PTEN
Akt
mTORC2
TSC2
TSC1
LKB1
Energy and
nutrient
sensing
mTORC1
AMPK
FNIP1
FNIP2
S6K
FLCN
Translational
control of HIF-α

B

TABLE 63.2

International Tumor, Node, Metastasis Staging System for Renal Cell Carcinoma and Survival Rates

T: Primary Tumor				**Five-Year Survival (%)**
TX	Primary tumor cannot be assessed			
T0	No evidence of primary tumor			
T1a	Tumor ≤4 cm and confined to the kidney			90–100
T1b	Tumor >4 cm and ≤7 cm and confined to the kidney			80–90
T2a	Tumor >7 cm and ≤10 cm and confined to the kidney			65–80
T2b	Tumor >10 cm and confined to the kidney			50–70
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 fascia			40–65
T3b	Tumor grossly extends into the vena cava below the diaphragm			30–50
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava			20–40
T4	Tumor invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)			0–20
N: Regional Lymph Nodes				
NX	Regional lymph nodes cannot be assessed			
N0	No regional lymph nodes metastasis			
N1	Metastasis in regional lymph node(s)			0–20
M: Distant Metastases				
MX	Distant metastasis cannot be assessed			
M0	No distant metastasis			
M1	Distant metastasis present			0–10
Stage Grouping				
Stage I	T1	N0	M0	
Stage II	T2	N0	M0	
Stage III	T3	Any N	M0	
	T1 or T2	N1	M0	
Stage IV	T4	Any N	M0	
	Any T	Any N	M1	

Prognostic and surgical staging systems of IVC tumor thrombus

Anatomic landmark	Staging systems				
	TNM	Neves	Novick	Hinman	Robson
RV	T3b	0	I	I	IIIa
IVC <2 cm above RV		I	II		
IVC >2 cm above RV and below hepatic veins		II			
IVC above hepatic veins and below diaphragm		III	III	II	
IVC above diaphragm	T3c	IV	IV	III	

Figure 63.5 Classification of renal cell carcinoma venous tumor thrombi. Level 0 (*green*): Thrombus within main renal vein (RV) or its branches and not reaching into the inferior vena cava (IVC). Level I (*yellow*): IVC thrombus is present within the IVC, <2 cm above renal vein. Level II (*orange*): IVC thrombus extends along the IVC, but not to the level of the main hepatic veins. Level III (*purple*): IVC thrombus extends within the IVC above the level of the main hepatic veins, but below the diaphragm. Level IV (*red*): IVC thrombus extends above the diaphragm, near to or into the right atrium and occasionally beyond. TNM, tumor, node, metastasis. (Reproduced with permission from Pouliot F, Shuch B, Larochelle JC, et al. Contemporary management of renal tumors with venous tumor thrombus. *J Urol* 2010;184:833–841.)

TABLE 63.7

Prognostic System in Metastatic Renal Cell Carcinoma

Schema	Factors	Comments
MSKCC[215]	■ Low Karnofsky performance status ■ High lactate dehydrogenase ■ Low serum hemoglobin ■ High corrected serum calcium ■ Time from initial RCC diagnosis to start of therapy <1 y	Developed from patients with metastatic RCC patients treated with IFN-based therapy on clinical trials at MSKCC
Heng et al.[187]	■ Low Karnofsky performance status ■ Low serum hemoglobin ■ High corrected serum calcium ■ Time from initial RCC diagnosis to start of therapy <1 y ■ Elevated neutrophils ■ Elevated platelets	Developed from retrospective data for a global multicenter consortium of patients receiving targeted therapy for metastatic RCC

MSKCC, Memorial Sloan-Kettering Cancer Center; RCC, renal cell carcinoma; IFN, interferon.

Treatment

- Tumors <4cm show 1% yearly progression to metastatic disease
- 5% progress to be symptomatic.
- Partial nephrectomy may be utilized.
- Nephrectomy curative only for localized disease.
- Lymphadenectomy if retroperitoneal lymphadenopathy present.
- Ipsilateral adrenalectomy reserved for patients with large upper pole disease.

Treatment

- If patient has retroperitoneal lymphadenopathy and metastasis, nephrectomy and retroperitoneal lymphadenectomy indicated.
- Do not respond as well to adjuvant therapy as those patients without retroperitoneal lymphadenopathy but with metastasis.
- Solitary metastasis may be resected.

Treatment

- Stage I T1a cancer is treated with partial nephrectomy or nephron-sparing total nephrectomy.
- Stage I T1b cancer is treated with partial nephrectomy or radical nephrectomy.
- No adjuvant therapy follows for Stage I cancers.
- There is no uniform treatment for Stage II cancers following partial nephrectomy or radical nephrectomy.

Treatment

- Sunitinib is recommended for systemic adjuvant therapy following nephrectomy only for clear cell histology as well as high-risk renal cell carcinoma.
- The presence of sarcomatoid or rhabdoid histology is associated with a more aggressive disease course and a low likelihood of response to TKI monotherapy

Treatment

- 87% are PD-L1 positive
- Ipilimumab and nivolumab if intermediate or poor prognosis in clear cell type
- Axitinib and pembrolizumab are the better choice across all histologic types
- Sunitinib and cabozantib (tyrosine kinase inhibitors) prolong time to disease progression.
- PD1/PDL-1 and CTLA-4 or VEGFR inhibitors are the standard of care in metastatic renal cell carcinoma

See Evidence Blocks on KID-C (EB-1)

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY			
Risk	Preferred regimens	Other recommended regimens	Useful in certain circumstances
Favorable[a]	• Axitinib + pembrolizumab[b] • Cabozantinib + nivolumab[b] • Pazopanib • Sunitinib	• Ipilimumab + nivolumab[b] • Axitinib + avelumab[b] • Cabozantinib (category 2B)	• Active surveillance[c] • Axitinib (category 2B) • High-dose IL-2[d]
Poor/ intermediate[a]	• Axitinib + pembrolizumab[b] (category 1) • Ipilimumab + nivolumab[b] (category 1) • Cabozantinib + nivolumab[b] • Cabozantinib	• Pazopanib • Sunitinib • Axitinib + avelumab[b]	• Axitinib (category 2B) • High-dose IL-2[d] • Temsirolimus[e]

See Evidence Blocks on KID-C (EB-2)

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY		
Preferred regimens	Other recommended regimens	Useful in certain circumstances
• Cabozantinib (category 1) • Nivolumab[b] (category 1) • Ipilimumab + nivolumab[b]	• Axitinib (category 1) • Lenvatinib + everolimus (category 1) • Axitinib + pembrolizumab[b] • Everolimus • Pazopanib • Sunitinib • Axitinib + avelumab[b] (category 3)	• Bevacizumab[f] (category 2B) • Sorafenib (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Temsirolimus[e] (category 2B)

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

SYSTEMIC THERAPY FOR NON-CLEAR CELL HISTOLOGY[g]		
Preferred regimens	Other recommended regimens	Useful in certain circumstances
• Clinical trial • Sunitinib	• Cabozantinib • Everolimus • Lenvatinib + everolimus	• Axitinib • Bevacizumab[f] • Erlotinib • Nivolumab[b] • Pazopanib • Bevacizumab[f] + erlotinib for selected patients with advanced papillary RCC including hereditary leiomyomatosis and renal cell cancer (HLRCC) • Bevacizumab[f] + everolimus • Temsirolimus[e] (category 1 for poor-prognosis risk group; category 2A for other risk groups)

Treatment

- Under some circumstances and if not poor risk, bevacizumab (anti-VEGF antibody) may be useful
- Hypertension, bleeding common with bevacizumab, particularly in elderly.
- Those who develop hypertension have better outcomes.

EVIDENCE BLOCKS FOR SYSTEMIC THERAPIES FOR NON-CLEAR CELL CARCINOMA

SYSTEMIC THERAPY FOR NON-CLEAR CELL HISTOLOGY	
Preferred regimen	
Sunitinib	
Other recommended regimens	
Cabozantinib	
Everolimus	
Lenvatinib/everolimus	
Useful under certain circumstances	
Axitinib	
Bevacizumab	
Erlotinib	
Nivolumab	
Pazopanib	
Bevacizumab/erlotinib for selected patients with advanced papillary RCC including hereditary leiomyomatosis and renal cell cancer (HLRCC)	
Bevacizumab/everolimus	
Temsirolimus (poor-prognosis risk)	
Temsirolimus (risk groups other than poor-risk)	

https://www.nccn.org/professionals/physician_gls/pdf/kidney_blocks.pdf
Accessed 03/17/2021

KIDNEY-SPECIFIC SURGICAL RECOMMENDATIONS FOR PATIENTS WITH CONFIRMED HEREDITARY RCC

- Preoperative alert: Patients with a suspected or known diagnosis of PGL/PCC or VHL are at increased risk of pheochromocytomas and should have blood and/or urine screening for this prior to any surgical procedure.

BAP1-TPDS
- No specific guidelines in surgical management for this syndrome (See KID-A).

BHDS
- Nephron-sparing surgery is the treatment of choice for renal tumors whenever possible, with consideration that an individual may have multiple tumors during their lifetime.[1]
- Ablative treatment options may be considered for those with significant medical or surgical risk to undergo an operation.

HLRCC
- As these tumors can be aggressive, surveillance of renal tumors is not recommended, and total radical nephrectomy should be considered.[2]

HPRC
- Nephron-sparing surgery is the treatment of choice for renal tumors whenever possible, with consideration that an individual may have multiple tumors during their lifetime.
- Ablative treatment options may be considered for those with significant medical or surgical risk to undergo an operation.

PGL/PCC
- Malignant tumors absent aggressive histology and early stage should undergo surgical resection; partial nephrectomy can be considered.
- For larger tumors and those with aggressive histology (eg, high grade, sarcomatoid), radical nephrectomy should be considered.[3]

TSC
- AML is a benign lesion associated with TSC and managed separately.[4,5,6]
- Nephron-sparing surgery is the treatment of choice for malignant renal tumors whenever possible, with consideration that an individual may have multiple tumors during their lifetime.[7]
- Ablative treatment options may be considered for those with significant medical or surgical risk to undergo an operation.

VHL
- Management of localized renal masses in patients with VHL are typically guided under the "3 cm rule."[7]
- The idea is to intervene at a time point of maximal benefit to the patient to limit the chance of development of metastatic disease but also to consider the recurrent and multiple resections many of these patients will have over the course of their lifetime with subsequent development of chronic and progressive renal failure.[7,8]
- Patient should undergo partial nephrectomy if at all possible and consider referral to centers with surgical expertise in complex partial nephrectomies and management of VHL patients.[8]
- Ablative treatment options may be considered for those with significant medical or surgical risk to undergo an operation.

https://www.nccn.org/professionals/physician_gls/pdf/kidney_blocks.pdf
Accessed 03/17/2021

KIDNEY-SPECIFIC SYSTEMIC THERAPY FOR PATIENTS WITH CONFIRMED HEREDITARY RCC

HLRCC

- There are no specific FDA-approved therapies for HLRCC. Treatment with erlotinib plus bevacizumab[1] demonstrated benefit in patients with metastatic RCC from HLRCC (See KID-C).[2]

TSC

- Everolimus is an FDA-approved therapy for asymptomatic, growing angiomyolipoma measuring >3 cm in diameter.[3]

VHL Disease

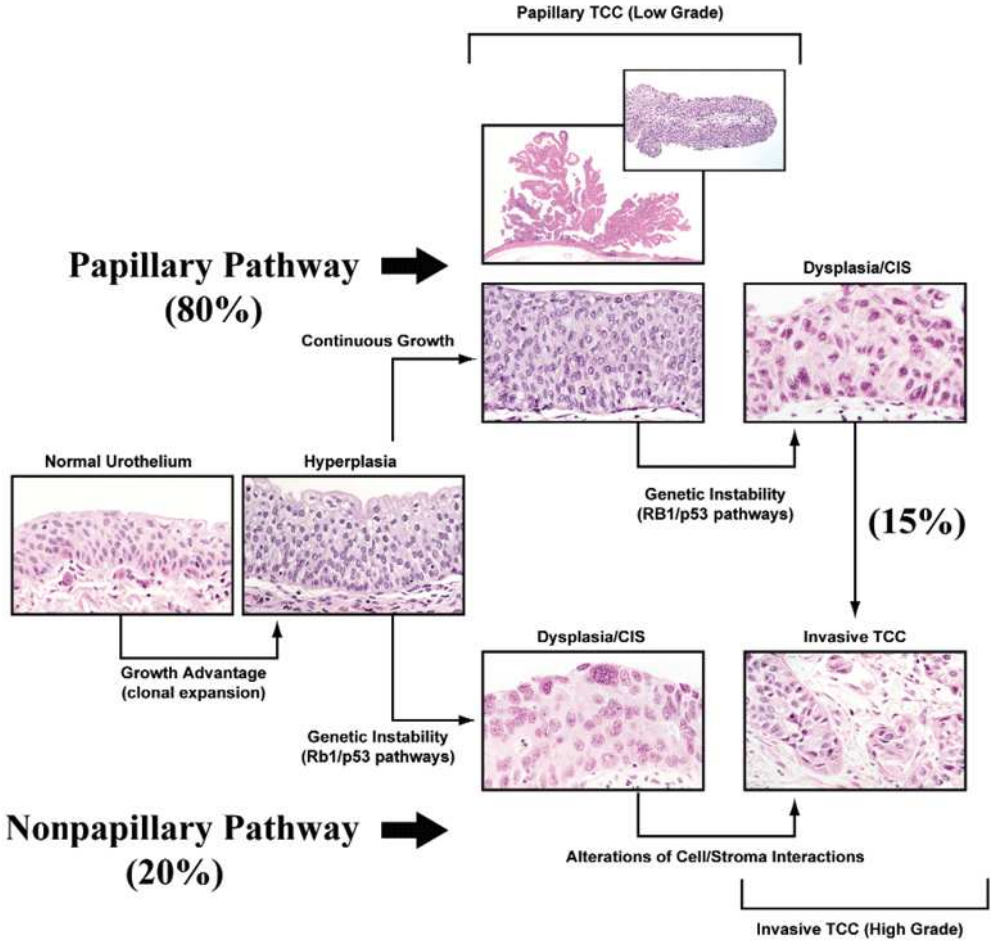
- At this time there are no FDA-approved therapies for nonmetastatic RCC arising in VHL disease. However, pazopanib was associated with a >50 % objective response rate in renal lesions in a 31-patient phase II study.[4]

https://www.nccn.org/professionals/physician_gls/pdf/kidney_blocks.pdf
Accessed 03/17/2021

DISORDERS OF URETER, BLADDER, URETHRA

Kenneth Alonso, MD, FACP

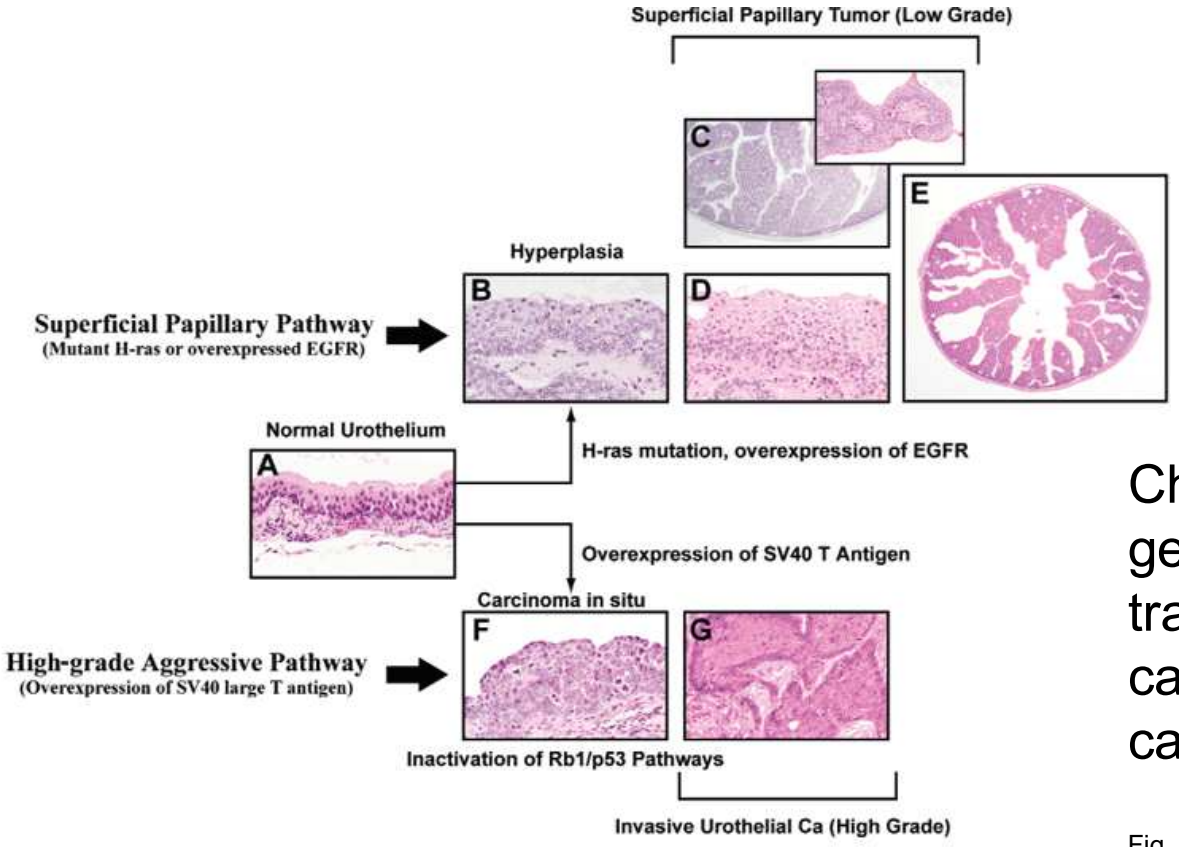
Urothelial (transitional) cell carcinoma



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Fig. 28-1
Accessed
08/01/2010

Urothelial (transitional) cell carcinoma

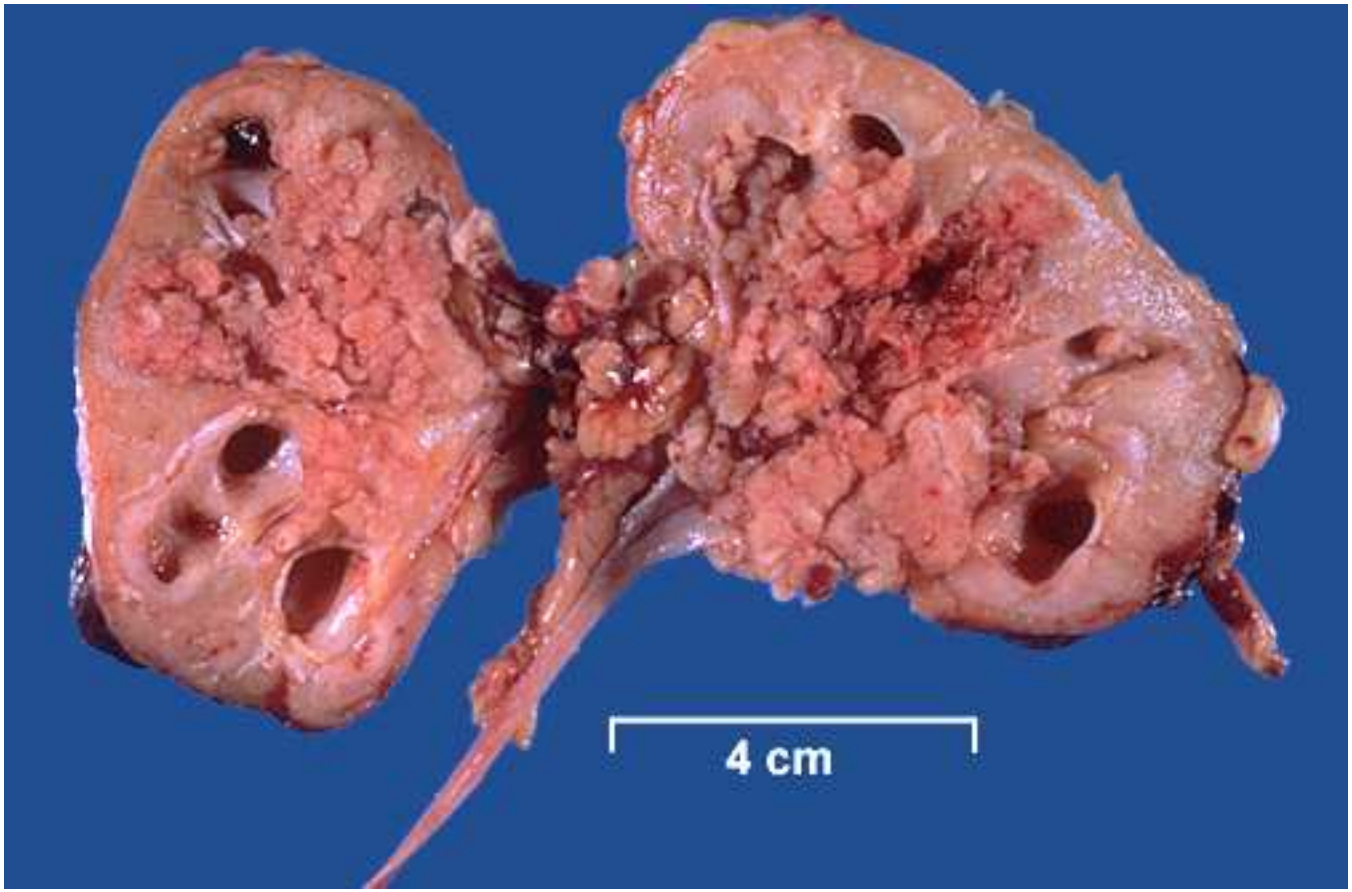


Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Characteristic genetic lesions in transitional cell carcinoma carcinogenesis.

Fig. 28-2 Accessed 08/01/2010

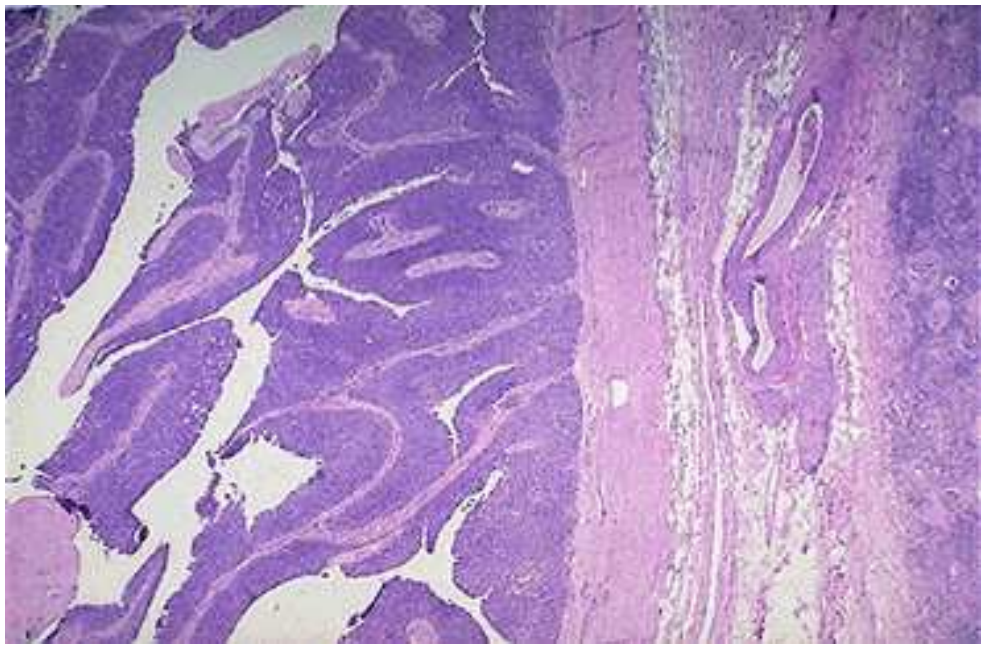
Urothelial cancer

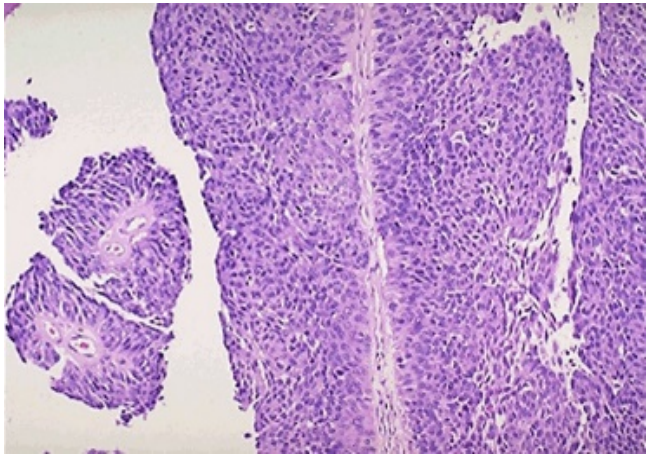


There is invasion of the renal parenchyma with obstruction and dilatation of the pelvis and the calyces to produce hydronephrosis.

https://webpath.med.utah.edu/RENAHTML/RENAL056.html Accessed 01/20/2020

Urothelial carcinoma





Note the frond-like papillary projections to the left. It is differentiated enough to resemble urothelium, but it is producing a mass effect. No invasion is seen to the right.

Below the thickness is much greater than normal urothelium, and the neoplastic cells show more pleomorphism.

https://webpath.med.utah.edu/RENAHTML/BLAD063.html and BLAD064.html
Accessed 01/20/2020

Ureteral cancer

- Ureteral carcinoma may present with ureteral obstruction
- And retrograde hydronephrosis or shrunken kidney depending upon time course.
- Painless hematuria may also be seen.
- Papillary lesions
- 9p- or 9q- abnormalities found in up to 60% of urothelial lesions
- (9p21 involves p16/INK4α as well as the related tumor suppressor gene p15).
- With loss of chromosome 9, frank invasion identified.

Ureteral cancer

- 17p- found in carcinomas (p53).
- Flat lesions
- FGFR3/ cyclin D mutation (11p-)
- Inverted papilloma cured by excision (not malignant).
- Excise and stent ureteral carcinomas.

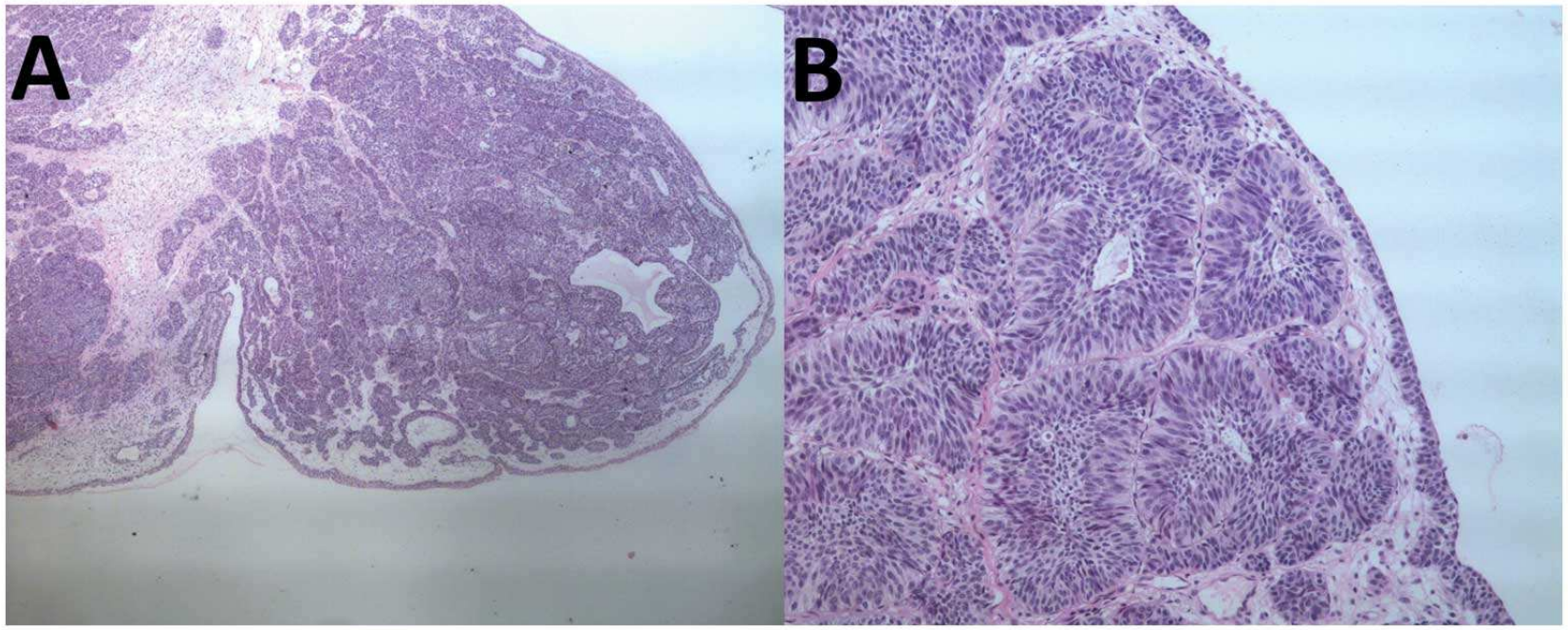
Inverted bladder papilloma

- <1% bladder neoplasms
- Generally benign
- Men, 6th and 7th decades
- Painless hematuria
- May have irritative bladder symptoms (urgency)
- Solitary with minimal exophytic component
- May have squamous differentiation

Inverted bladder papilloma

- Trabecular subtype is classic.
- Urothelial buds at various points underlying urothelial surface
- Irregular downward growing cords from overlying epithelium
- Spindle cells with central streaming and in palisade
- Glandular subtype
- Nests of urothelium with pseudoglandular urothelial lined spaces or true glands containing mucous secreting goblet cells

Inverted bladder papilloma



A. The polypoid growth of the lesion is demonstrated. B. Thin cords are present in the lamina propria. Urothelium with central streaming and peripheral palisading.

https://www.spandidos-publications.com/article_images/ol/4/1/OL-04-01-0071-g00.jpg Accessed 01/20/2020

Bladder cancer

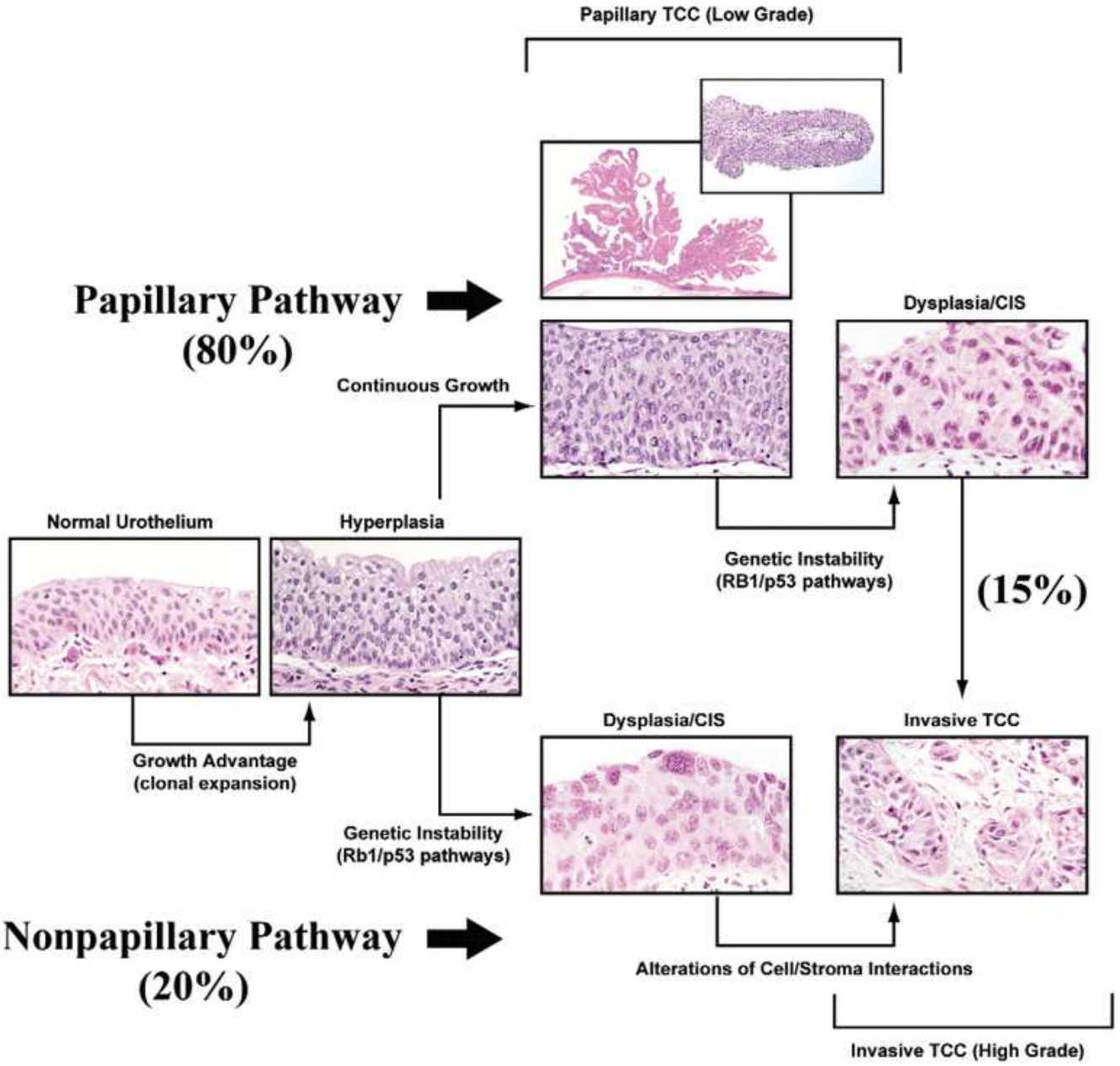
- 3:1 men
- 80% are 50-80 years of age
- Not familial
- 50-80% associated with cigarette use
- Painless hematuria
- Cystoscopy with hexaminolevulinate imaging and urine cytology critical for detection and surveillance of bladder cancer.

Bladder cancer

- Risks:
- Exposure to 2-naphthylamine
- Cancers occur 15-40 years after exposure
- Schistosoma hematobium infection
- Chronic inflammatory changes from encystation in bladder wall
- 70% are adenocarcinomas
- Radiation exposure
- Cyclophosphamide use
- Long term analgesic use

Bladder cancer

- Two distinct precursors to invasive bladder cancer:
- Papillary tumors
- Arising from previous transitional cell hyperplasia, 9q- (usually CDKN2A; PTCH and TSC1 loss also possible with loss of mTOR signaling)
- FGFR3 gain of function mutation
- Flat urothelial carcinoma in situ
- FGFR3/cyclin D, HRAS, 11p-
- p53 mutation needed for high grade dysplasia.
- Rb inactivation, 8p- needed for invasion.



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Fig. 28-1
Accessed
08/01/2010

Infiltrating Urothelial Carcinoma
Urothelial carcinoma with divergent differentiation
Squamous differentiation
Glandular differentiation
Trophoblastic differentiation
Nested, including large nested
Microcystic
Micropapillary
Lymphoepithelioma-like
Plasmacytoid
Sarcomatoid
Giant cell
Poorly differentiated
Lipid-rich
Clear cell (glycogen-rich)

Data based on and derived from [1]Moch H, Humphrey PA, Ulbright TM, et al., eds. *WHO Classification of Tumours of the Urinary System and Male Genital Organs*. 4th ed. Lyon, France: IARC Press; 2016. *World Health Organization Classification of Tumours*; vol 8.

Bladder cancer

- Presents with painless hematuria
- Irritative signs common
- 95% are urothelial cancers.
- 3-5% are squamous carcinomas
- Embryonal rhabdomyosarcoma occurs in children <5 years of age
- "Field change" disease as the entire urothelium is at risk for tumor formation.
- Tobacco, exposure to aniline dyes, Schistosoma infection are major environmental risk elements.
- Lifelong surveillance needed.
- Men three times more likely to have bladder cancer

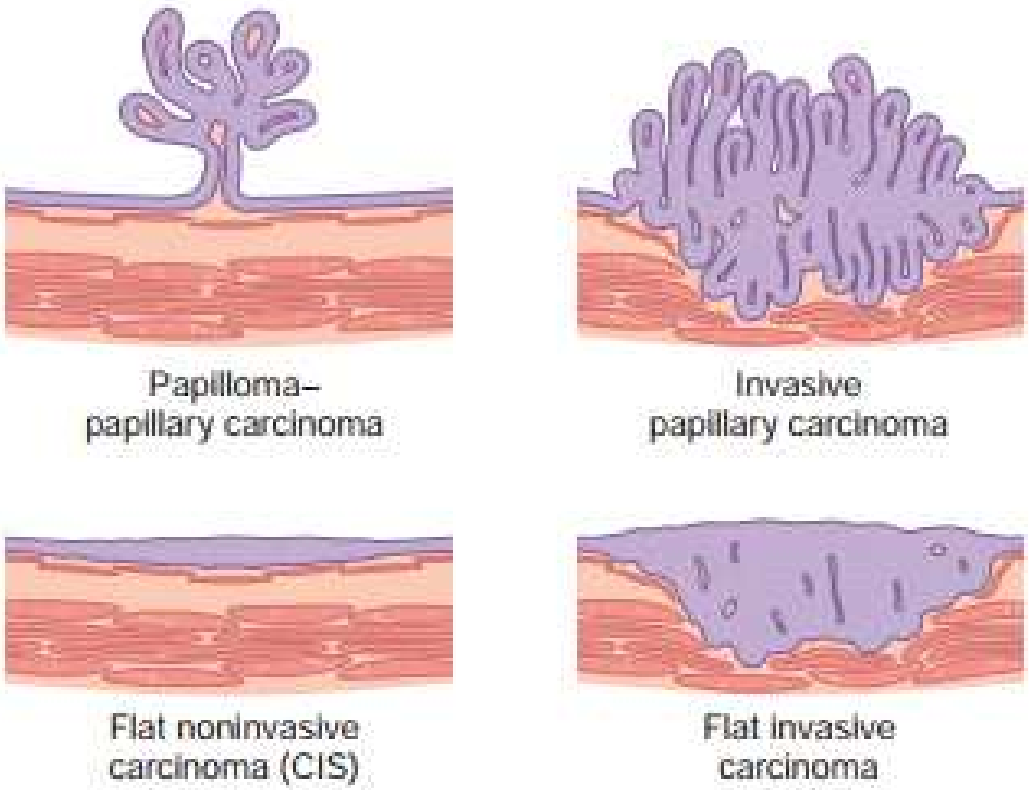


Figure 21-6 Four morphologic patterns of bladder tumors. CIS, Carcinoma in situ.

Papillary lesions

- Papillary lesions are red, elevated excrescences ranging in size from less than 1 cm in diameter to large masses up to 5 cm in diameter
- Most arise from the lateral or posterior walls at the bladder base.
- Multiple discrete tumors are often present
- Exophytic papillary lesions are attached to the mucosa by a stalk
- Individual finger-like papillae have a central core of loose fibrovascular tissue covered by bland epithelium
- Recurrences and progression are rare

Papillary lesions

- Papillary urothelial neoplasms of low malignant potential have a thicker epithelium
- Low-grade papillary urothelial carcinomas
- Have an orderly architectural and cytologic appearance. The cells are evenly spaced (maintain polarity) and cohesive.
- There is a mild degree of nuclear atypia consisting of scattered hyperchromatic nuclei, infrequent mitotic figures predominantly toward the base, and slight variation in nuclear size and shape
- <10% of low-grade cancers invade muscle

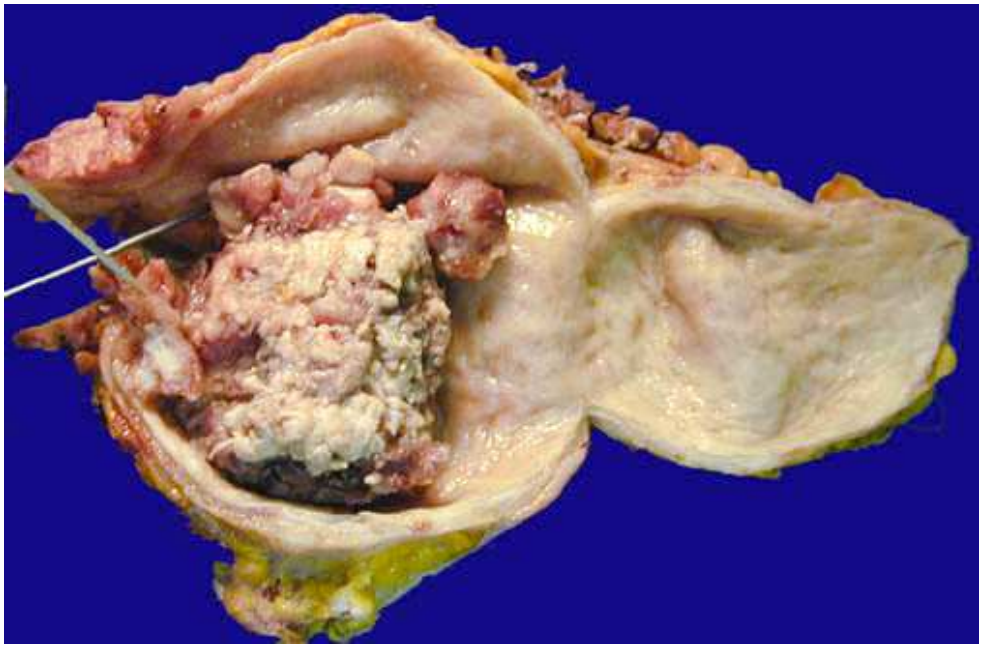
Papillary lesions

- High-grade papillary urothelial cancers contain poorly cohesive cells with large hyperchromatic nuclei.
- Mitotic figures are frequent.
- Architecturally, there is disarray and loss of polarity.
- 80% are invasive.
- May extend into the bladder wall and adjacent structures.
- About 40% of these deeply invasive tumors metastasize to regional lymph nodes.
- Hematogenous dissemination, principally to the liver, lungs, and bone marrow, may result.

Bladder cancer

- Carcinoma in situ (CIS) may range from full-thickness cytologic atypia to scattered malignant cells in an otherwise normal urothelium (pagetoid spread)
- A common feature shared with high-grade papillary urothelial carcinoma is a lack of cohesiveness, which leads to the shedding of malignant cells into the urine
- Invasive bladder cancer.
- The extent of the invasion into the muscularis mucosae is of prognostic significance

Bladder cancer



https://webpath.med.utah.edu/RENAHTML/BLAD069.html
Accessed 01/20/2020

The opened bladder removed surgically reveals a mass of a neoplasm that histologically proved to be urothelial carcinoma (previously known as a transitional cell carcinoma).

Urothelial carcinoma can arise anywhere in the urothelium lining the urinary tract from the urethra to the calyces, but is most common in bladder.

Urothelial carcinoma is often multifocal and has a tendency to recur.

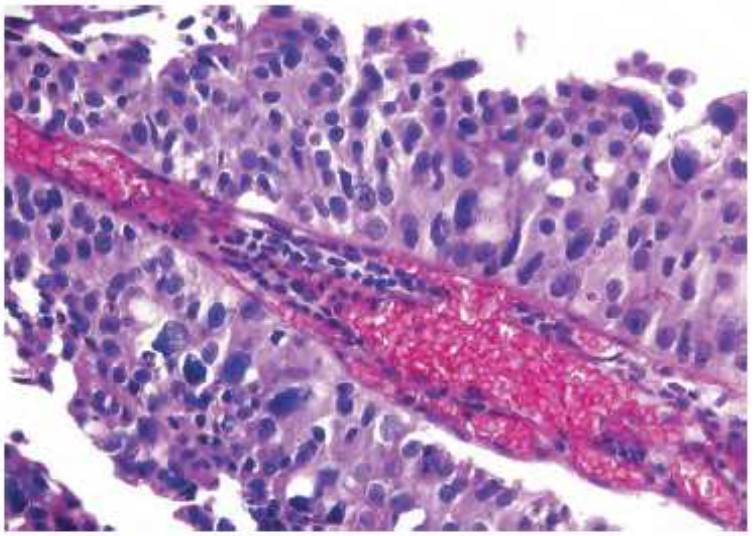


Figure 21-10 High-grade papillary urothelial carcinoma with marked cytologic atypia.

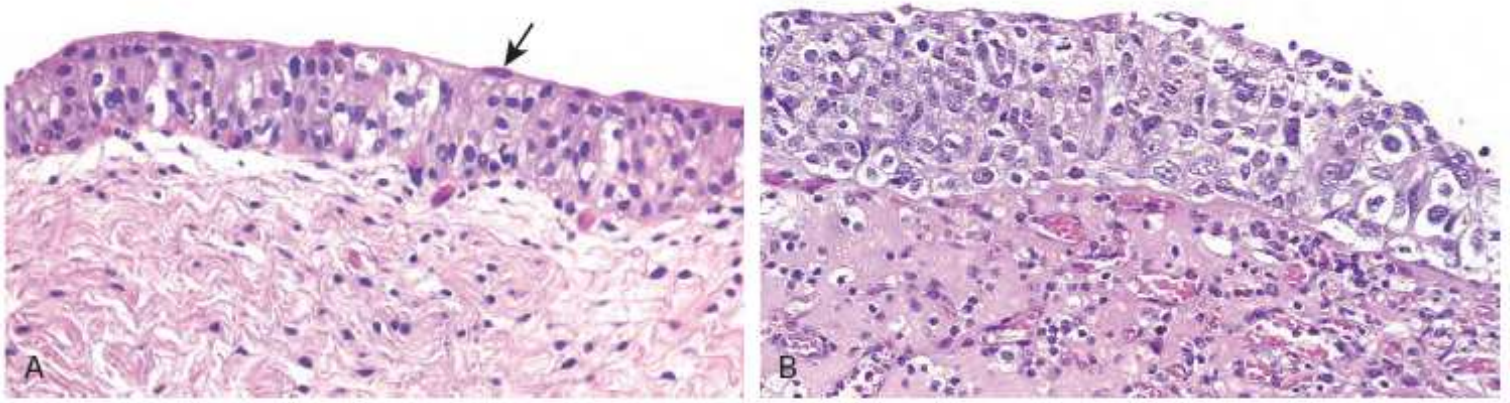


Figure 21-11 **A,** Normal urothelium with uniform nuclei and well-developed umbrella cell layer *(arrow)*. **B,** Flat carcinoma in situ with numerous cells having enlarged and pleomorphic nuclei.

Urothelial carcinoma variants

- Micropapillary urothelial carcinoma
- HER2 amplifications or mutations
- Plasmacytoid urothelial carcinoma
- Loss of E-cadherin and CDH1 gene loss of function mutations or methylation
- Worse prognosis associated with micropapillary and plasmacytoid urothelial carcinoma variants
- Uniformly poor prognosis for sarcomatoid, poorly differentiated and giant cell urothelial carcinoma

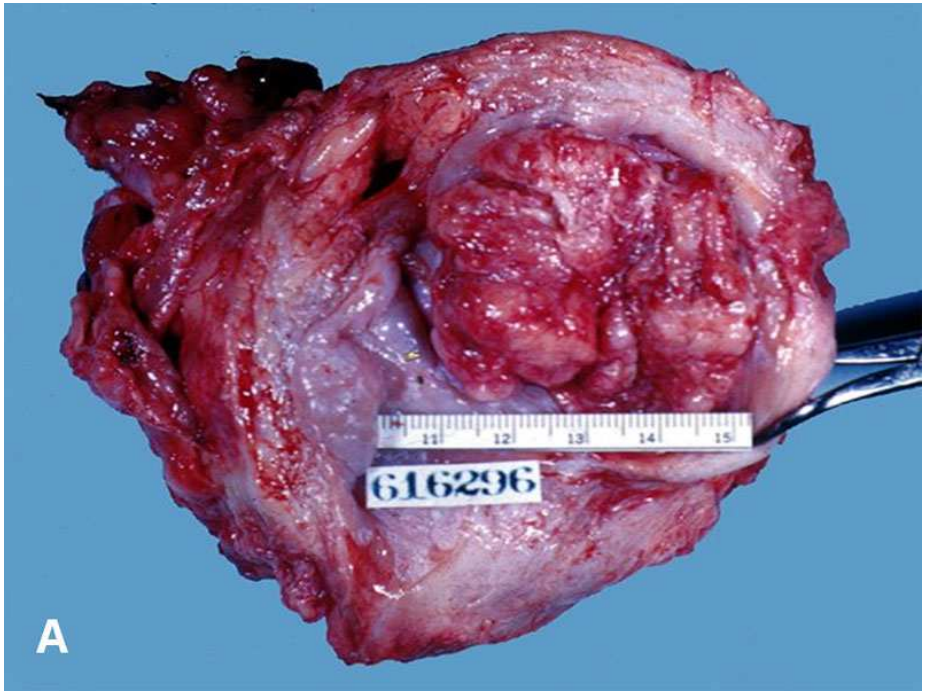
Urothelial carcinoma variants

- No significant association with Epstein-Barr virus (EBV) or human papillomavirus (HPV) infection and urothelial carcinoma development
- Nested variant, lipid rich and urothelial carcinoma with divergent differentiation (squamous, glandular, or trophoblastic) are more likely to present with advanced disease but when adjusted by stage had no survival differences with respect to conventional urothelial carcinoma.

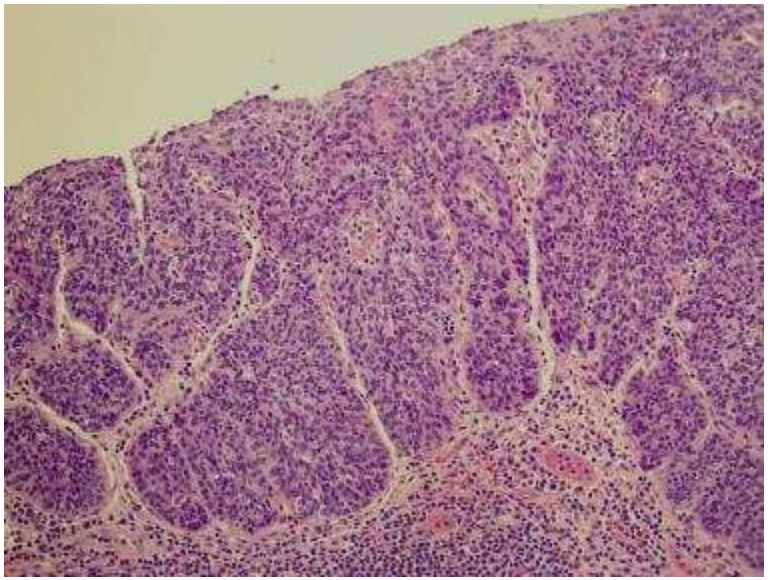
Squamous carcinoma

- Pure squamous carcinomas associated with chronic inflammation.
- Mixed urothelial carcinomas with areas of squamous carcinoma are more frequent than pure squamous cell carcinomas.
- Most are invasive, fungating tumors or are infiltrative and ulcerative.
- 7% of bladder cancers
- Other cancers include adenocarinoma and small cell carcinoma

Squamous carcinoma



https://www.auanet.org/images/education/pathology/bladder-carcinomas/squamous-figureA_Big.jpg



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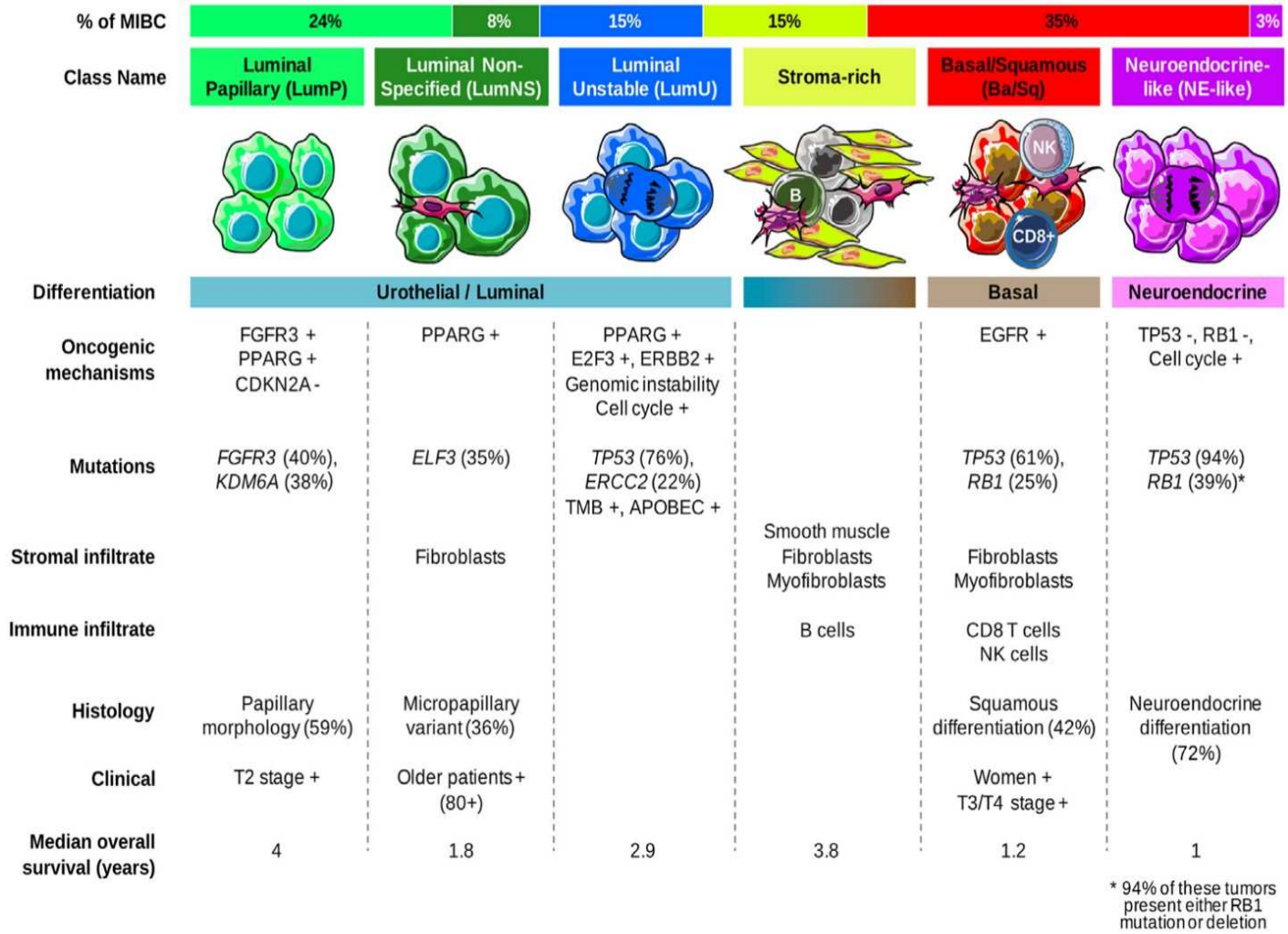
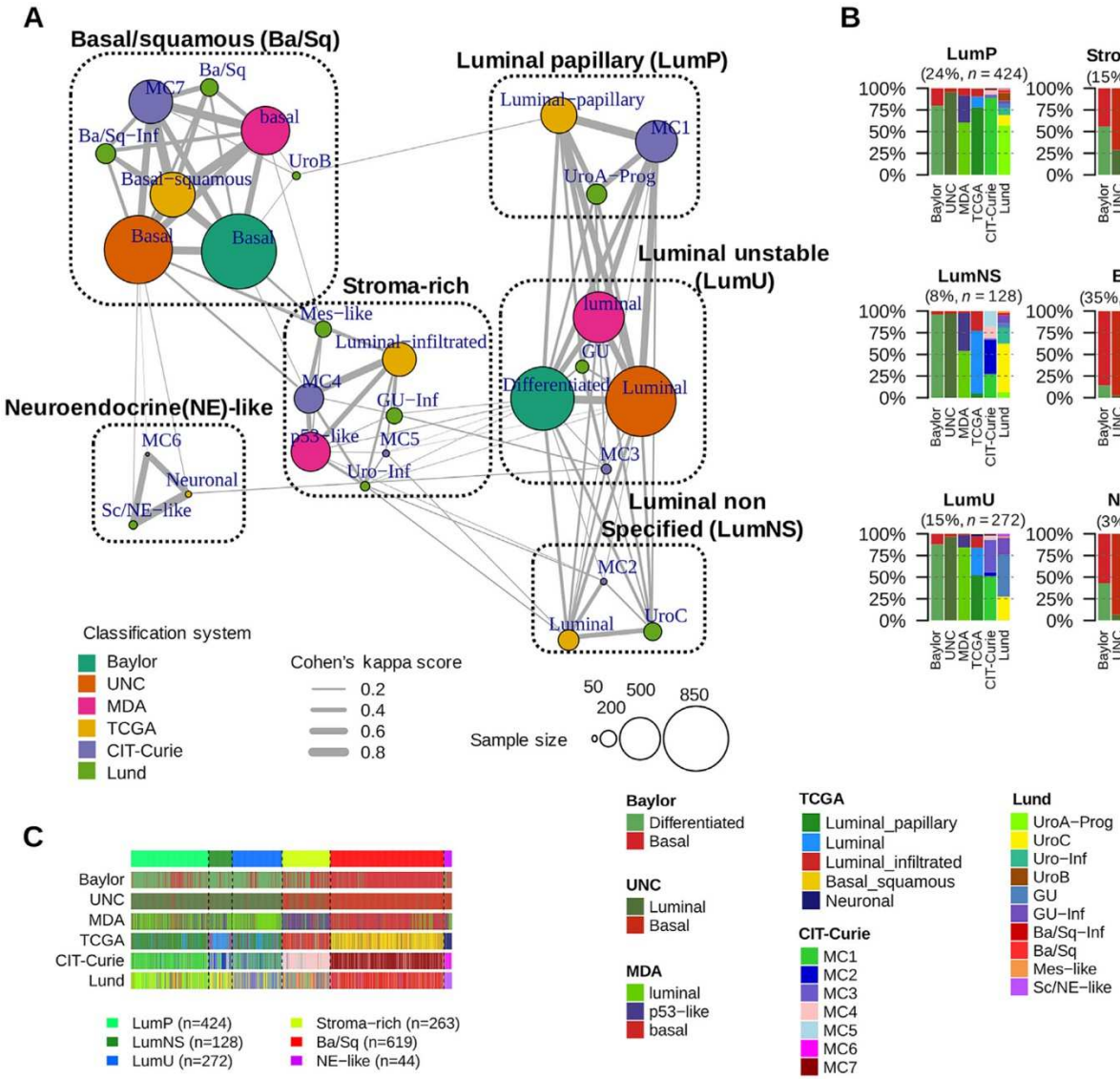


https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7690647/



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7690647/

Molecular characterization of subtypes

- Luminal Papillary tumors were mainly enriched in FGFR3 (55%)
- Homozygous/deep deletions of CDKN2A in 33%.
- Younger age at presentation
- The Luminal Non-specified subtype was mainly characterized by enrichment of mutations in ELF3 (35%), which is an early regulator of urothelial differentiation and is activated by PPARG
- PPARG was significantly altered as well (76%)
- Older age at presentation

Molecular characterization of subtypes

- Luminal Unstable tumors harbored frequent PPARG alterations (89%)
- High-level amplifications of a 6p22.3 region that contains E2F3 and SOX4 (76%),
- ERBB2 amplifications were noted in 39%
- No significant association was found between ERBB2 mutations and any of the consensus classes
- Frequent mutations in TP53 (76%) and in ERCC2, which codes for a core nucleotide-excision repair component (22%)
- Generally the most genomically altered subtype

Molecular characterization of subtypes

- For Basal/Squamous tumors, the most frequently mutated genes based are TP53 (63% of cases) and RB1.
- Found principally in women
- For Neuroendocrine-like tumors, TP53 was almost always mutated (94%)and co-occurred with RB1 alteration by either mutations or deletions (94%)
- The Stroma enriched subtype is characterized by the presence of smooth muscle, fibroblasts and myofibroblasts, as well as B cell infiltrates
- No characteristic mutations

Chemotherapy response

- FGFR mutations found in up to 20%
- Defective DNA repair (DDR) germline mutations found in 13-19%
- Somatic mutations of ATM/RB1/FANCC/ERCC2 were found to correlate with better response and survival in patients treated with cisplatin-based neoadjuvant chemotherapy followed by radical cystectomy

Chemotherapy response

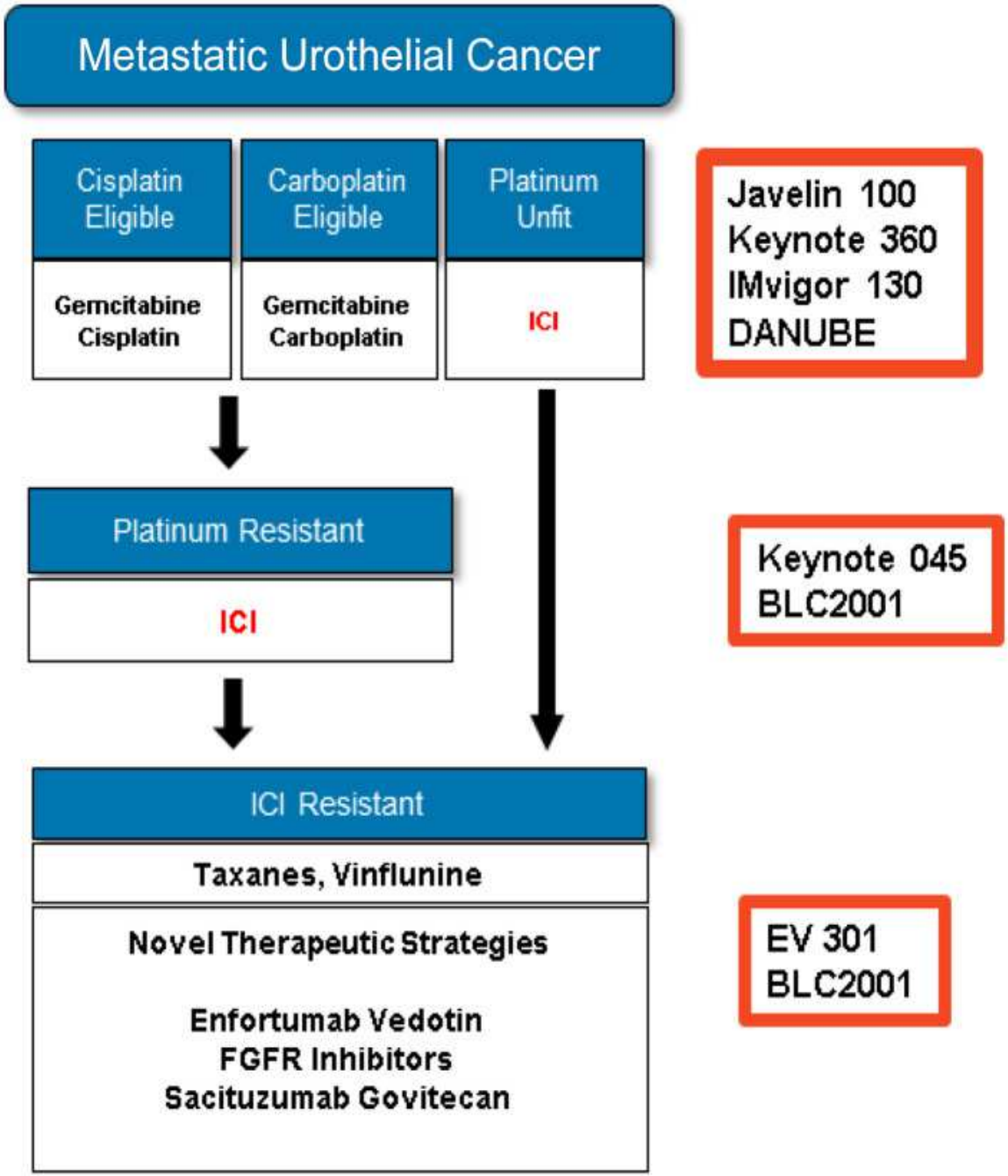
- DDR genomic alterations (excluding ATM) are associated with overall survival benefit in general but not with response to platinum-based chemo-therapy.
- ATM mutations associated with shorter survival

Chemotherapy response

- ATM gene at 11q22–23, encodes a PI3K-related serine/threonine protein kinase
- Maintains genomic integrity by its central role in activation of DDR pathways, including those involved in cell-cycle checkpoint arrest (CHK2), DNA repair(BRCA1 and RAD51), and apoptosis (p53)
- ATM acts as a binary switch that dictates the effect of p53 activation on tumor response to chemotherapy in lung and breast cancer

Chemotherapy response

- ATM function loss has been implicated in accelerated epithelial mesenchymal transformation (and metastasis)
- FAS inhibitors sensitize cancer cells to cisplatin through apoptosis


Metastatic Urothelial Cancer
Cisplatin Eligible
Carboplatin Eligible
Platinum Unfit
Gemcitabine Cisplatin
Gemcitabine Carboplatin
ICI
Javelin 100
Keynote 360
IMvigor 130
DANUBE
Platinum Resistant
ICI
Keynote 045
BLC2001
ICI Resistant
Taxanes, Vinflunine
Novel Therapeutic Strategies
Enfortumab Vedotin
FGFR Inhibitors
Sacituzumab Govitecan
EV 301
BLC2001

Bladder cancer treatment

- Transurethral resection of the bladder tumor is the first step in the initial management of bladder cancer.
- Resection of the prostatic urethra considered if tumor is at the bladder neck or within the prostatic urethra.
- Following transurethral resection, intravesical therapy is instituted within 6 hours.
- Mitomycin C (with heat) and gemcitabine are the agents of choice for non-muscle invasive bladder cancer.
- BCG is also an option

Bladder cancer

- Patients who fail an initial course of intravesical chemotherapy will respond to BCG.
- Patients who fail an initial course of intravesical BCG therapy will likely not respond to chemotherapy.
- A second course of BCG (with interferon-α) may be effective in up to half these failures.
- Refractory patients should be considered for cystectomy.

Bladder cancer treatment

- 20% low risk develop invasive disease, 10% metastasize
- High grade, high risk (45% invade and 50% metastasize)
- Non-urothelial carcinomas, those urothelial carcinomas with lymphovascular invasion, as well as those with deep prostatic involvement should be considered for cystectomy even though no muscle invasion is detected.

Bladder cancer

- Invasion into the detrusor muscle is associated with high mortality rates.
- Radical cystectomy is the treatment of choice.
- Patients with large or extensive bladder lesions as well as those with metastatic disease are treated with gemcitabine and cisplatin chemotherapy or methotrexate, vinblastine, doxorubicin, cisplatin chemotherapy.
- Entry into a clinical trial is recommended as no optimal chemotherapy regimen has been identified.

Bladder cancer treatment

- Invasion into the detrusor muscle is associated with high mortality rates.
- Radical cystectomy is the treatment of choice.
- Considered for cystectomy even though no muscle invasion is detected:
- Non-urothelial carcinomas
- Urothelial carcinomas with lymphovascular invasion
- Urothelial carcinomas with deep prostatic invasion

Bladder cancer treatment

- Radiation therapy may be given following trans-urethral resection of the bladder
- Patients with large or extensive bladder lesions
- Are treated with radiation therapy as well in combination with chemotherapy with cisplatin (with or without 5-FU) or mitomycin C with 5FU.
- No optimal chemotherapy regimen has been identified.

Bladder cancer treatment

- Those with metastatic disease are treated with gemcitabine and cisplatin chemotherapy or dose-dense methotrexate, vinblastine, doxorubicin, cisplatin chemotherapy.
- No optimal chemotherapy regimen has been identified.

Bladder cancer treatment

- A PD1/PDL1 inhibitor such as avelomab post platinum based chemotherapy has shown to be active in refractory disease
- Bladder cancer cells usually have the Nectin-4 protein on their surface.
- Enfortumab vedotin-ejfv is an anti-Nectin-4 antibody attached to the drug, monomethyl auristatin E (MMAE). Is an FGFR inhibitor.
- Useful in platinum-pretreated, post-PD1/PDL1 failures

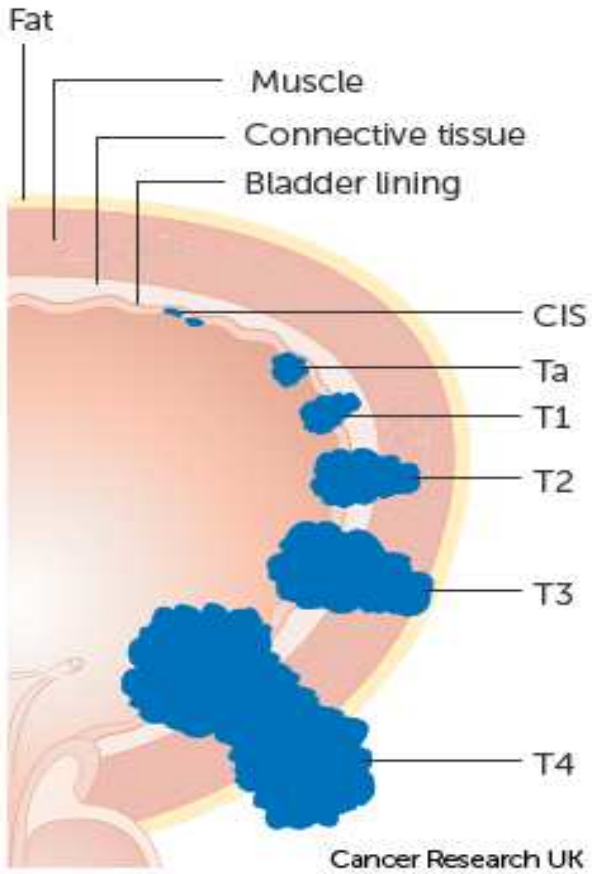


Table 21-4 Pathologic T (Primary Tumor) Staging of Bladder Carcinoma

Depth of Invasion	AJCC/UICC
Ta	Noninvasive, papillary
Tis	Carcinoma in situ (noninvasive, flat)
T1	Lamina propria invasion
T2	Muscularis propria invasion
T3a	Microscopic extravesicle invasion
T3b	Grossly apparent extravesicle invasion
T4	Invades adjacent structures

AJCC/UICC, American Joint Commission on Cancer/Union Internationale Contre le Cancer.

Prognosis depends on the histologic grade and the stage at diagnosis

Urethra

- Urethritis is either gonococcal or non-gonococcal in origin
- Chlamydia trachomatis or Mycoplasma urealyticum each as causes of >25% of cases
- May be accompanied by cystitis (woman) or prostatitis (man)
- Reactive arthritis (Reiter's syndrome) is manifest by urethritis, uveitis, and reactive polyarthritis
- HLA-B27 common
- Salmonella, Shigella, or Campylobacter as triggers
- May resolve spontaneously in 12 months
- Primary carcinomas are uncommon

Urethra

- Tumors arising within the proximal urethra tend to show urothelial differentiation and are analogous to those occurring within the bladder
- Tumors arising within the distal urethra are more often squamous cell carcinomas (males).

Squamous cell carcinoma of the urethra

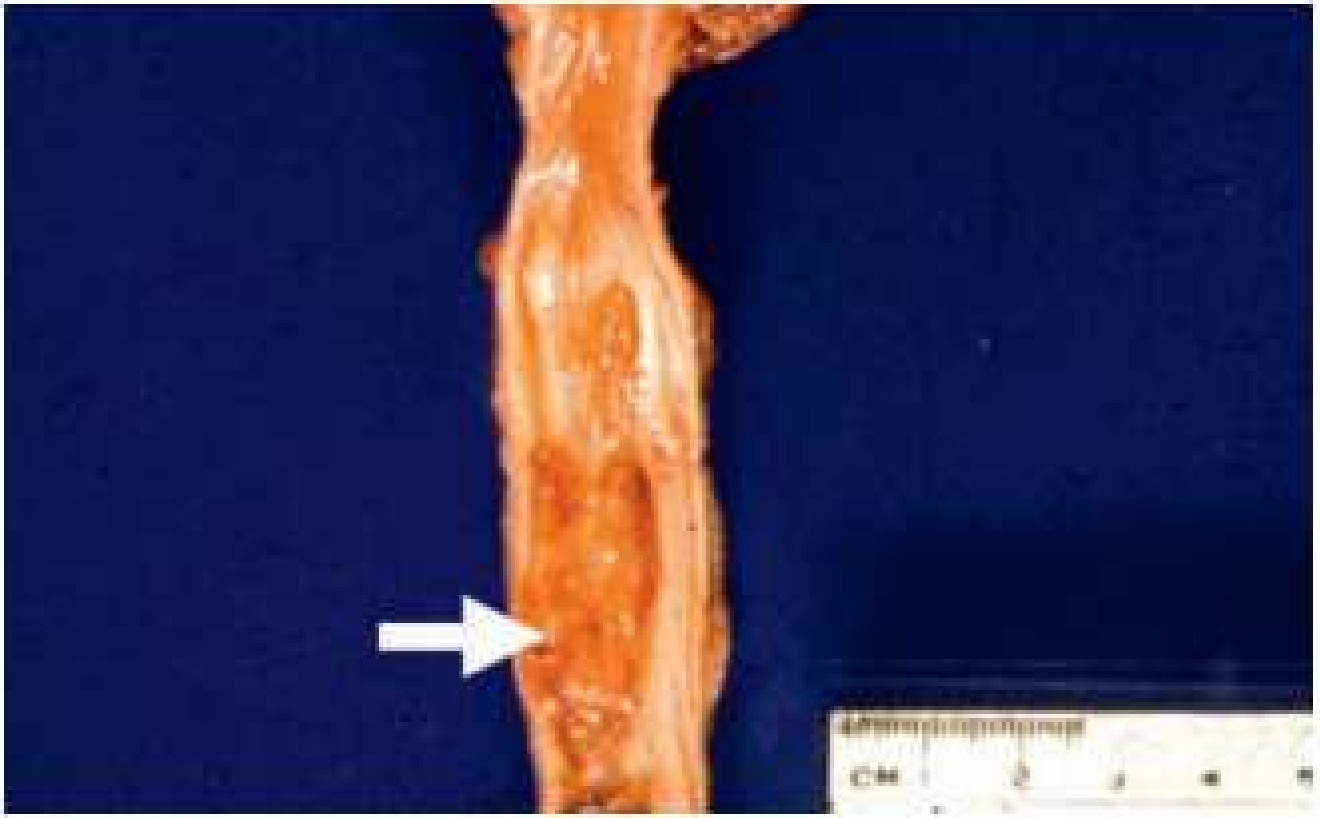


Figure 21-14 Carcinoma of urethra with typical fungating growth.

Squamous cell carcinoma of urethra

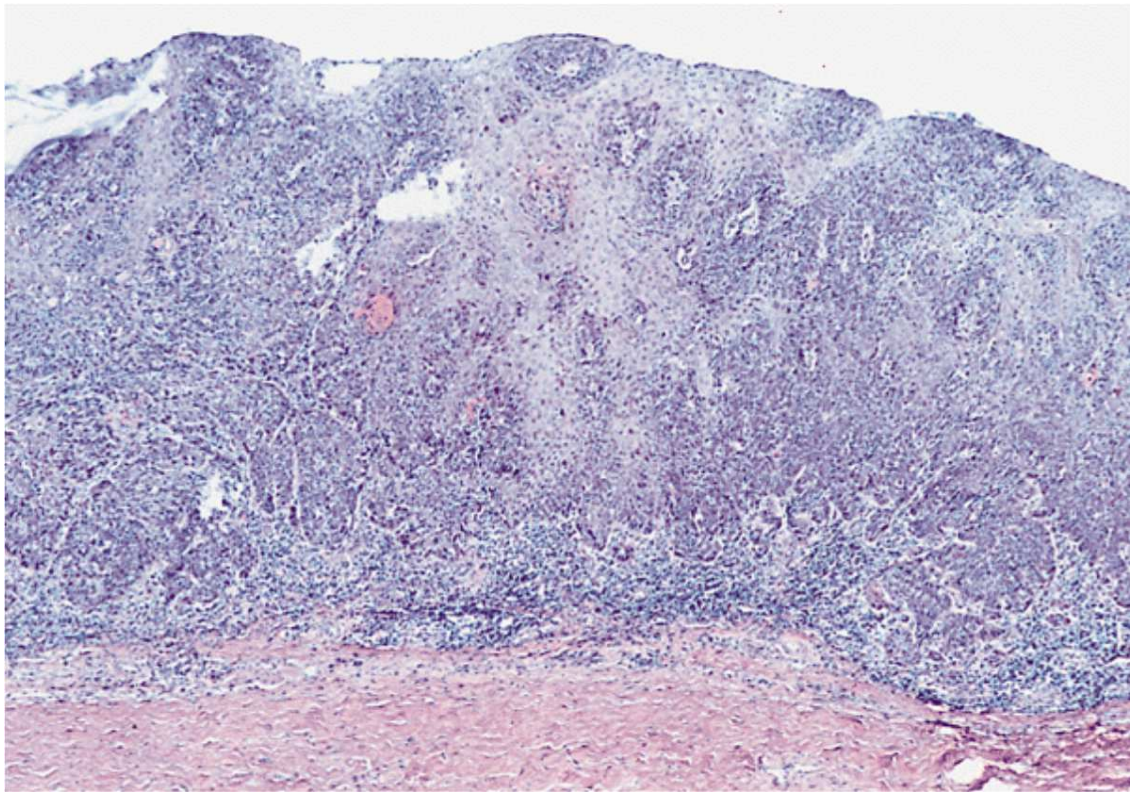


Fig. 9-14

Young, Robert H., Srigley, John R., Amin, Mahul B., Ulbright, Thomas, M, Cubrilla, Antonio, L. , “Tumors of the prostate gland, seminal vesicles, male urethra, and penis.” Atlas of Tumor Pathology. Third series. Fascicle 28. Armed Forces Institute of Pathology. Washington, DC. 2000.