I. Selected non-neoplastic renal diseases
  A. Non-progressive acute renal injury
    1. Acute tubular necrosis
      a. Ischemic type
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    2. Acute interstitial nephritis
  B. Progressive to chronic renal failure (ESRD)
    1. Renovascular disease
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      b. Hypertensive nephropathy
        i. Ordinary type
        ii. Malignant hypertension
    2. Renal cystic disease
      a. Adult polycystic kidney disease
      b. Dialysis-associated cystic disease
      c. Pediatric cystic diseases & others
II. Selected renal neoplasms (next lecture...)

What are the **4 most common causes of chronic renal failure** in the US?

Answer: next slide

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Answer:
1) **Diabetic nephropathy**
2) **Hypertensive nephropathy**
3) **Glomerulonephritis**
4) **Renal cystic disease**

Cystic kidney disease: term used for bunch of diseases with not much in common other than the end stage of them are the same: **kidney with lots of cysts.**

Cystic kidney disease

- U.S. prevalence about 600,000 cases
- Fourth-leading cause of ESRD
- About 90% of cases are adult (autosomal dominant) polycystic kidney disease

APKD accounts for ~ 90% of cases.

Cystic kidney diseases

Mechanism	Age at presentation: Infant/child	Age at presentation: Adult
Hereditary	Infantile PCKD Juvenile nephronophthisis Glomerulocystic kidney	Adult PCKD VHL/TS Medullary sponge Glomerulocystic
Non-hereditary (developmental or acquired)	Multicystic dysplastic kidney	Dialysis-associated cystic disease

talking about today.

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Adult polycystic kidney disease

- Hereditary basis
  - Frequency ~1:750
  - "Most common genetic disease"
  - Autosomal dominant ("ADult")
  - 25% no family Hx←new mutation

- Presents in adulthood
  - Widely variable expressivity
  - 100% penetrance by age 80
  - Most present in 30's to 40's

APKD is second most common autosomal dominant genetic disease - Dr. H

APKD is **A**utosomal **D**ominant. However, ~ 25% of Pts have no family history; could be due to new mutations.

Could present in 20s or 80s, but **most present in middle age (30s, 40s)**.

APKD: Clinical

- Symptoms
  - Flank pain, acute or chronic
  - Hematuria
  - Infection

Usually the cause of the pain they have.

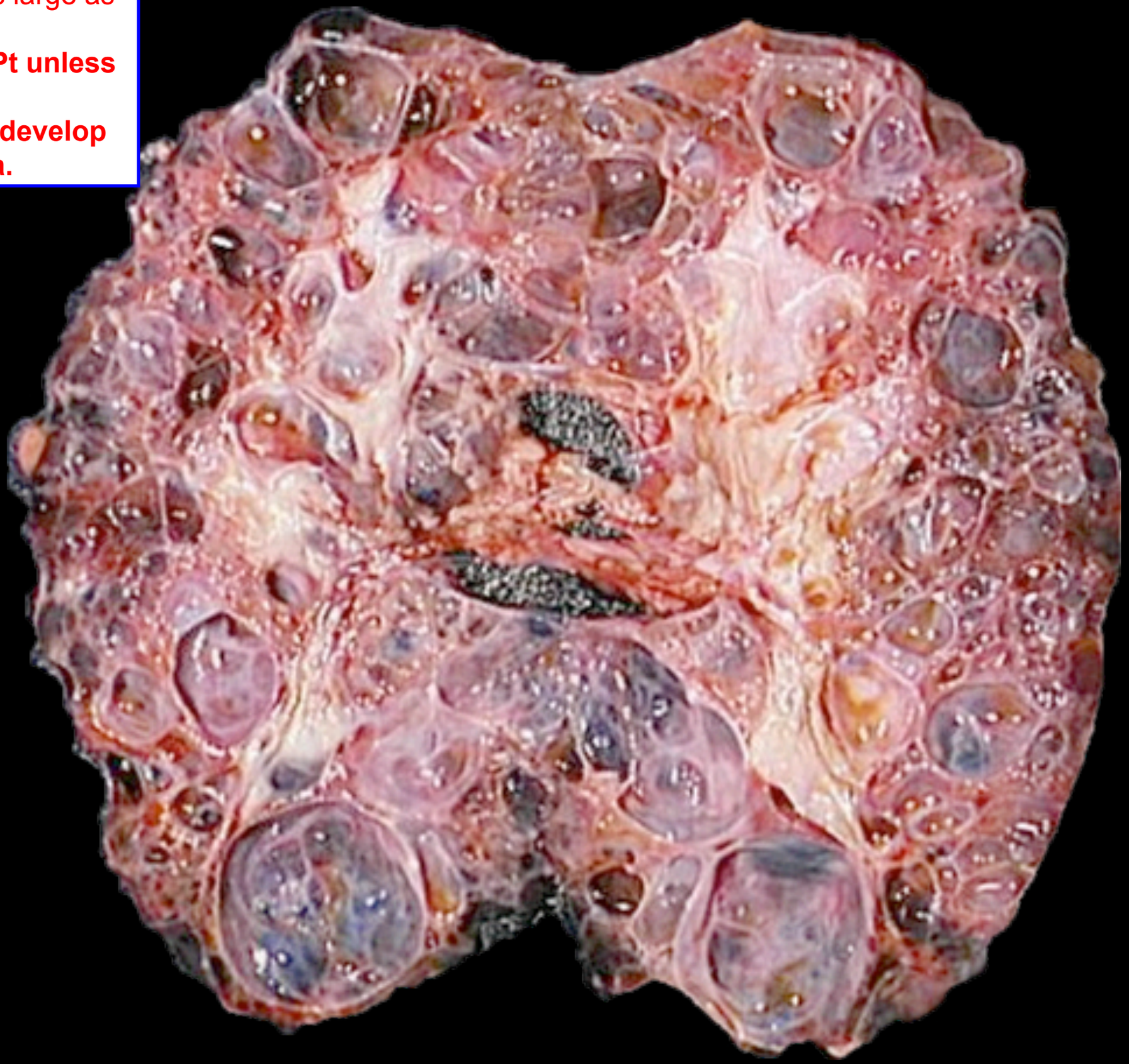
Other reason for pain/ discomfort could be from mass effect of having an enlarged kidney.

- Complications
  - Hypertension (10%)
  - Nephrolithiasis (10%)
  - Perinephric abscess
  - Renal cell carcinoma (up to 5%)

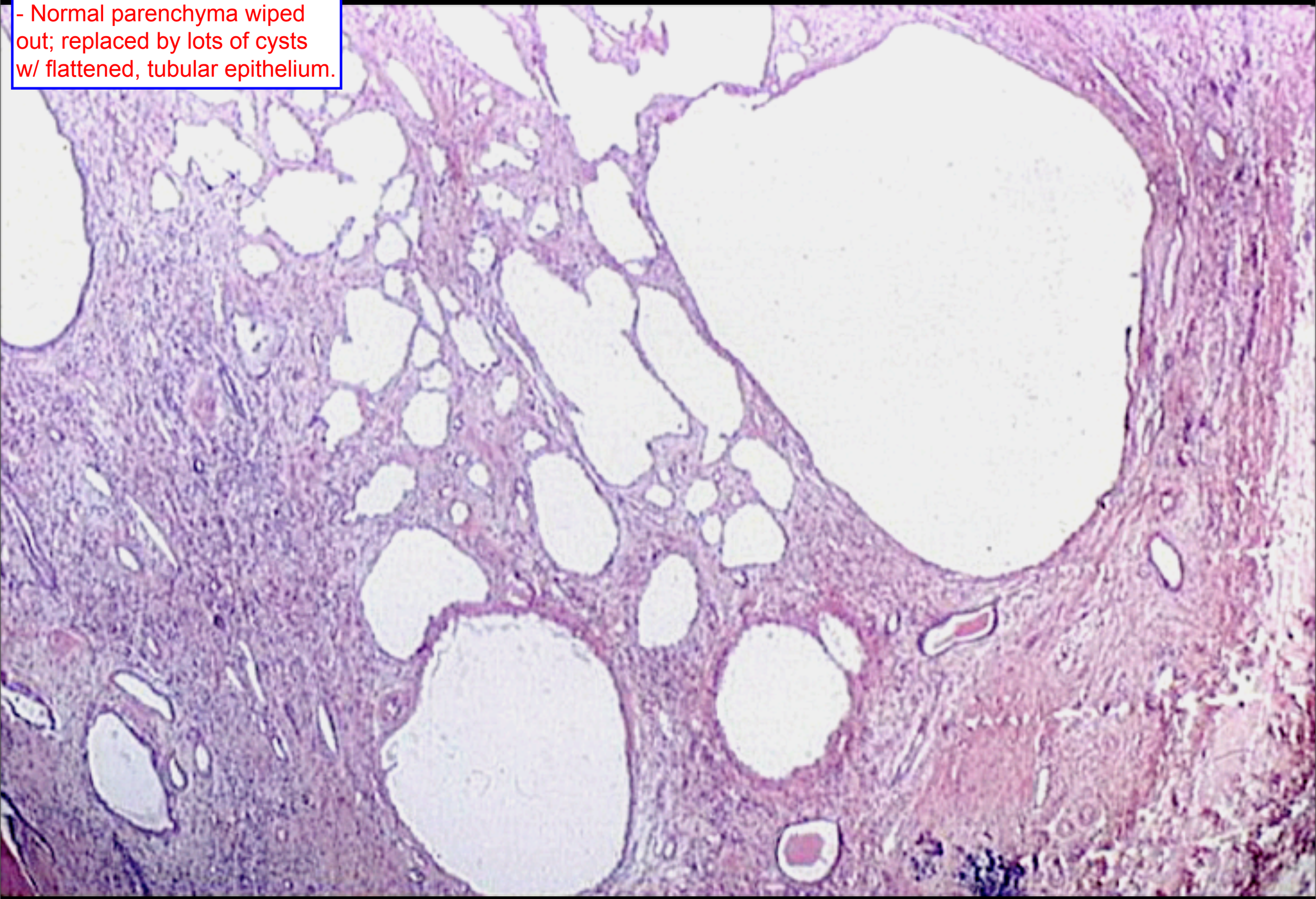
aka, kidney stones

a risk for any cystic disease of any cause

- Pic of a cystic kidney.
- Can get to be as large as a loaf of bread.
- **Usually left in Pt unless they become symptomatic or develop into a carcinoma.**



- Histo pic of cystic kidney.
- Normal parenchyma wiped out; replaced by lots of cysts w/ flattened, tubular epithelium.



- **Genes associated w/ APKD:**
1) **PKD1**
2) **PKD2**
- Gene products are polycystin proteins (calcium ion channel regulatory proteins)

APKD: Molecular basis

PKD1: chromosome 16

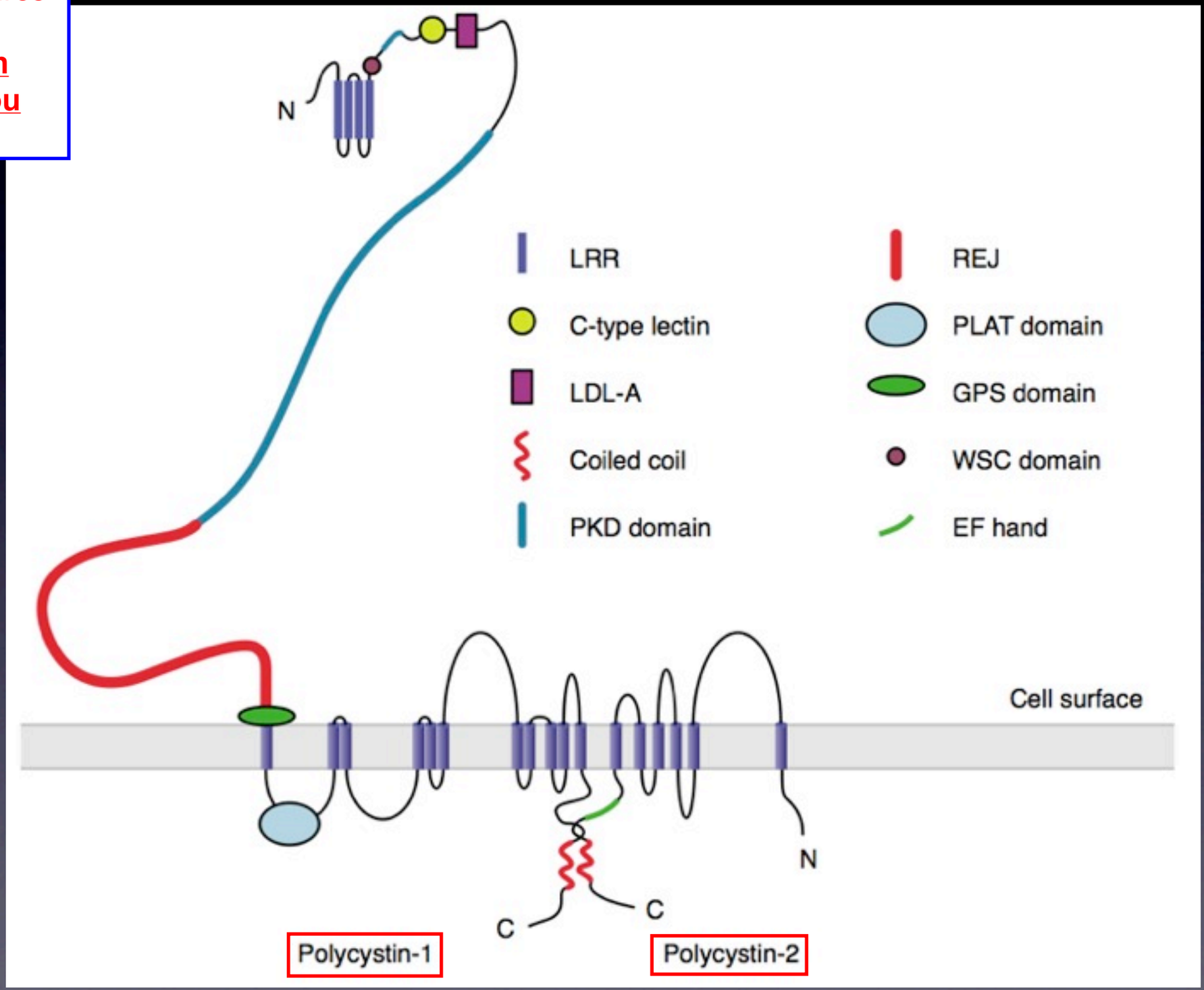
- ***PKD1*** (16p13.3) → polycystin 1
  - 4302 AA transmembrane protein
  - Protein binding and ion channel regulatory domains
  - Mutation in 90% of cases

PKD2: chromosome 4

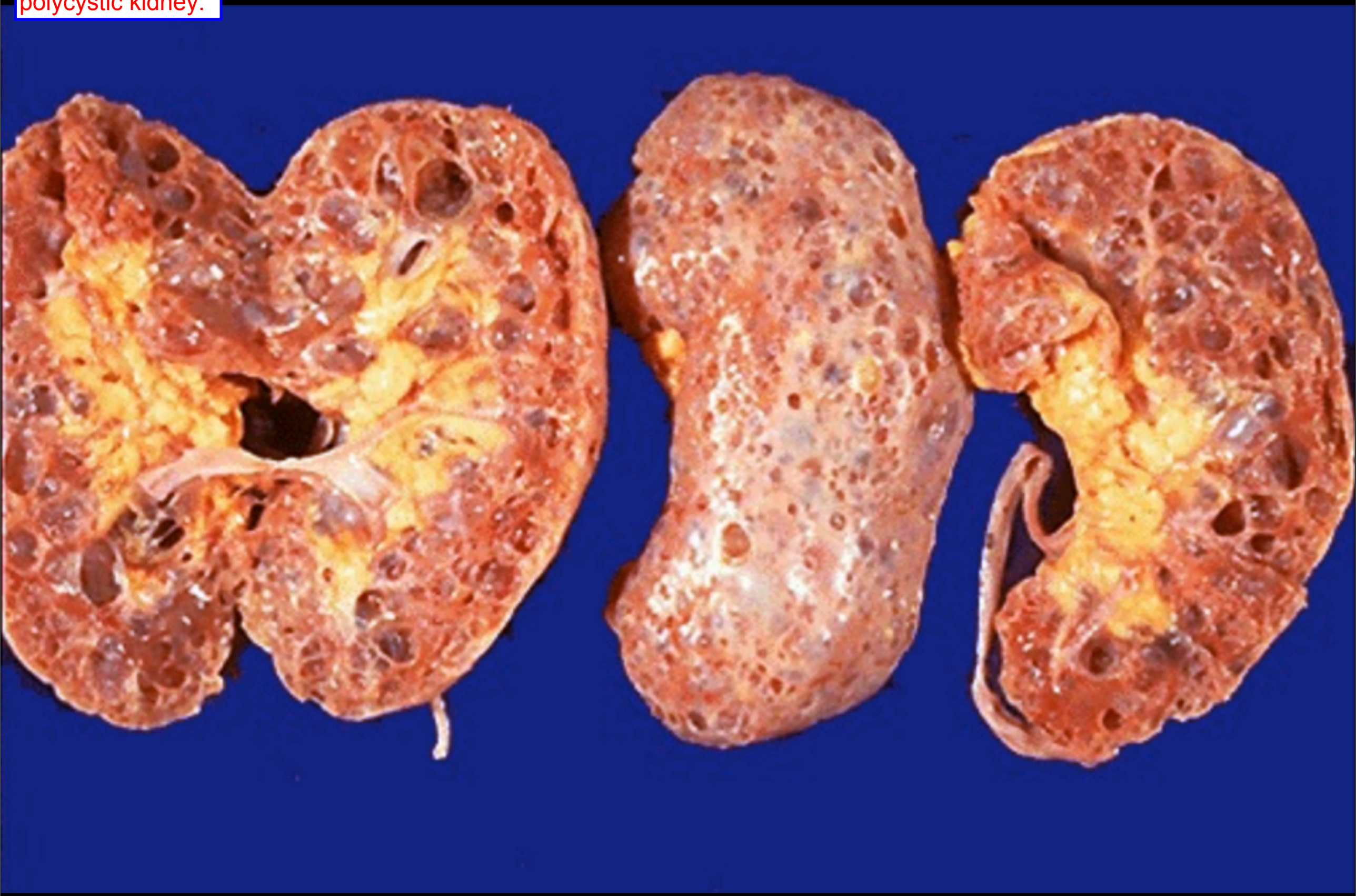
- ***PKD2*** (4q21) → polycystin 2
  - 968 AA transmembrane protein
  - Ca^{2+}-permeable nonselective cation channel
  - Mutation in remaining 10%

Domain structure of polycystins

- Predicted structures of polycystins.
- **Mutations in ion channels give you PKD.**



Another pic of a polycystic kidney.



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Can happen to **anyone on chronic dialysis**.

II. Selected renal neoplasms (next lecture...)

Acquired cystic renal disease

- Chronically non-functioning kidneys in dialysis patients
- Undergo cystic transformation after many years
- Increased risk of renal cell carcinoma

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II. Selected renal neoplasms (next lecture...)

Infantile polycystic kidney disease

- Autosomal recessive
  - PKHD1 located at 6p21
  - 1 in 20,000 pregnancies

My 3 cents on **IPKD**:
1) **Autosomal recessive**
2) Occurs in **early infancy**
3) **Bilateral kidney enlargement**

- Multiorgan manifestations
  - Bilateral renal cysts
  - Liver cysts
  - Pulmonary hypoplasia (2°)
- Most die in utero or early infancy

Section through the pelvis of baby kidney with IPKD

IPKD - Saccular dilation of all collecting tubules

Skipped!

Multicystic renal dysplasia

- Non-hereditary
  - May occur as one component of multiple malformation syndrome
- Congenital presentation
  - 1 in 1500 births
- Maldevelopmental basis
  - Obstructive ureteral anomaly (90%)
  - May have other malformations

My 4 cents on **multicystic renal dysplasia**:
1) **Most common cystic disease in children**
2) **No inheritance pattern**
3) Associated w/ abnormal development resulting in **urinary tract obstruction and malformed kidneys**
4) Most cases **present as a unilateral flank mass in an otherwise asymptomatic infant**

What important* non-neoplastic kidney diseases have we missed today, and what should you do about it?

*Could mean many things, but among them—for you at this stage in your training—might mean "board-testable"!

- **Pre-renal diseases have no associated intrinsic renal pathology.**
- Keep your eye out for highlighted terms when you're thinking about renal diseases.

Pre-renal diseases

- Remember what you have learned about atherosclerosis, the Goldblatt kidney, low cardiac output states, hypovolemia, shock etc. in other pathology and physiology lectures.
- Keep an eye open for hepatorenal syndrome.

Hepatorenal syndrome: **functional renal failure associated w/ hepatic failure.**

Intrarenal diseases

- **Most infectious diseases of the kidney are ASCENDING from the bladder.**
- Know highlighted terms.

Infectious

- Will say a bit about pyelonephritis next week in the bladder lecture
- For other infectious kidney diseases, check your Microbiology notes!
  - Tuberculosis
  - Polyomavirus

In transplant and immunosuppressed Pts.

- Know highlighted terms.

Deposition

- Read about kidney bladder stones (lithiasis) in your text
- Dr. Howell will talk about amyloidosis, myeloma kidney, etc.

Autoimmune

- Dr. Howell

- Know highlighted terms.

Post-renal

- We will talk in bladder lecture next week about some obstructive diseases of urinary tract and their effects on the kidney.

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II. Selected renal neoplasms (next lecture...)

Switching gears to neoplasms...

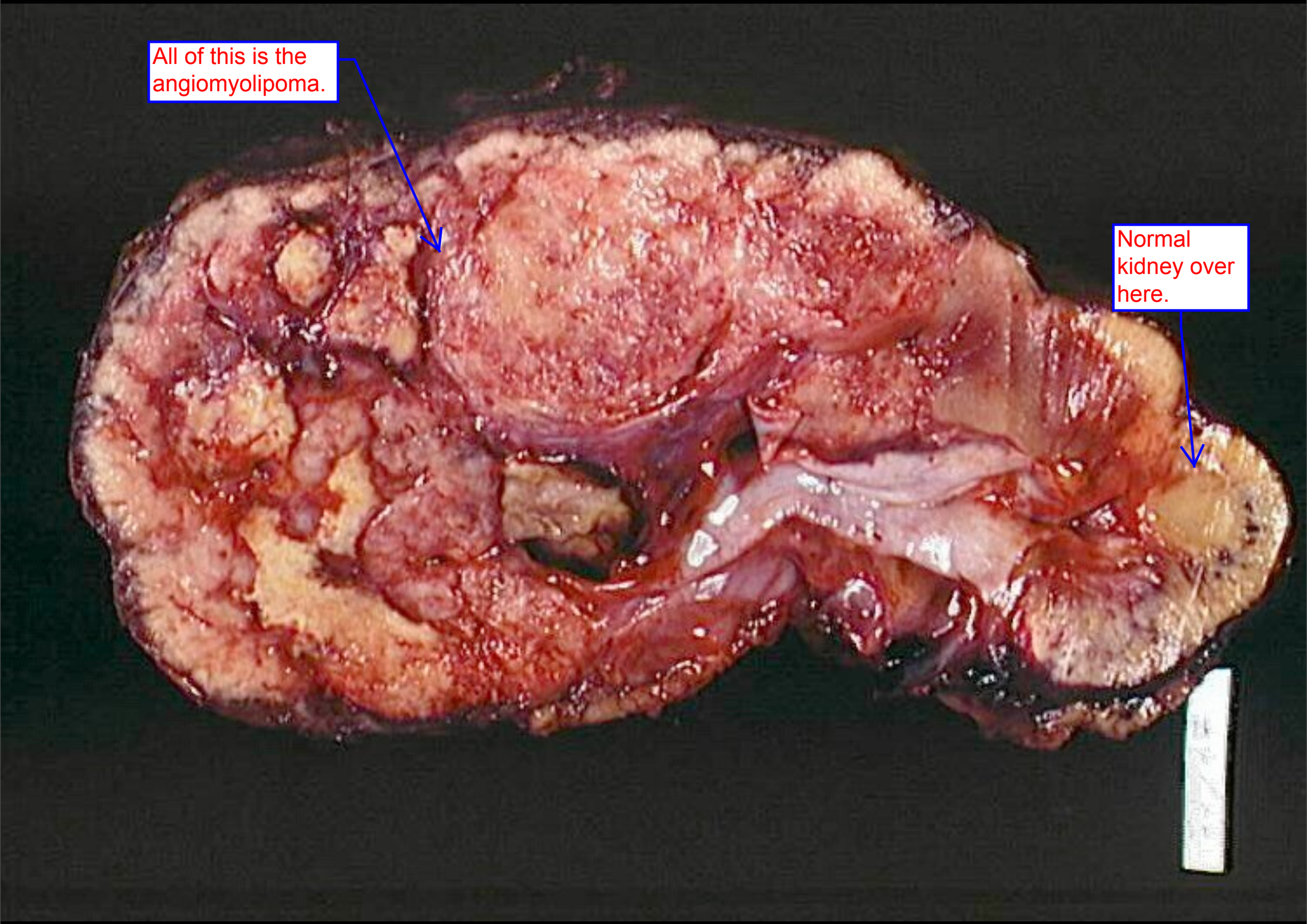
Featured kidney neoplasms

- Benign
  - Angiomyolipoma
  - Renal oncocytoma
  - Others
- Malignant
  - Renal cell carcinoma
  - Renal medullary carcinoma
  - Nephroblastoma
  - Others

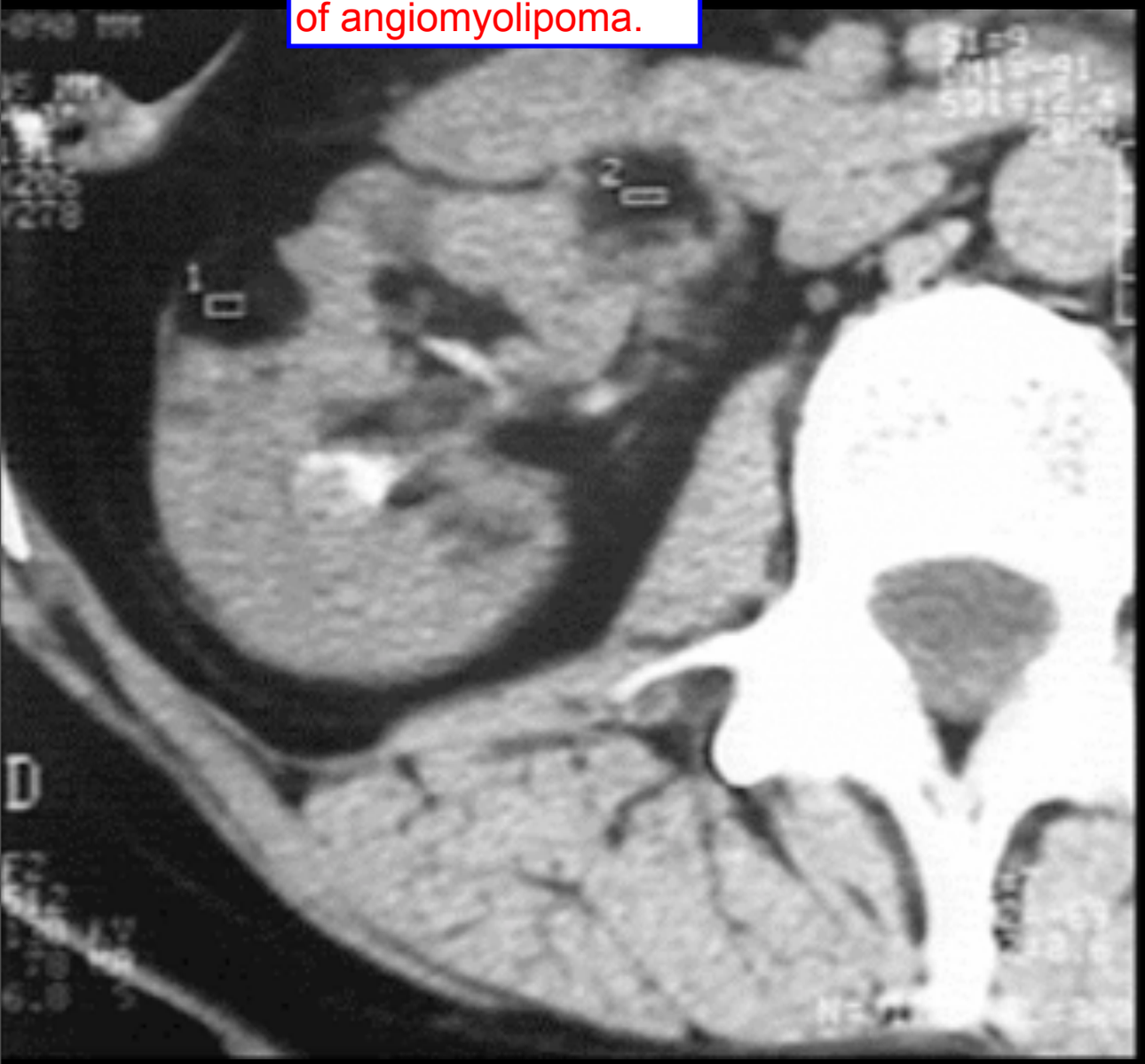
- **Often discovered incidentally.**
- **Association w/ tuberous sclerosis (TS)**
1) 70% of TS Pts have angiomyolipoma
2) 20-25% of angiomyolipoma Pts have TS

Angiomyolipoma

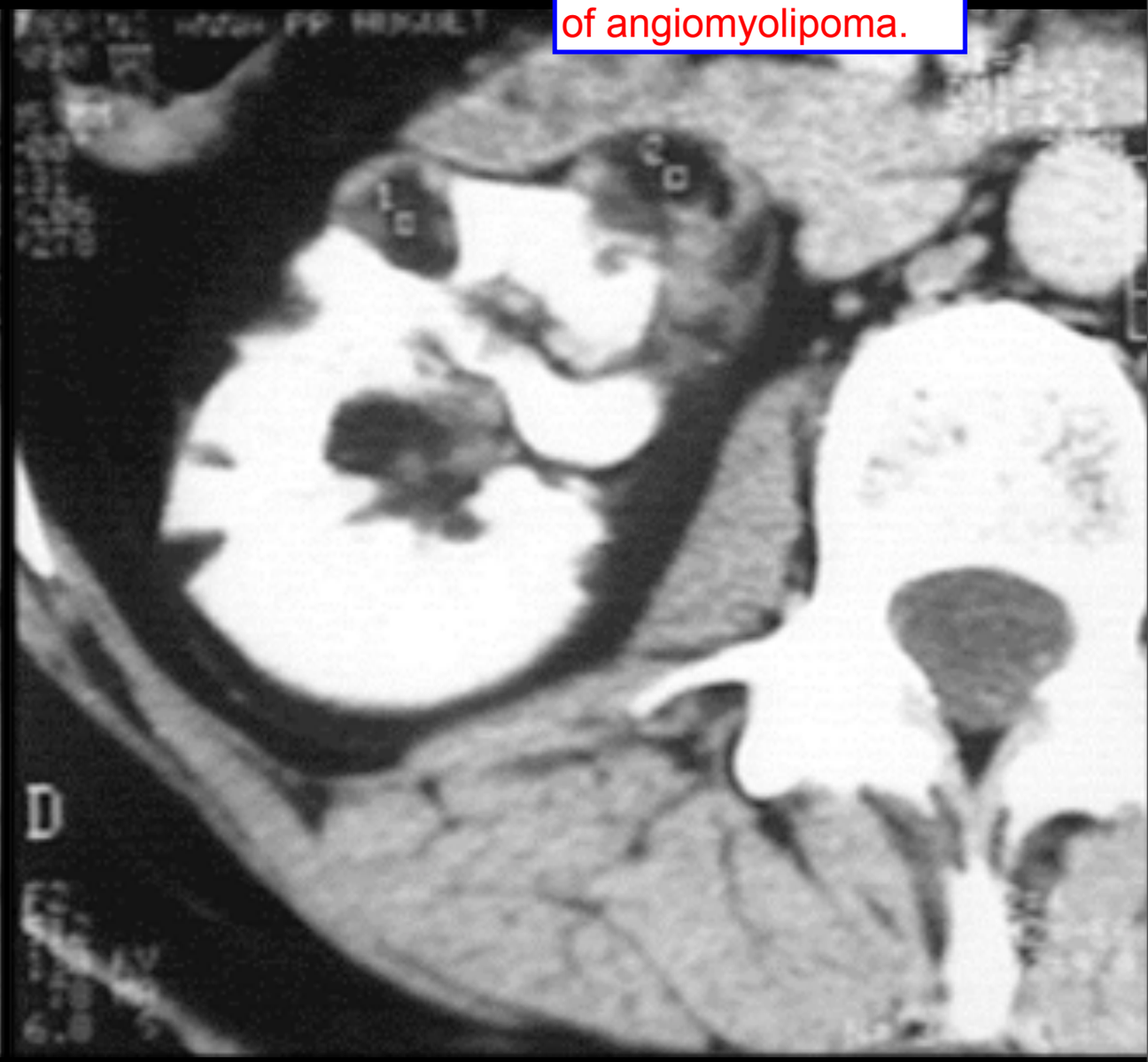
- Benign tumor consisting of:
  - abnormal blood vessels and has lots of them
  - proliferating smooth muscle
  - fat
- About 2% of renal tumors
- Middle-age
- Females > males
- 1 in 4 have tuberous sclerosis


All of this is the angiomyolipoma.
Normal kidney over here.

CT scan w/o contrast of angiomyolipoma.

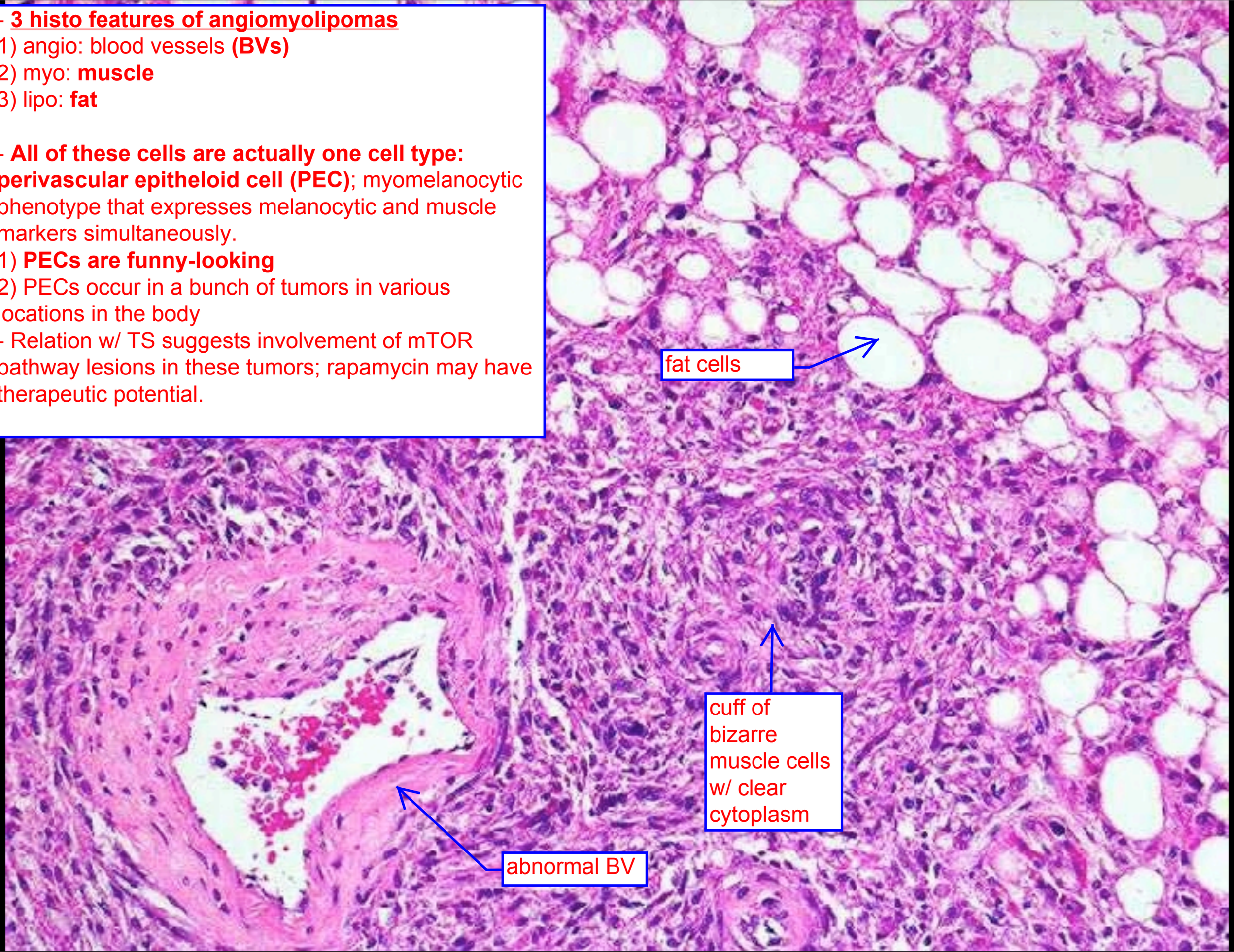


CT scan w/ contrast of angiomyolipoma.



- **3 histo features of angiomyolipomas**
1) angio: blood vessels **(BVs)**
2) myo: **muscle**
3) lipo: **fat**

- **All of these cells are actually one cell type: perivascular epitheloid cell (PEC)**; myomelanocytic phenotype that expresses melanocytic and muscle markers simultaneously.
1) **PECs are funny-looking**
2) PECs occur in a bunch of tumors in various locations in the body
- Relation w/ TS suggests involvement of mTOR pathway lesions in these tumors; rapamycin may have therapeutic potential.



Angiomyolipoma: clinical

- Larger tumors symptomatic, smaller tumors incidental
- Radiographic differential diagnosis = renal cell carcinoma

Radiographically, **look a lot like renal cell carcinoma**, which is also very vascular.

- Therapy
  - Symptomatic → nephrectomy
  - Asymptomatic ?→ embolization
- Workup patient for tuberous sclerosis

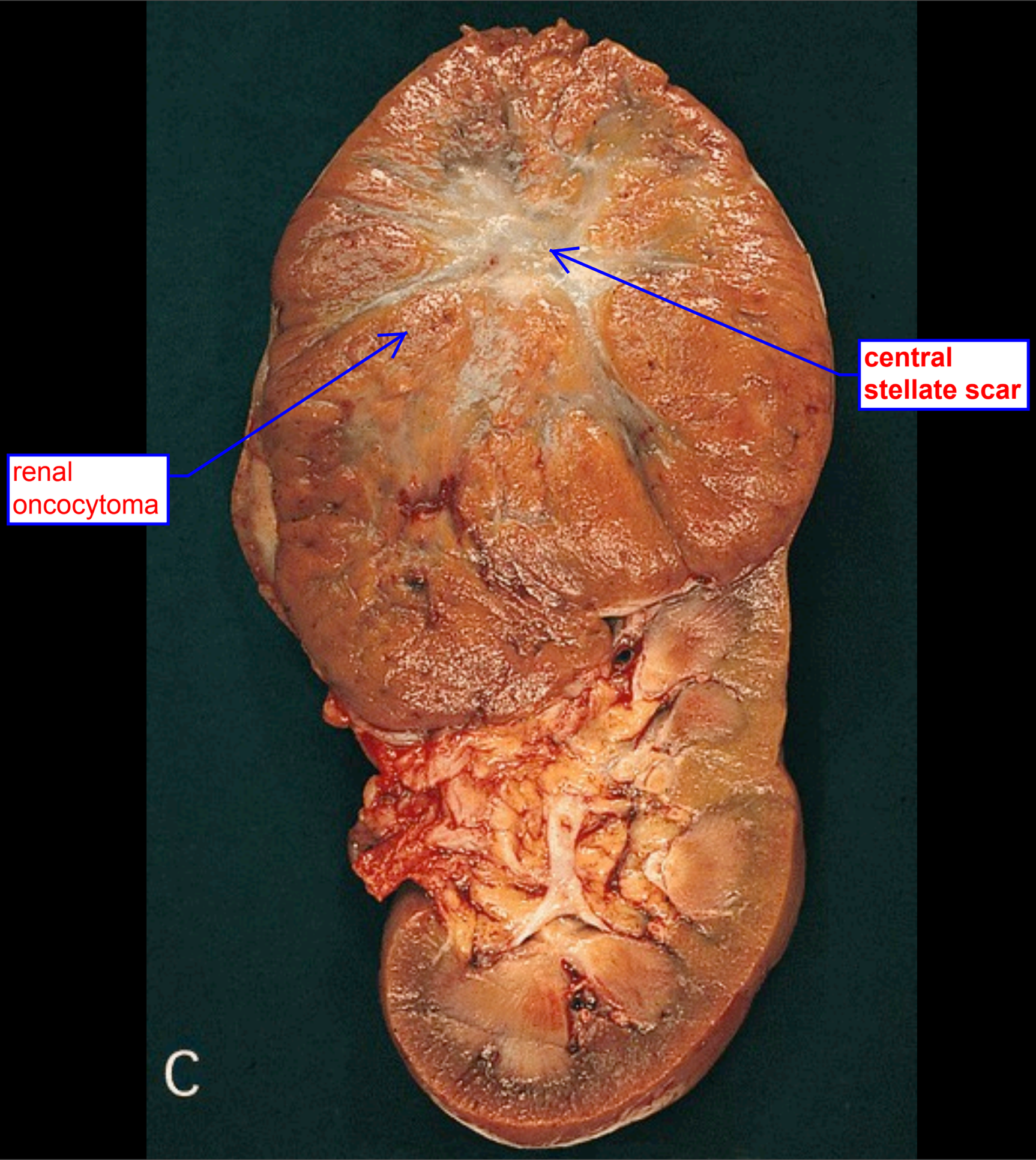
Remember to **check for TS in Pts w/ angiomyolipomas**!

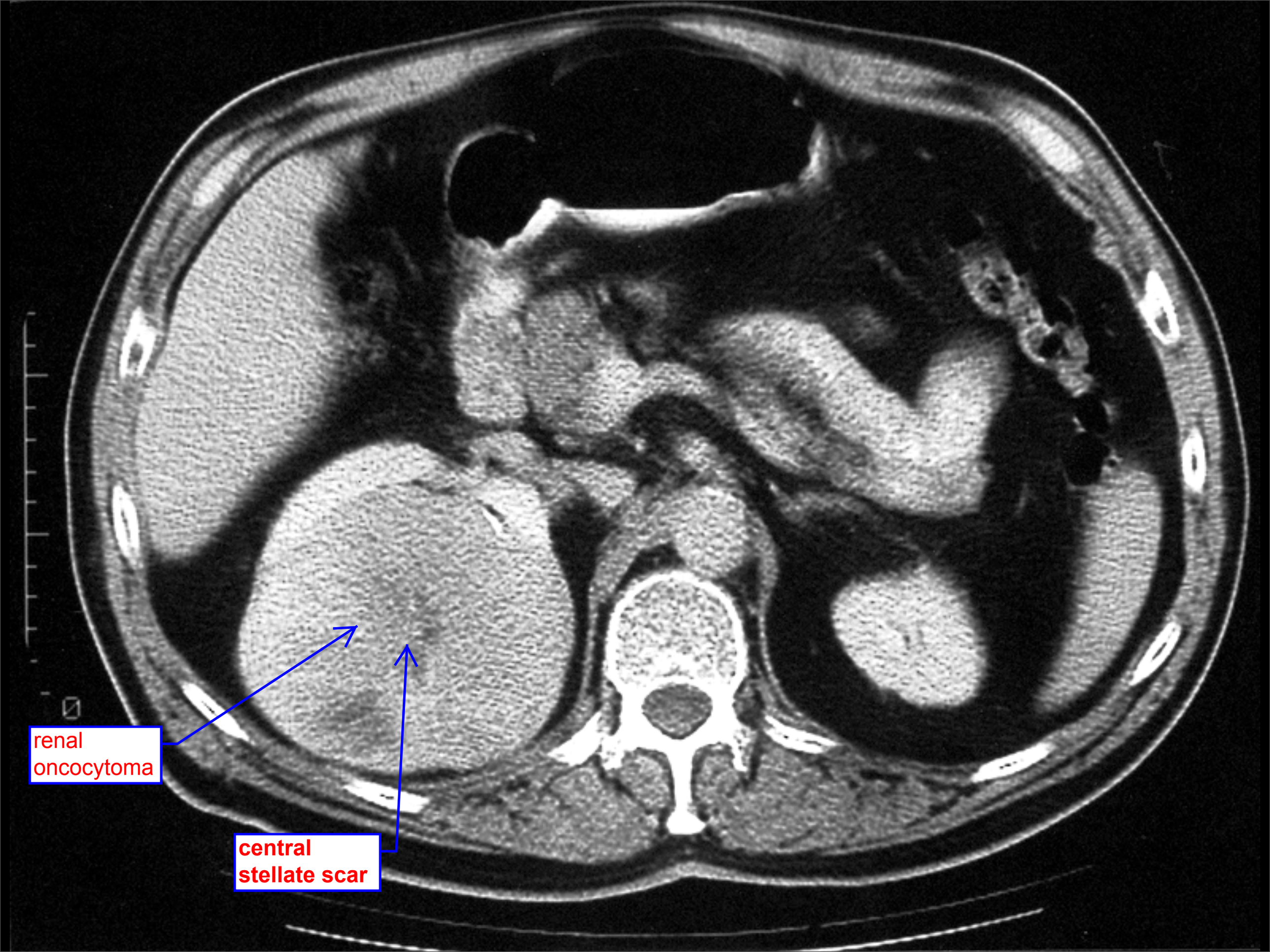
Renal oncocytoma

- Benign neoplasm consisting of "oncocytes"
- About 3% of nephrectomies for tumor
- Usually asymptomatic, incidental
  - ↑incidence ← ↑imaging
- Older adults
- Males > females
- Circumscribed cortical mass
- Central stellate scar

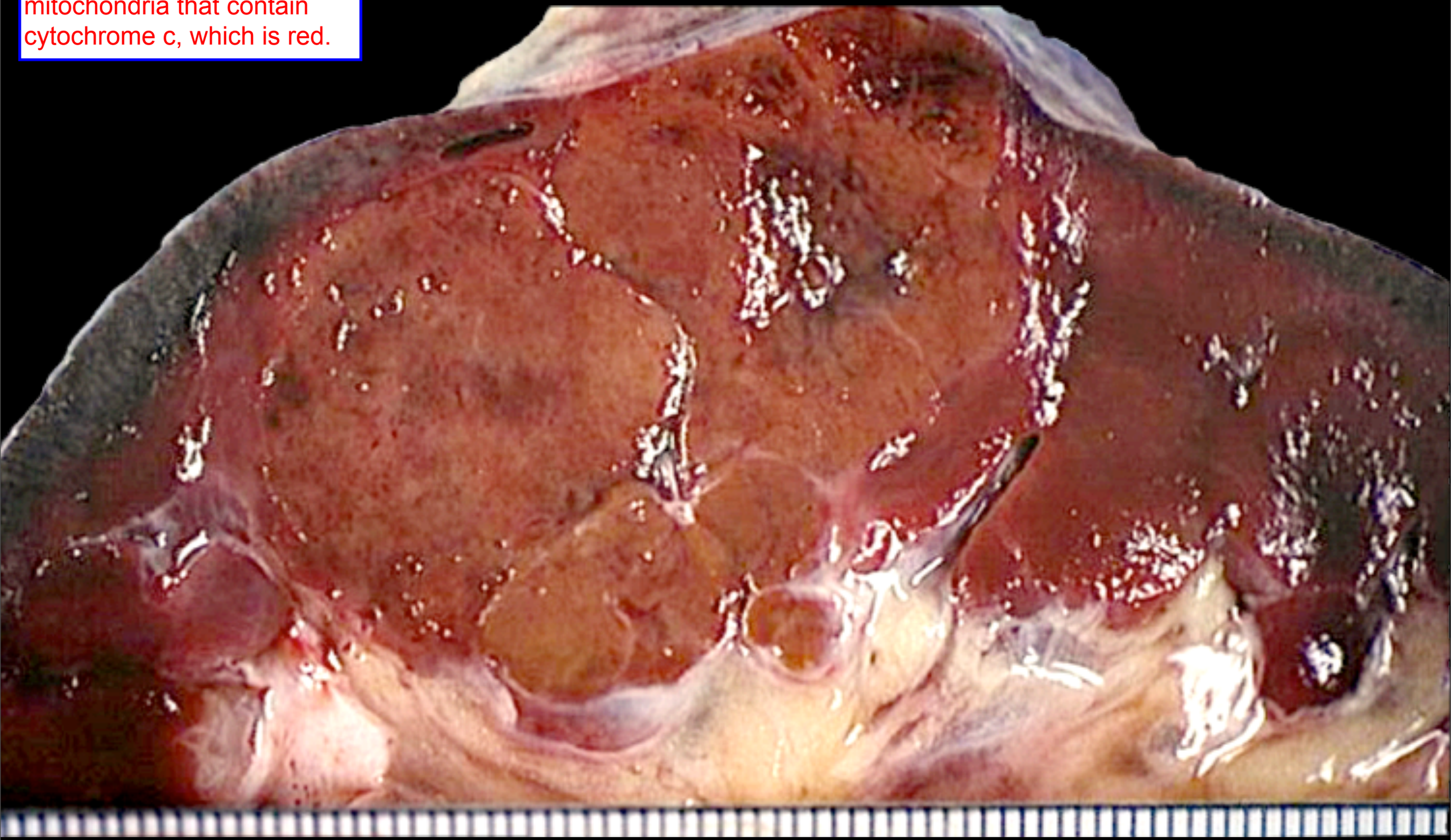
- Like w/ angiomyolipomas, renal oncocytomas **look like renal cell carcinoma (RCC)**, so surgeons take them out and find them to be otherwise post-op.
- **Benign**, so you won't die of them, but could end up having partial or complete nephrectomies on their account since they look like RCC.
- **Also made of odd cell type: oncocytes**
- Increased incidence likely due to increased imaging.
- Could get biopsy of them and if (+), then can treat w/ cryotherapy.

Central stellate scar: used by radiologists to indicate level of suspicion of a mass to be renal oncocytoma.

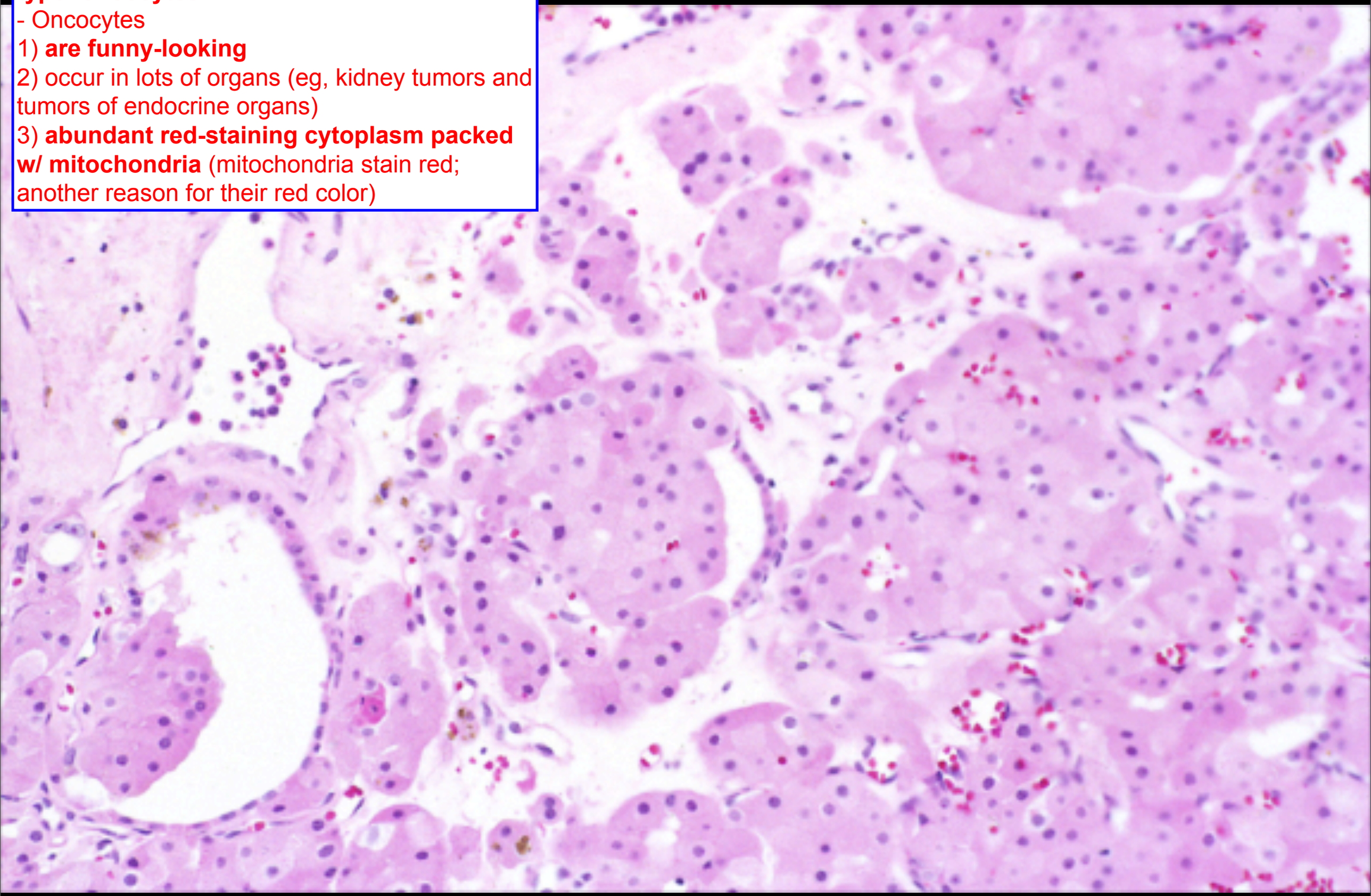

renal
oncocytoma
central
stellate scar
C

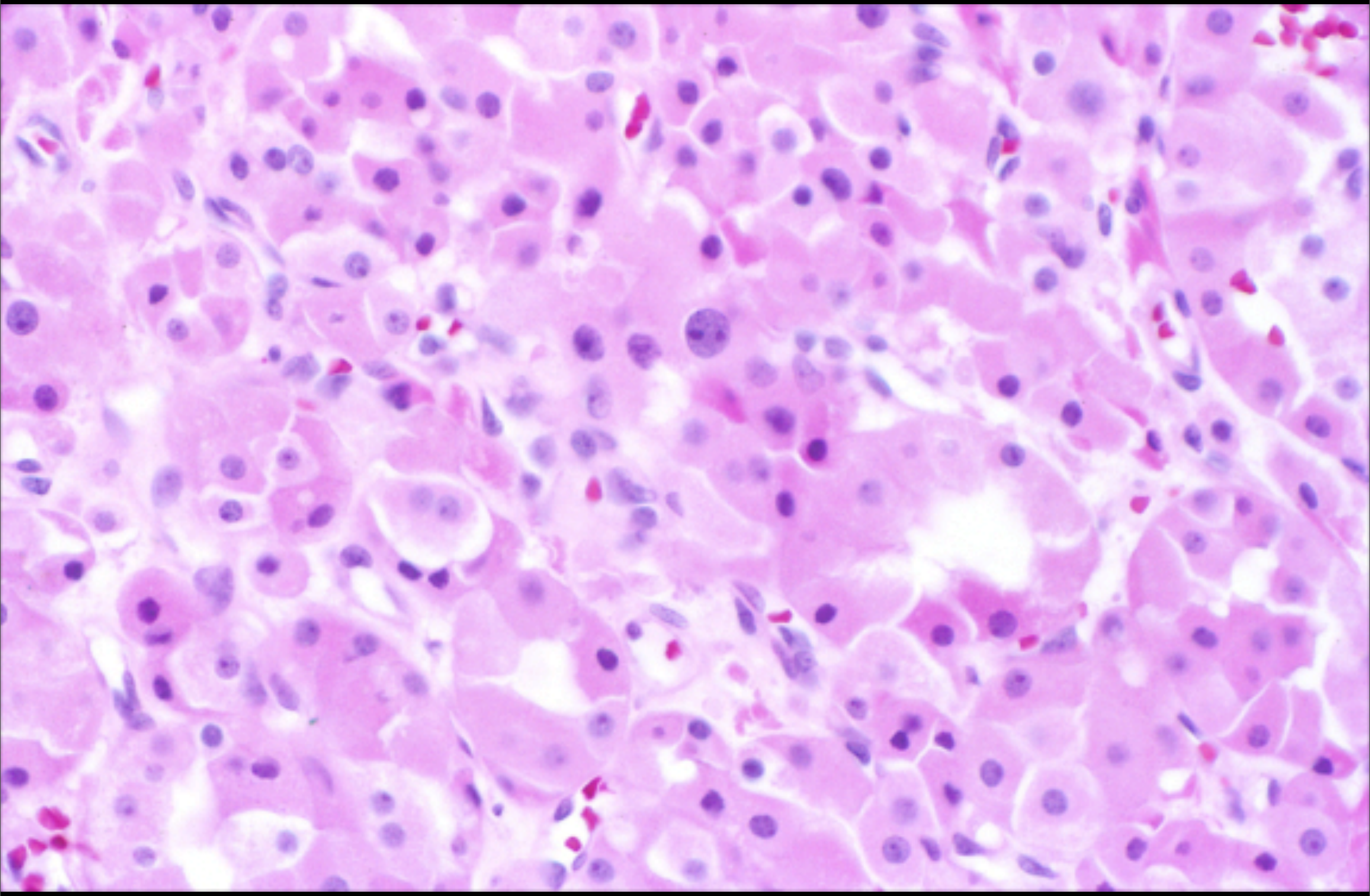

renal
oncocytoma
central
stellate scar

Renal oncocytomas are mahogany or red-colored: due to all the mitochondria that contain cytochrome c, which is red.

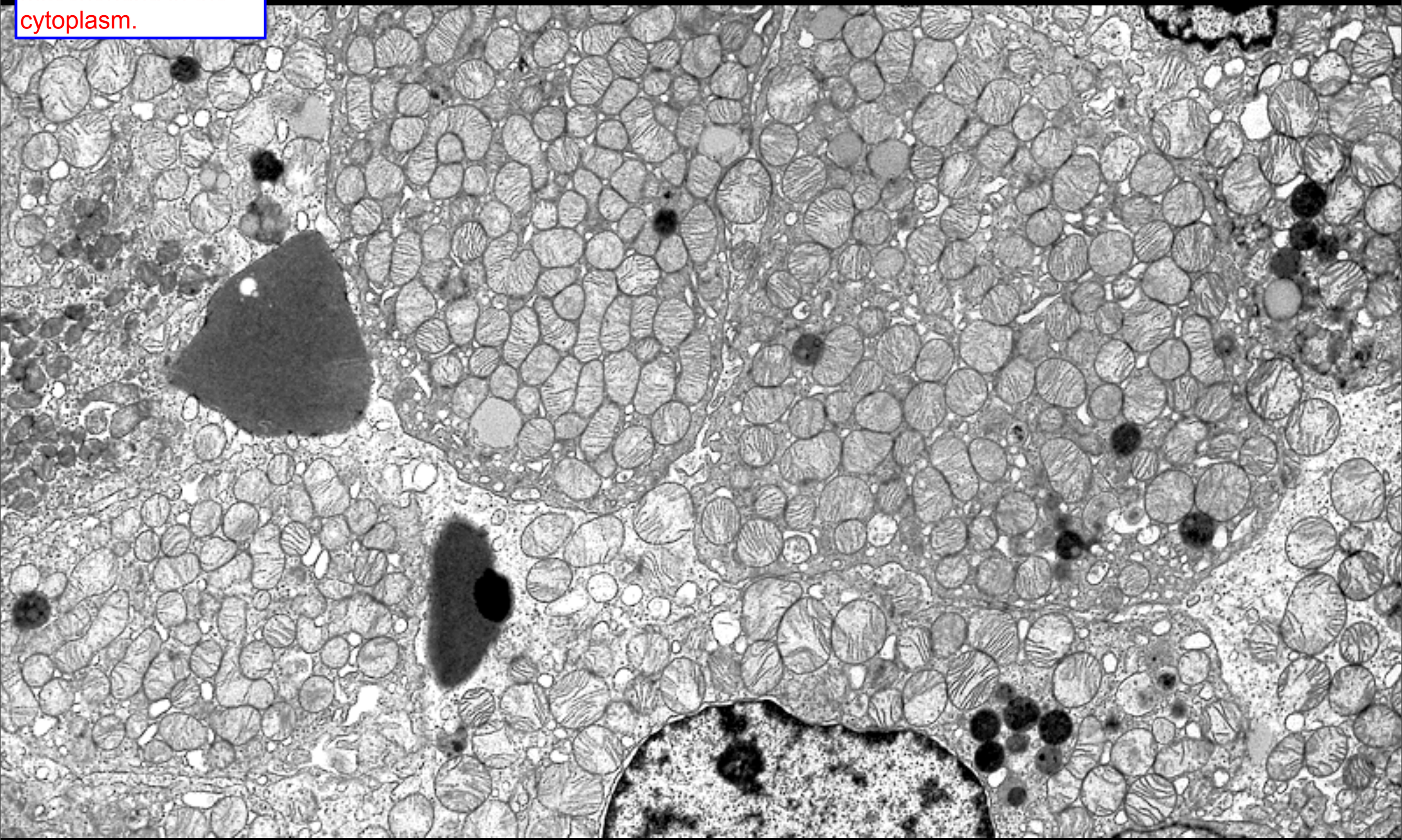


- **Renal oncocytomas are made of odd cell type: oncocytes.**
- Oncocytes
1) **are funny-looking**
2) occur in lots of organs (eg, kidney tumors and tumors of endocrine organs)
3) **abundant red-staining cytoplasm packed w/ mitochondria** (mitochondria stain red; another reason for their red color)





EM pic of oncocytes with lots of mitochondria in the cytoplasm.

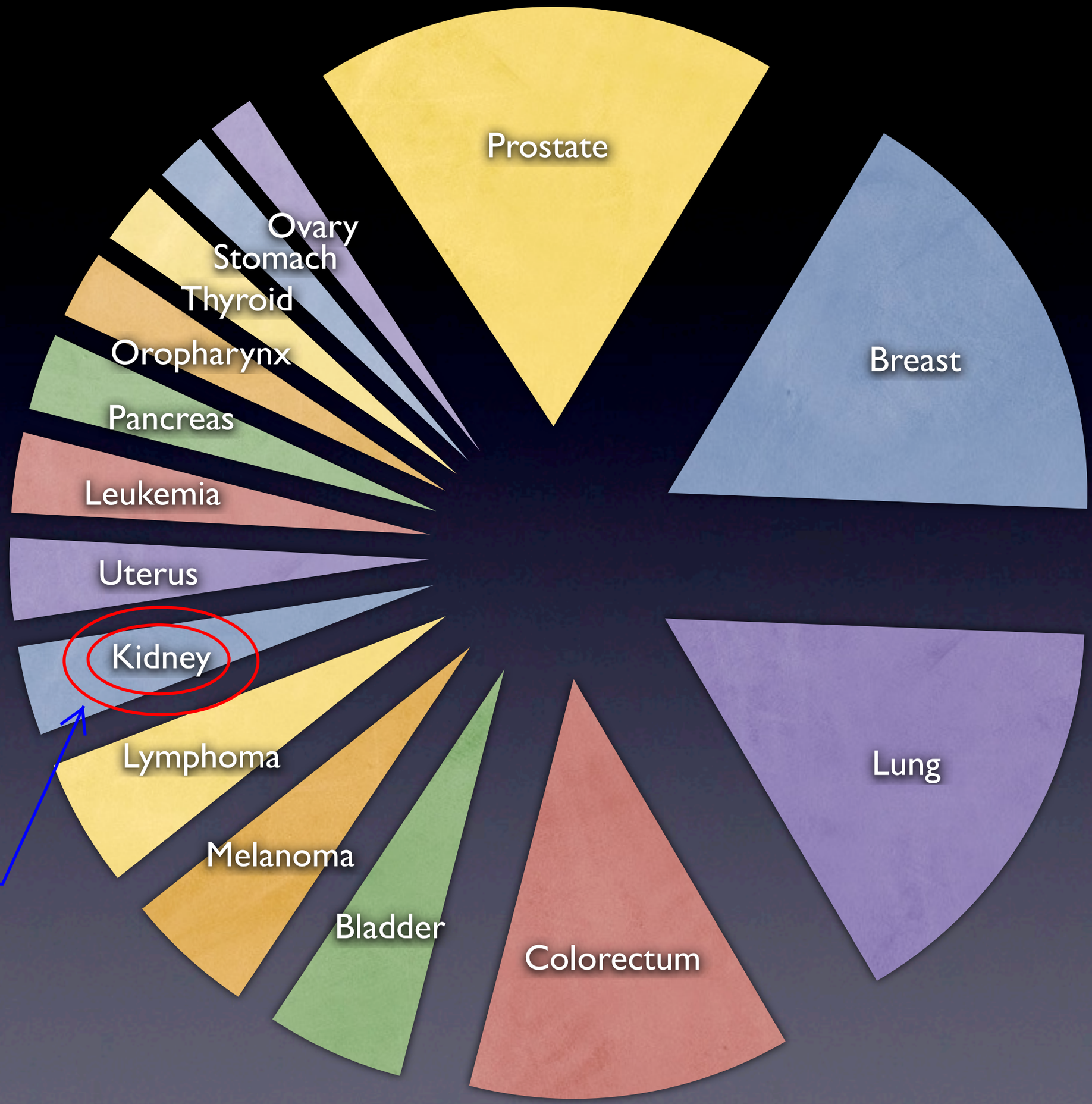


RCC
1) **malignant**
2) **most common renal tumor**
3) usually presents in mid-50s
4) slight male predominance

Renal cell carcinoma (RCC)

- Most common renal tumor
  - 3% of adult malignancies
- Median age 55 years
- Male : female :: 1.6 : 1
- Risk factors ← Not well-defined, but here are some of them.
  - Tobacco
  - Hereditary/acquired cystic disease
  - von Hippel-Lindau syndrome

Relative US Cancer Incidence by Site, both sexes, all races, 2002-2006



RCC fairly common when compared to other cancers like pancreatic and endometrial.

RCC: Clinical

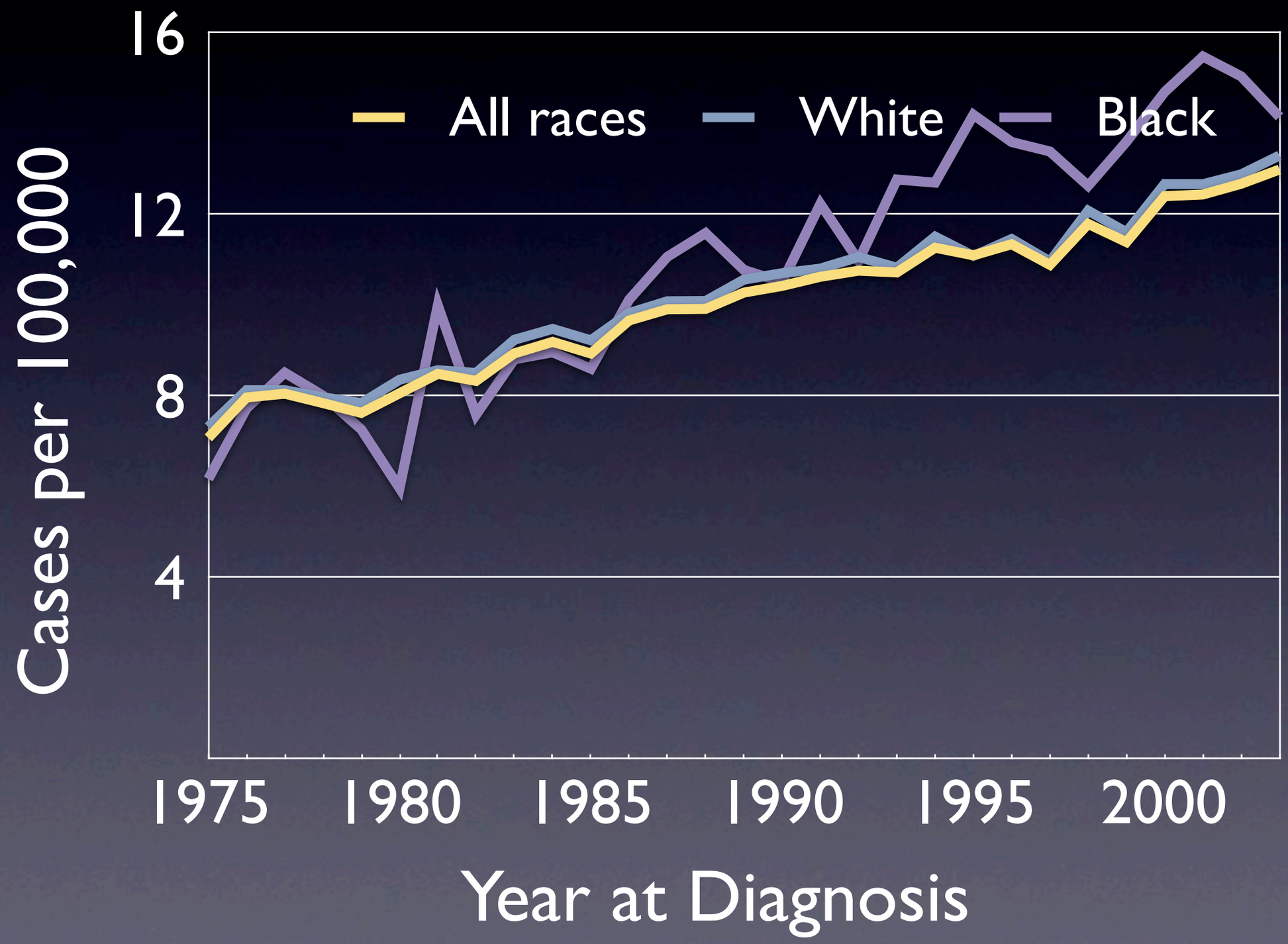
- Majority asymptomatic
- "Classic triad" ⇒ advanced disease
  - Hematuria
  - Flank pain
  - Flank mass
- Paraneoplastic syndromes
  - Erythrocytosis
  - Hypercalcemia
  - Liver dysfunction

'Classic triad' only shows up in advanced disease, so don't bank on it to make the diagnosis!

These might actually bring the Pt to the forefront of the physician's attention.

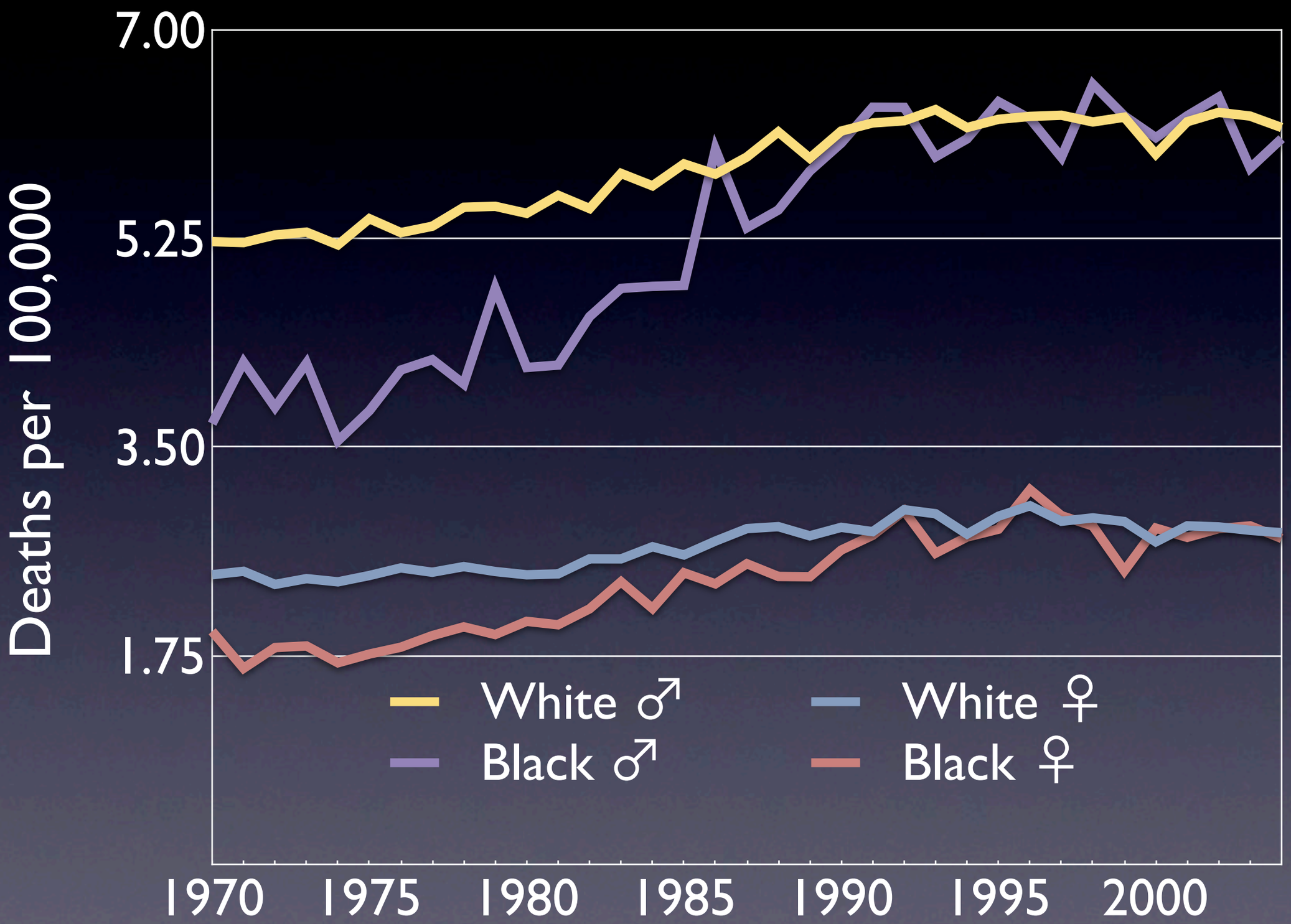
- **Increased incidence of kidney cancers** likely due to:
1) better imaging
2) better diagnoses

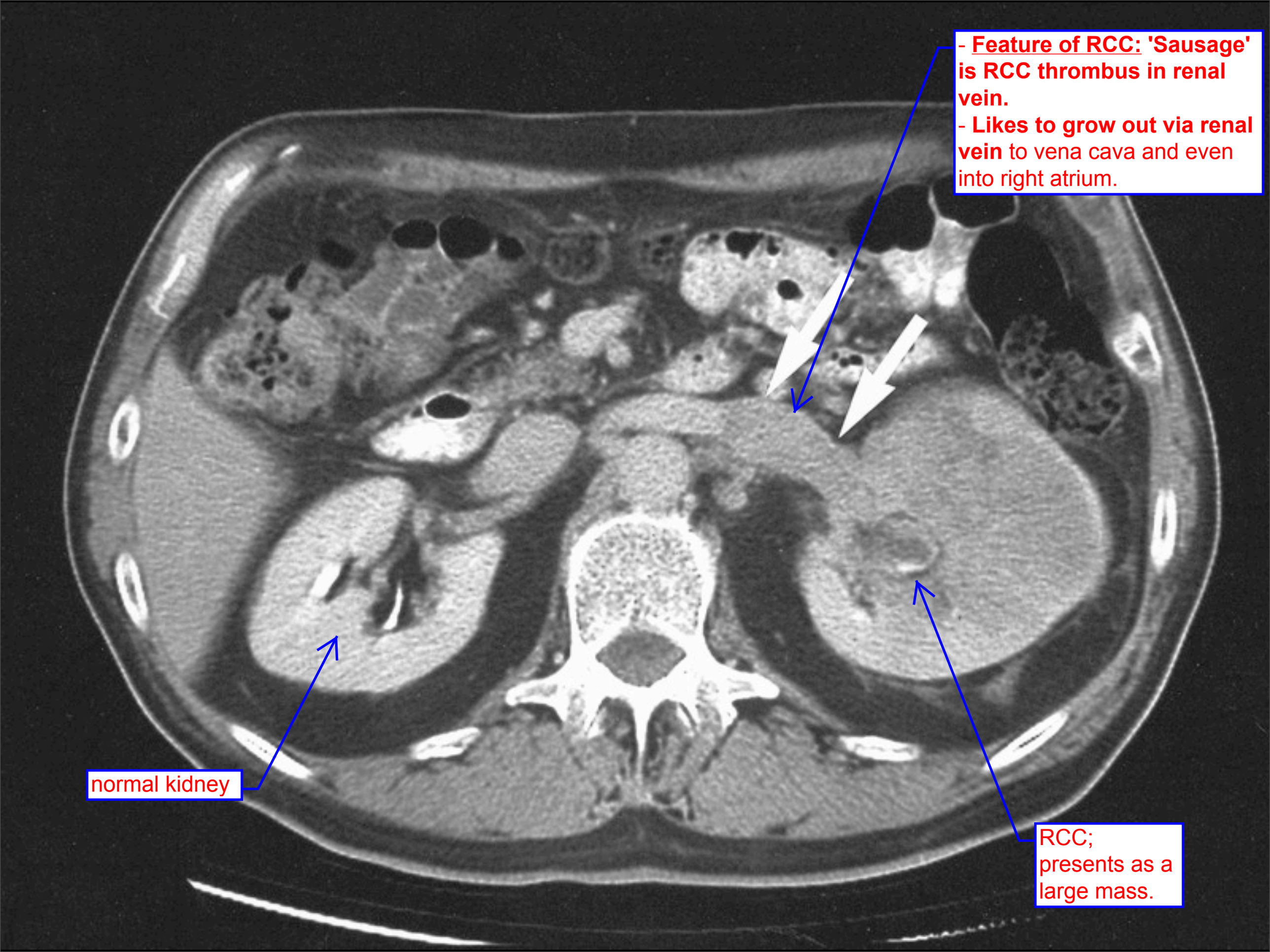
RCC Incidence



- **5-yr survival for RCC has increased due to better meds and possibly earlier diagnosis**; used to be treated only via surgery.

RCC mortality




- Feature of RCC: 'Sausage' is RCC thrombus in renal vein.
- Likes to grow out via renal vein to vena cava and even into right atrium.
normal kidney
RCC; presents as a large mass.

RCC Staging

whether it stays within the kidney or not

T1 Localized to kidney, ≤7 cm

T2 Localized to kidney, >7 cm

T3 Local extension

T4 Wide extension

N #/size of (+) nodes

M Distant metastasis

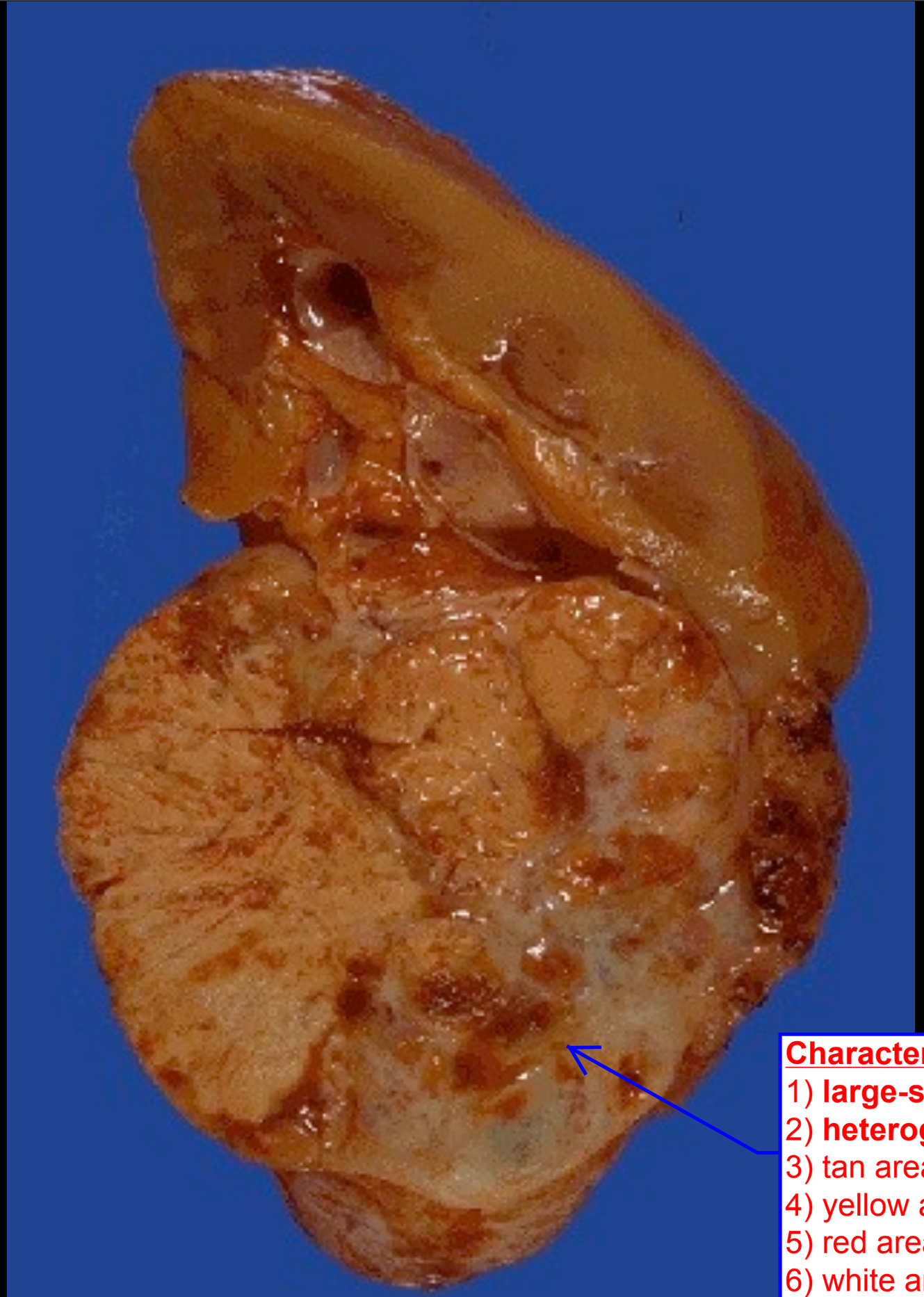
- There are **about a half-dozen RCC subtypes**.
- Although cytogenetically different, they **all have the same prognosis and you treat them the same**.

RCC Subtypes

- Characteristic cytogenetic abnormalities
- Prognostic significance
- Important for pathologic recognition

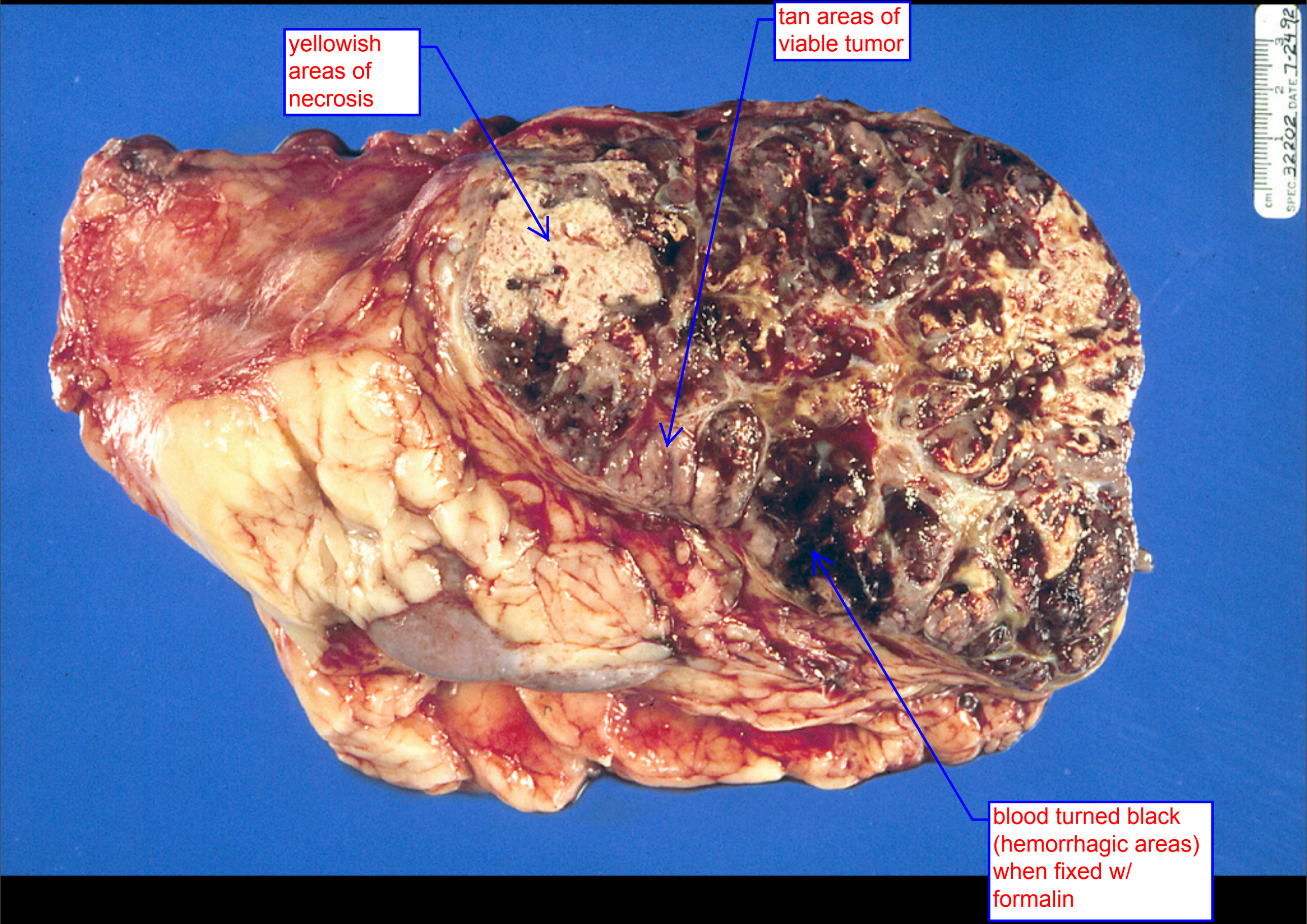
Conventional ("clear-cell") RCC

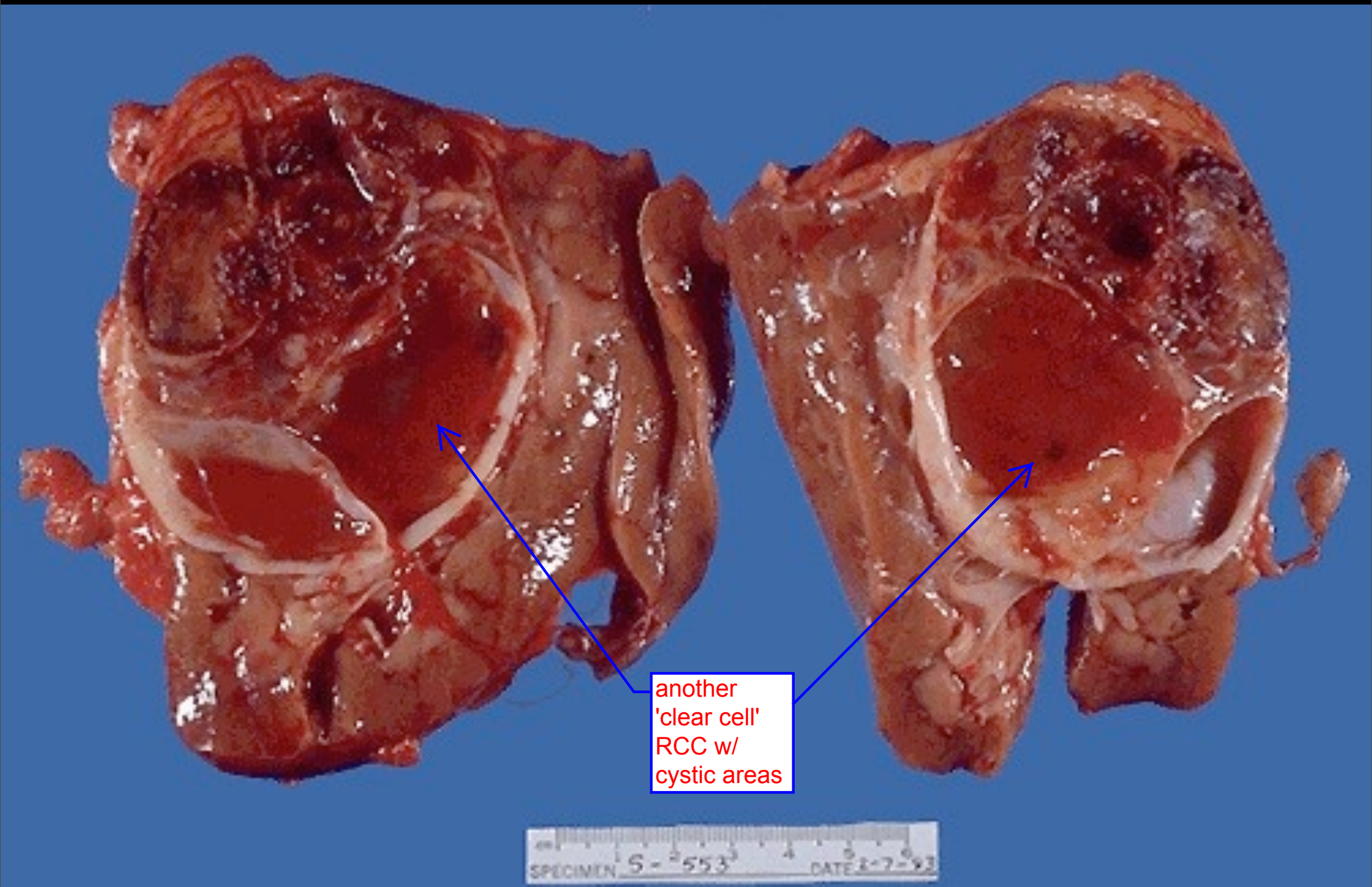
- Most common subtype (70%)
- Frequently has del 3p
- Characteristic appearance
- Rounded cortical mass
- Variegated cut surface
  Tan (viable tumor with lipid), yellow (necrosis), red (hemorrhage), white (calcification)
- Cystic areas (±)
- Extension into renal vein (±)



Characteristic appearance:

1) **large-sized mass**
2) **heterogeneous**
3) tan areas: viable tumor with **lipids**
4) yellow areas: **necrosis**
5) red areas: **hemorrhage**
6) white areas: **dystrophic calcification**

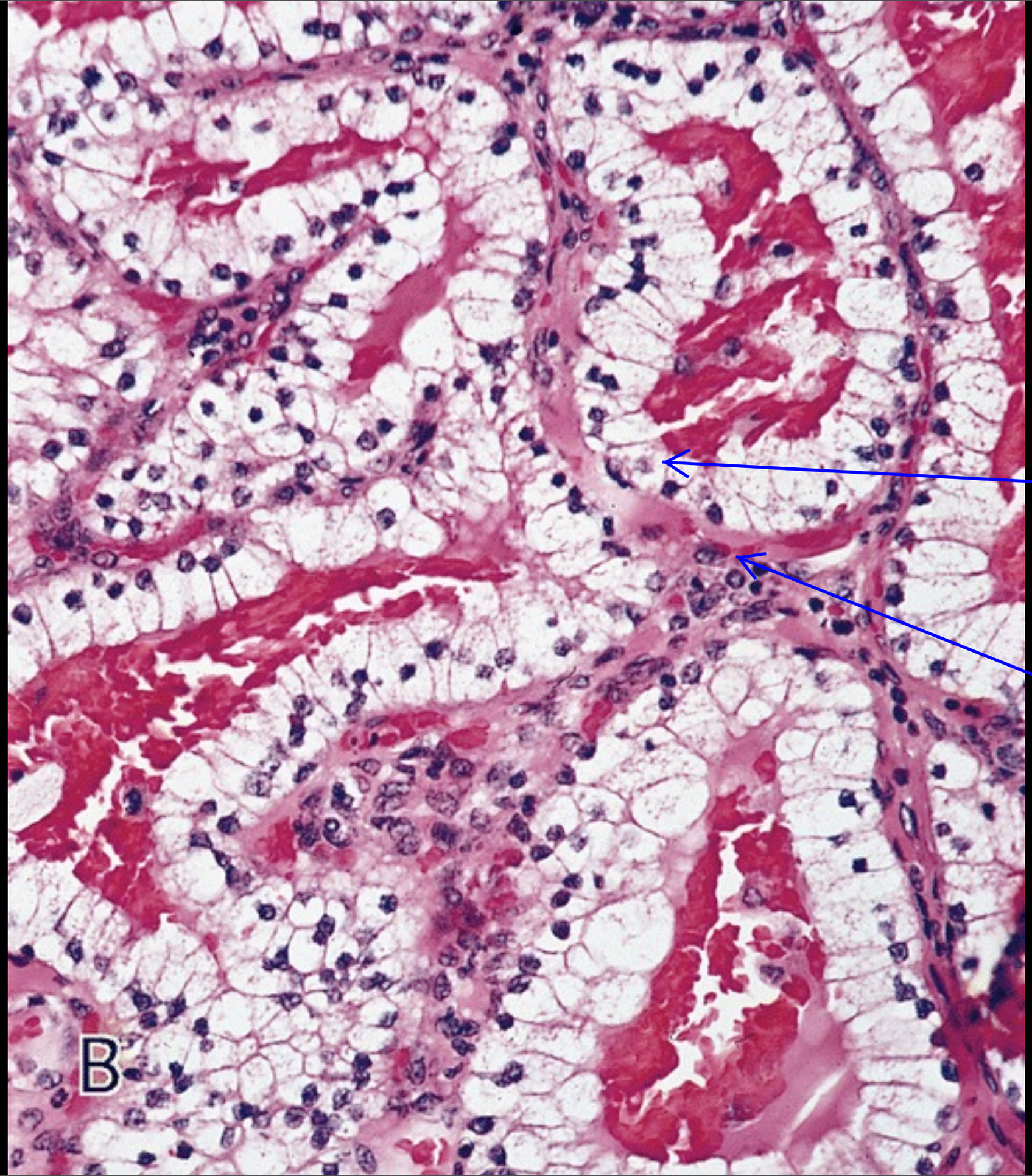

yellowish areas of necrosis
tan areas of viable tumor
blood turned black (hemorrhagic areas) when fixed w/ formalin

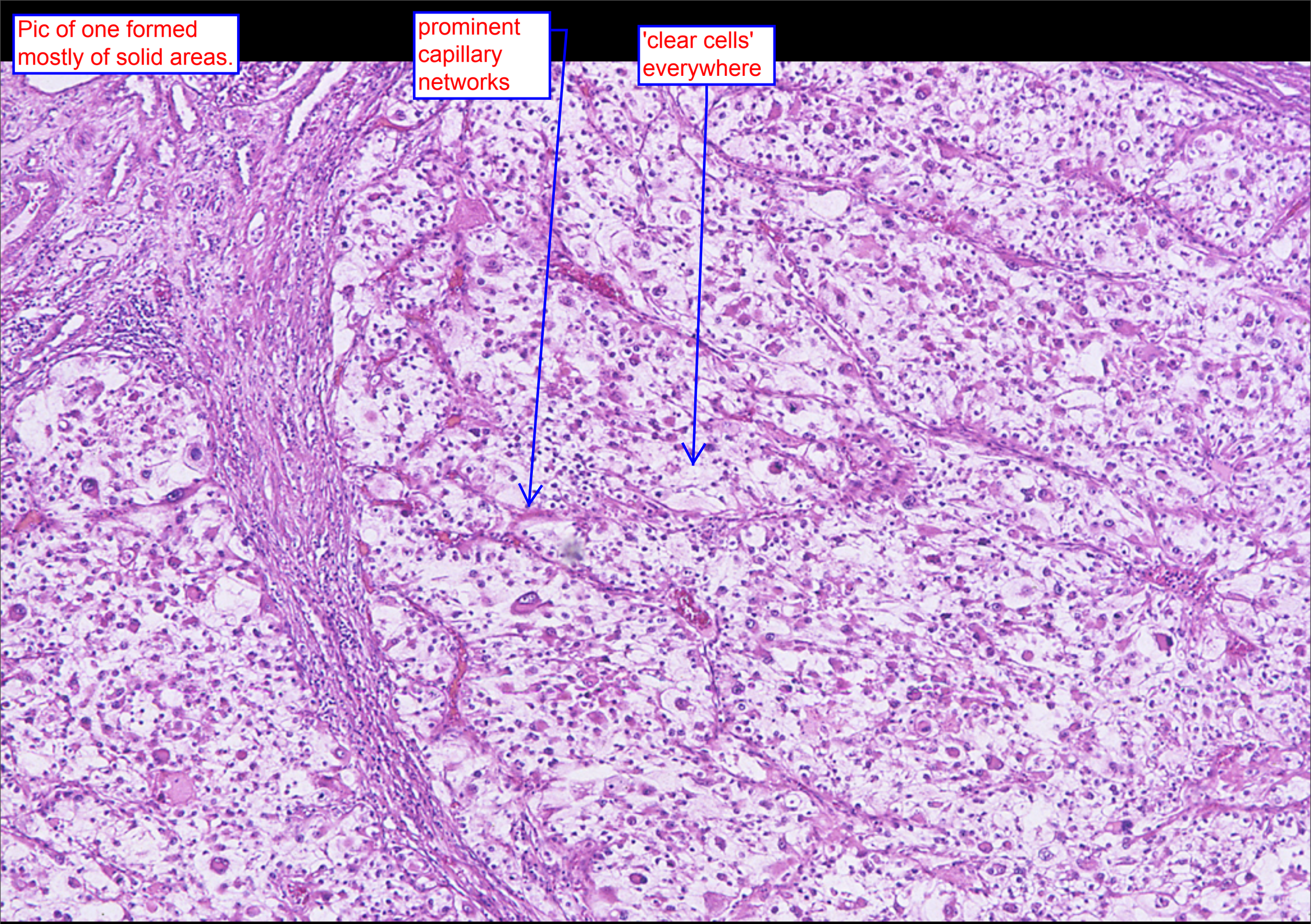

another
'clear cell'
RCC w/
cystic areas
SPECIMEN S-553
DATE 8-7-93

Conventional RCC: microscopic

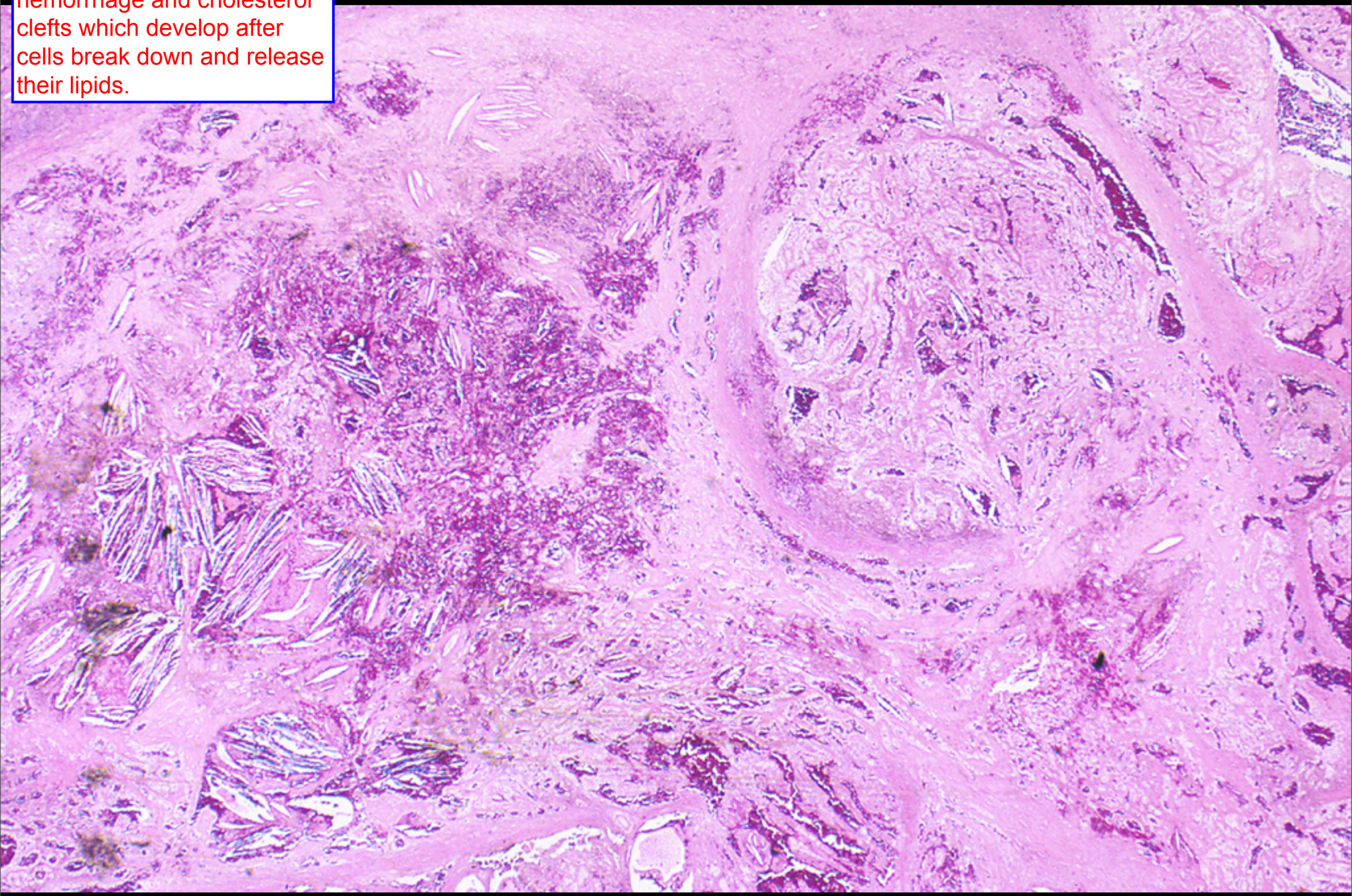
- "Clear cell"
- Cytoplasmic lipid and glycogen ← why cells are 'clear'
- Solid or glandular
- Prominent capillary network
- Frequent hemorrhage and necrosis

- Pic of 'clear cell' RCC.
- Can form glands, solid areas and cysts.

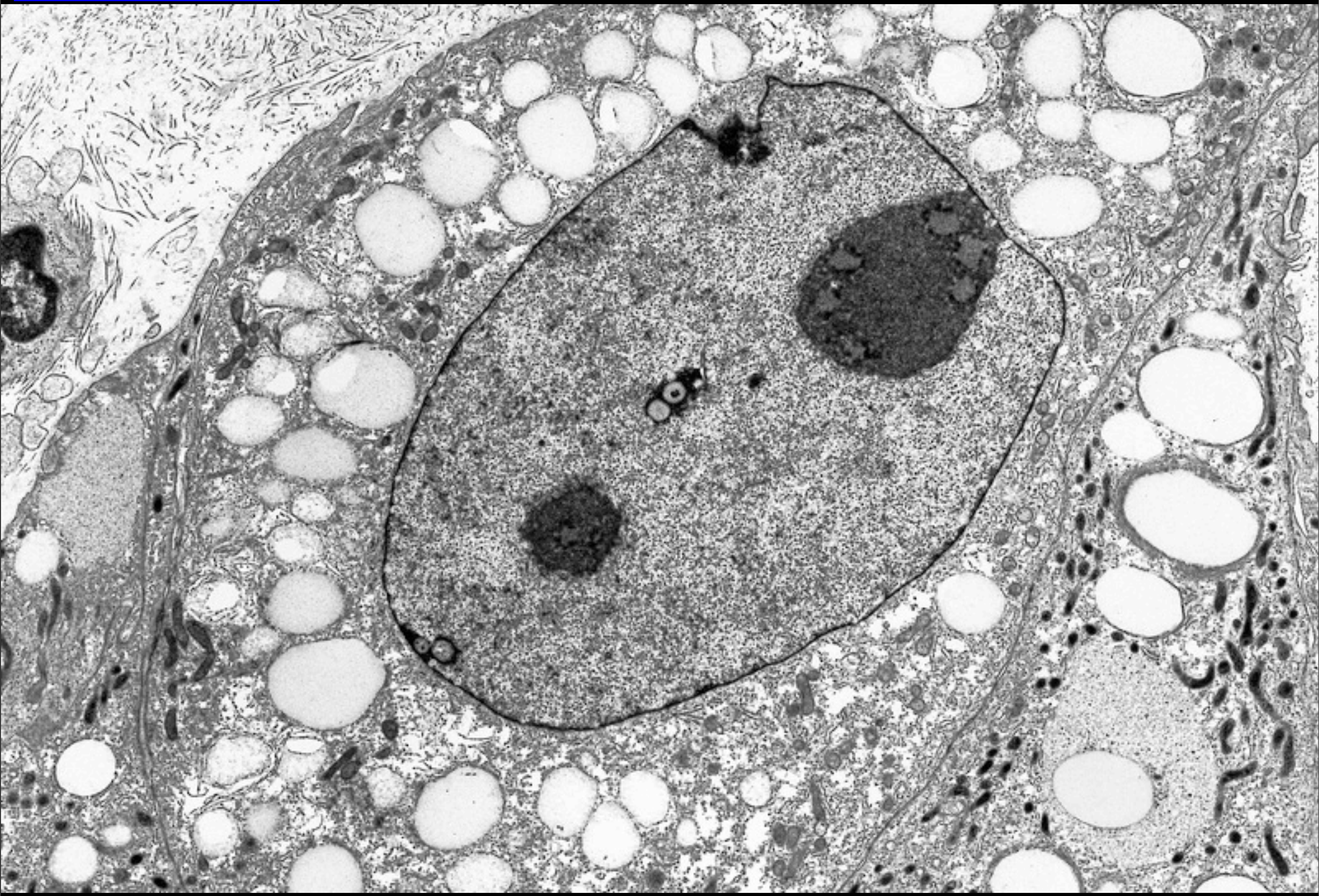



Pic of one formed mostly of solid areas.
prominent capillary networks
'clear cells' everywhere

Pic of one showing necrosis, hemorrhage and cholesterol clefts which develop after cells break down and release their lipids.



EM showing 'clear cells.'



- Of all the subtypes, it has the most consistent cytogenetics.
- **Frequently has deletions or abnormalities of genes in short arm of chromosome 3 (3p).**

Conventional (clear-cell) RCC (CCRCC): Molecular pathology

3p = hypermutable region rich in tumor suppressor genes (TSG's)

- VHL (3p25) — von Hippel-Lindau
  - Specific CCRCC association (next 2 slides)
- FHIT (3p14.2)
  - Nucleotide hydrolase inactivated in many cancers incl. familial CCRCC with t(3;8)
- LCTSGR1 (3p21.3)
  - "Lung/Breast Cancer TSG Region 1"
- LCTSGR2 (3p12)
  - "Lung/Breast Cancer TSG Region 2"

von Hippel-Lindau (VHL) tumor suppressor gene (3p25)

- Germline mutation → familial CCRCC
- Mutation in ~50% sporadic CCRCC
- Promoter hypermethylation (↓ transcription) in additional 15%
- Reintroduction of wild-type VHL into CCRCC cell lines suppresses tumorigenicity in vivo

- VHL tumor suppressor gene is found in 3p region (last slide).
- **VHL is a risk factor for getting 'clear cell' RCC.**
- VHL gene has the most clear association w/ RCC.
- **Pts w/ familial RCC typically have VHL germline mutation.**
- **In Pts w/ sporadic RCC, ~ 50% have VHL germline mutation.**

VHL gene product (pVHL)

- **VHL gene product**
1) **regulatory protein**
2) pleomorphic **effects on bunch of pathways**

From 2010 slides
- Inactivation of VHL results in mTOR up-regulation
- Forms a complex w/ E3 ubiquitin ligase that normally degrades HIF-alpha

- 213 AA soluble protein, not closely related to any other known proteins

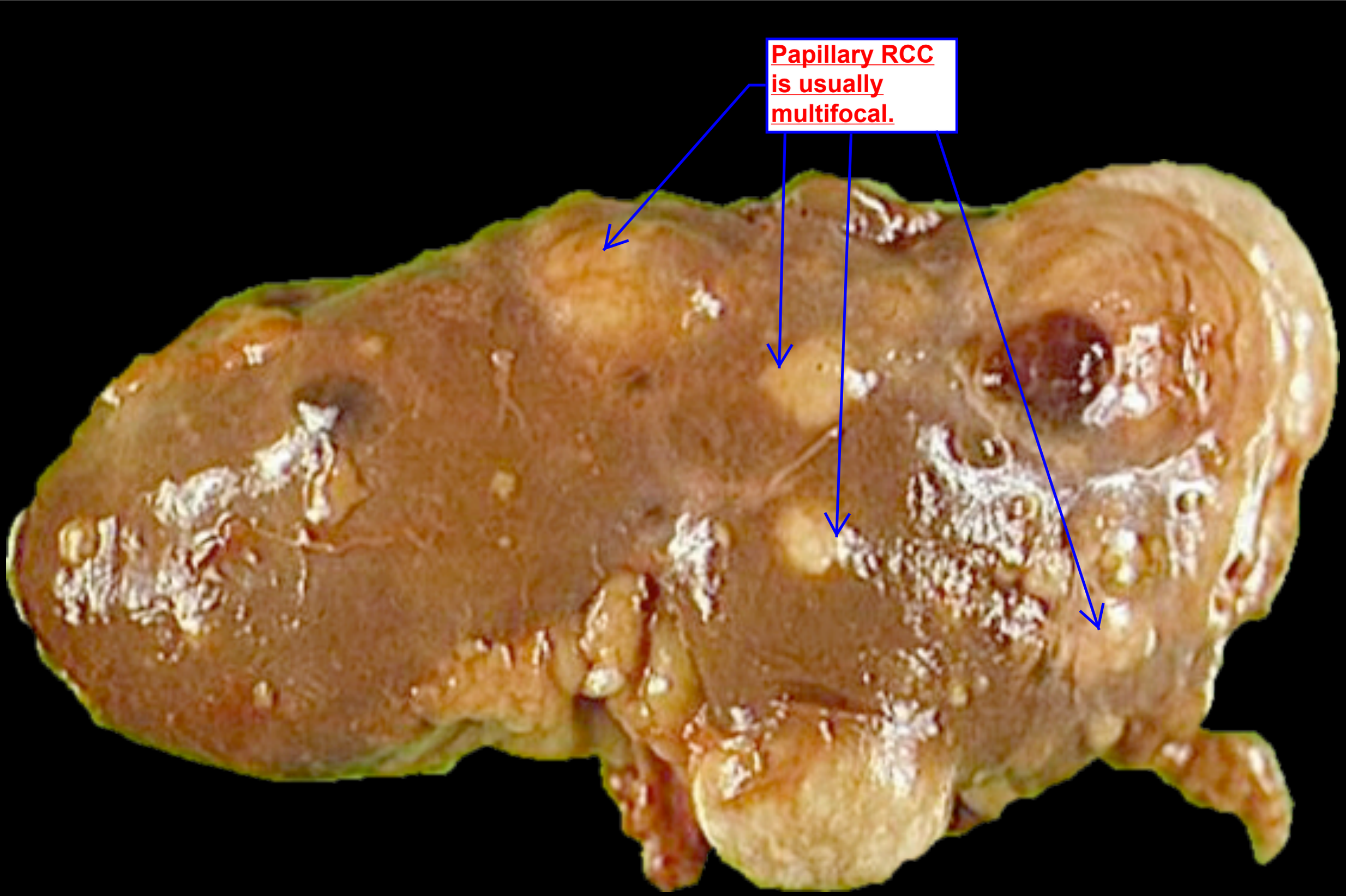
- Specifically binds to components of multiple regulatory pathways

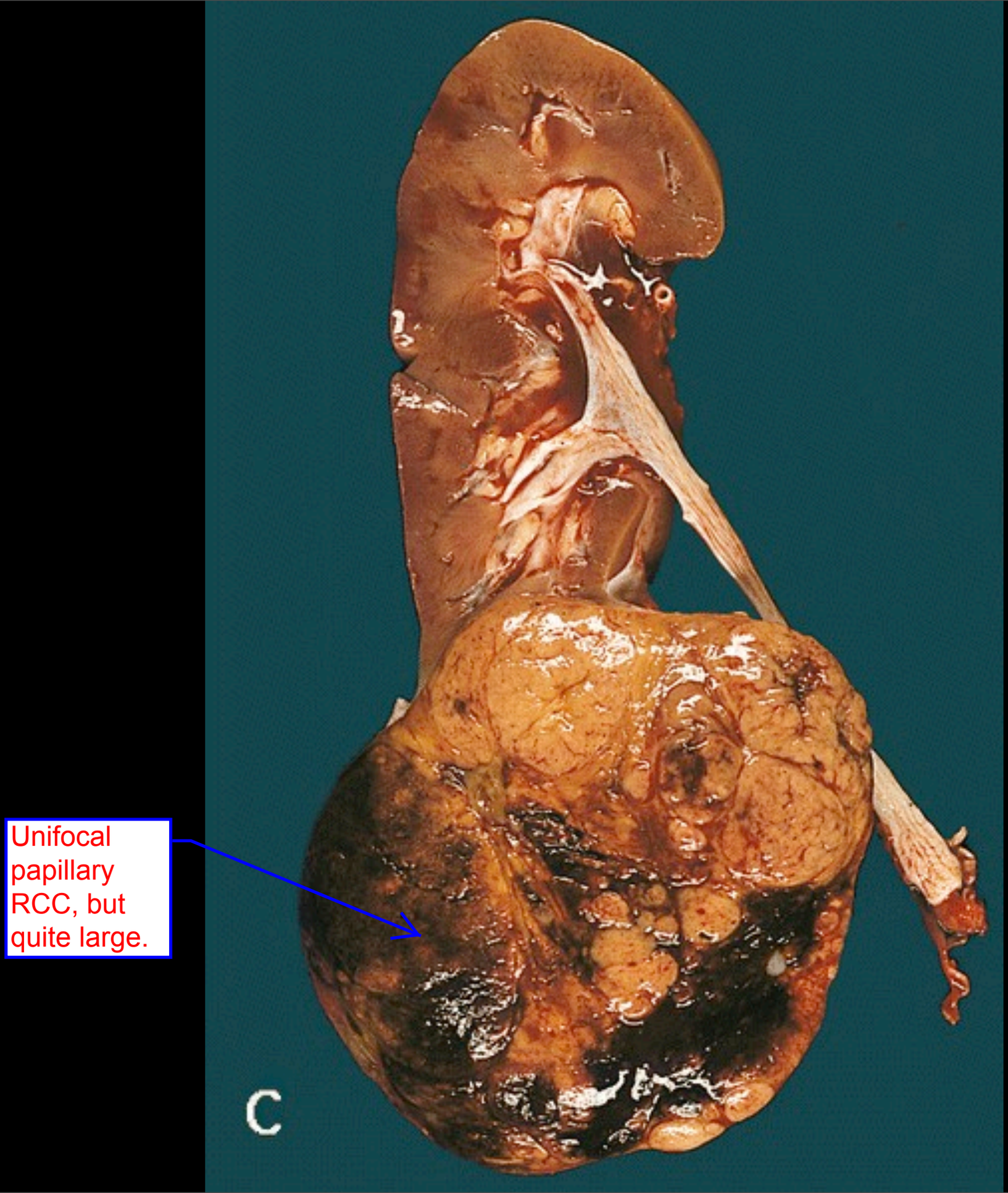
- Component of ubiquitin ligase that in normal cells indirectly downregulates:
  - Angiogenesis
  - Hypoxia-inducible gene expression

- Of the other subtypes of RCC, papillary RCC is the most imp.
- **Appears different histologically & radiographically from 'clear cell' RCC.**
1) **papillary RCC: often multifocal; better prognosis**
2) **'clear cell' RCC: often unifocal**
- Pts w/ acquired cystic disease usually have it.

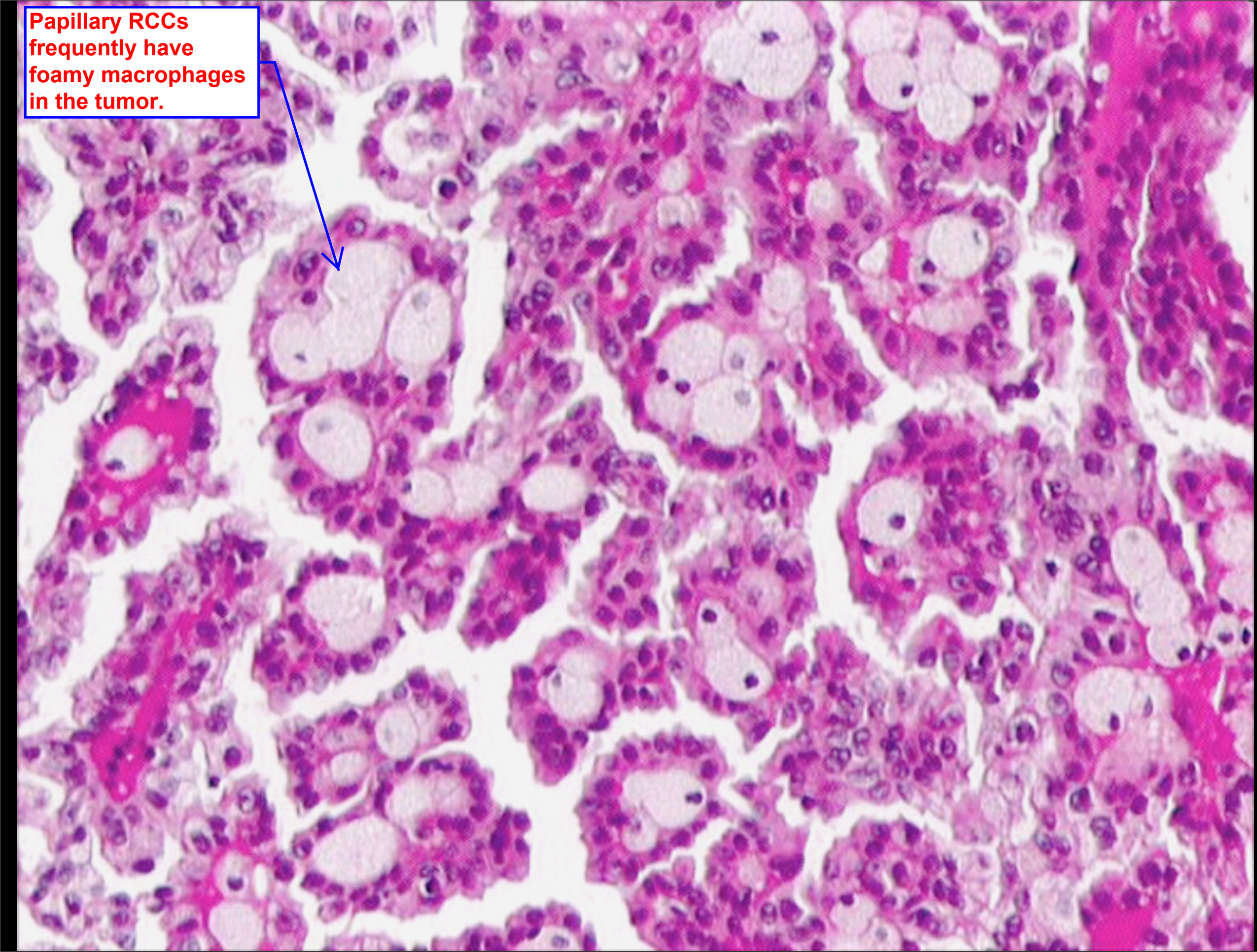
Papillary RCC

- Second-most common type (15%)
- Appearance different from CCRC
  - Peripheral cortex
  - Often multifocal
  - Can be very large, yet circumscribed
  - Usually low stage
- Better prognosis than CCRCC
- Acquired cystic disease associated


Papillary RCC
is usually
multifocal.


Unifocal papillary RCC, but quite large.
C

Papillary RCC are typically papillary!
(not solid or glandular or cystic like 'clear cell' RCC).


Papillary RCCs frequently have foamy macrophages in the tumor.

“Renal cell adenoma”

Unfashionable to say RCCs are adenomas unless it's the papillary subtype < 0.5cm in size.

- Historically, small tumors discovered incidentally (e.g. at autopsy)
- However, even small, localized RCC can metastasize ← Size doesn't dictate ability to metastasize.
- Term is currently reserved for papillary subtype RCC ≤0.5 cm

Pic of **'renal cell adenoma,' a papillary RCC < 0.5cm in size.**

A commonality in papillary RCCs is trisomy of chromosome 7.

Papillary RCC (PRCC): Molecular pathology

- Various trisomies and -Y common in sporadic cases

- *MET* proto-oncogene (7q31)
  - Many familial and some sporadic cases
  - Mutations in tyrosine kinase domain of pMET → constitutive activation
  - Trisomy 7 common in sporadic cases, can selectively amplify mutant *MET*

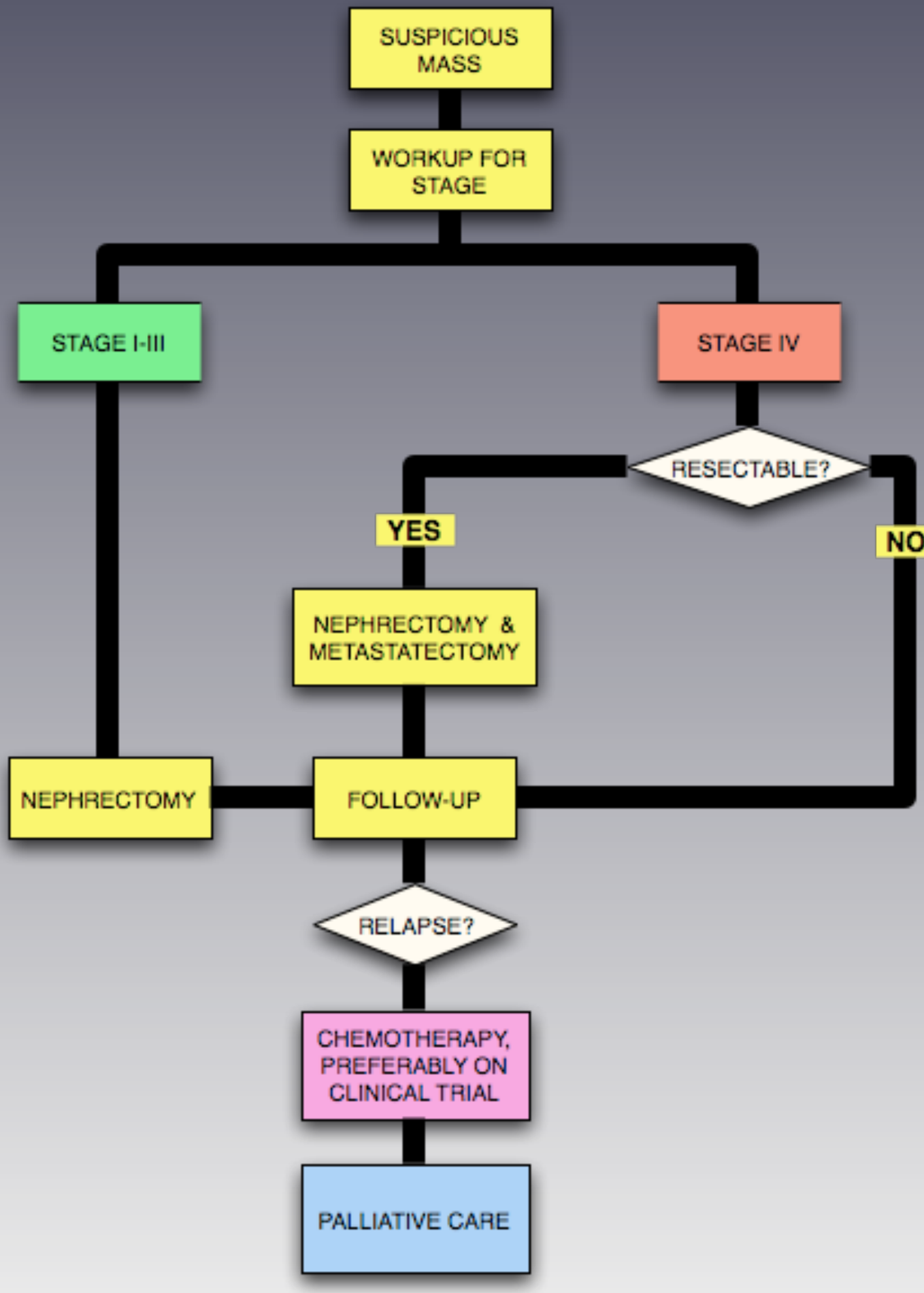
Less-common RCC

- Chromophobe cell type
  - Very distinctive cytology
  - Genetics not yet understood
- Collecting duct type
  - Arises near medulla
  - Very poor prognosis
- Sarcomatoid RCC
  - Not really a separate type
  - High grade, de-differentiated form of (usu.) CCRCC
  - Very poor prognosis

Found in association w/ renal oncocytoma.

Actually collecting duct type; tend to be very high grade.

- Flowchart of what to do when someone comes in w/ suspicious mass.
- **<u>First thing to do:</u> try to establish stage!**



Emerging treatment options

in lasts 5-10 yearrs

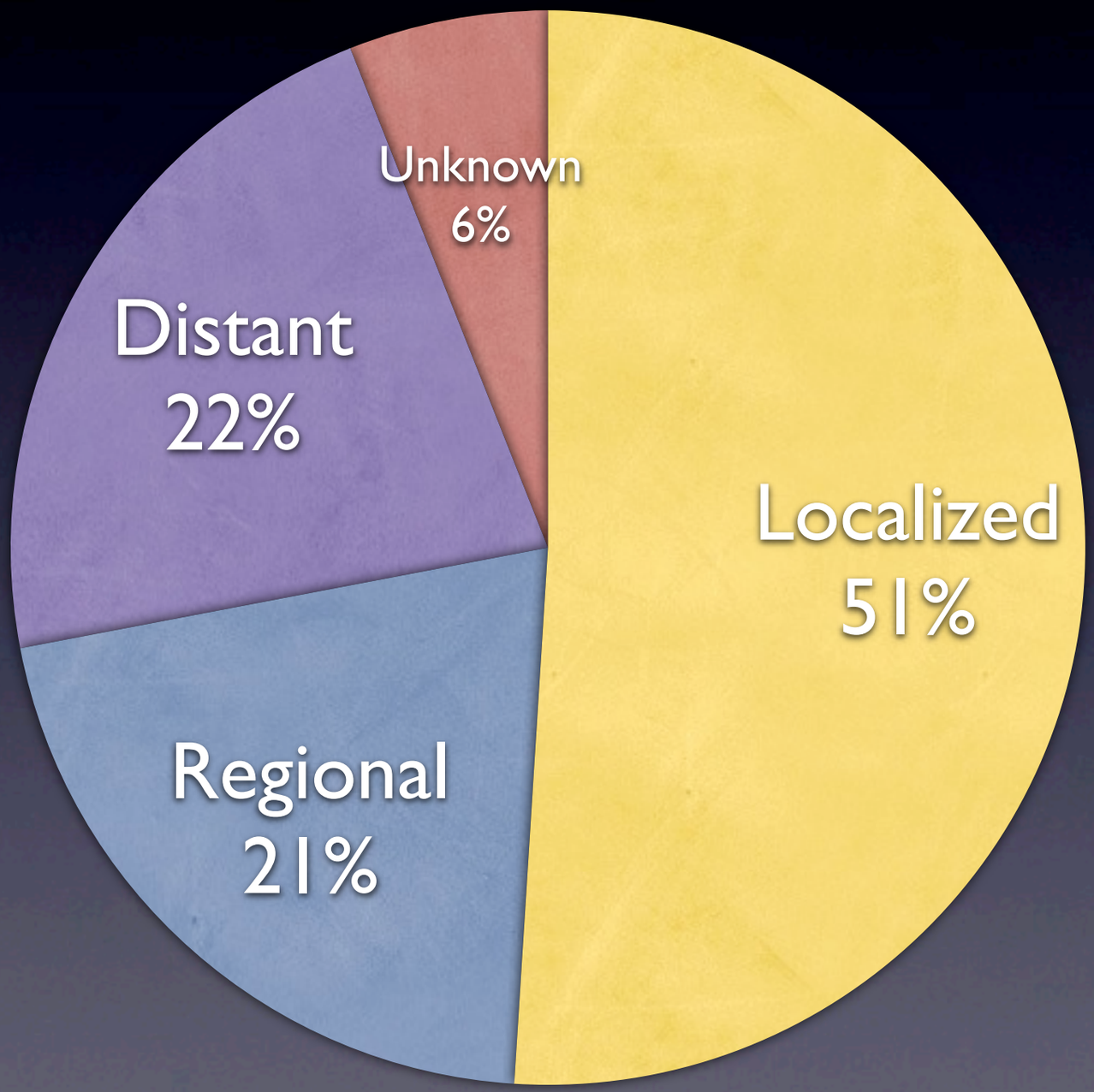
- **Kidney-sparing surgery** for smaller tumors
  - Partial nephrectomy
  - Cryosurgery, HIFU, radiofrequency ablation
- **Chemotherapy** biggest advancement
  - Kinase inhibitors (sunitinib, sorafenib)
    - Doubles progression-free survival in Stage IV RCC — means only a few more months, but still a very big deal
  - mTOR inhibitor (temsirolimus) — pretty routine in the care of Pts w/ 'clear cell' RCC; increase survival (months to a year on average)
  - Cytokines (IFNα, IL–2)
  - Antiangiogenic (bevacizumab/avastin) — especially in 'clear cell' RCC due to relationship w/ tons of BVs

- **Important criteria for RCC staging**
1) **size**
2) **localization to the kidney or not**
- A huge deal in RCC: **dictates prognosis**!

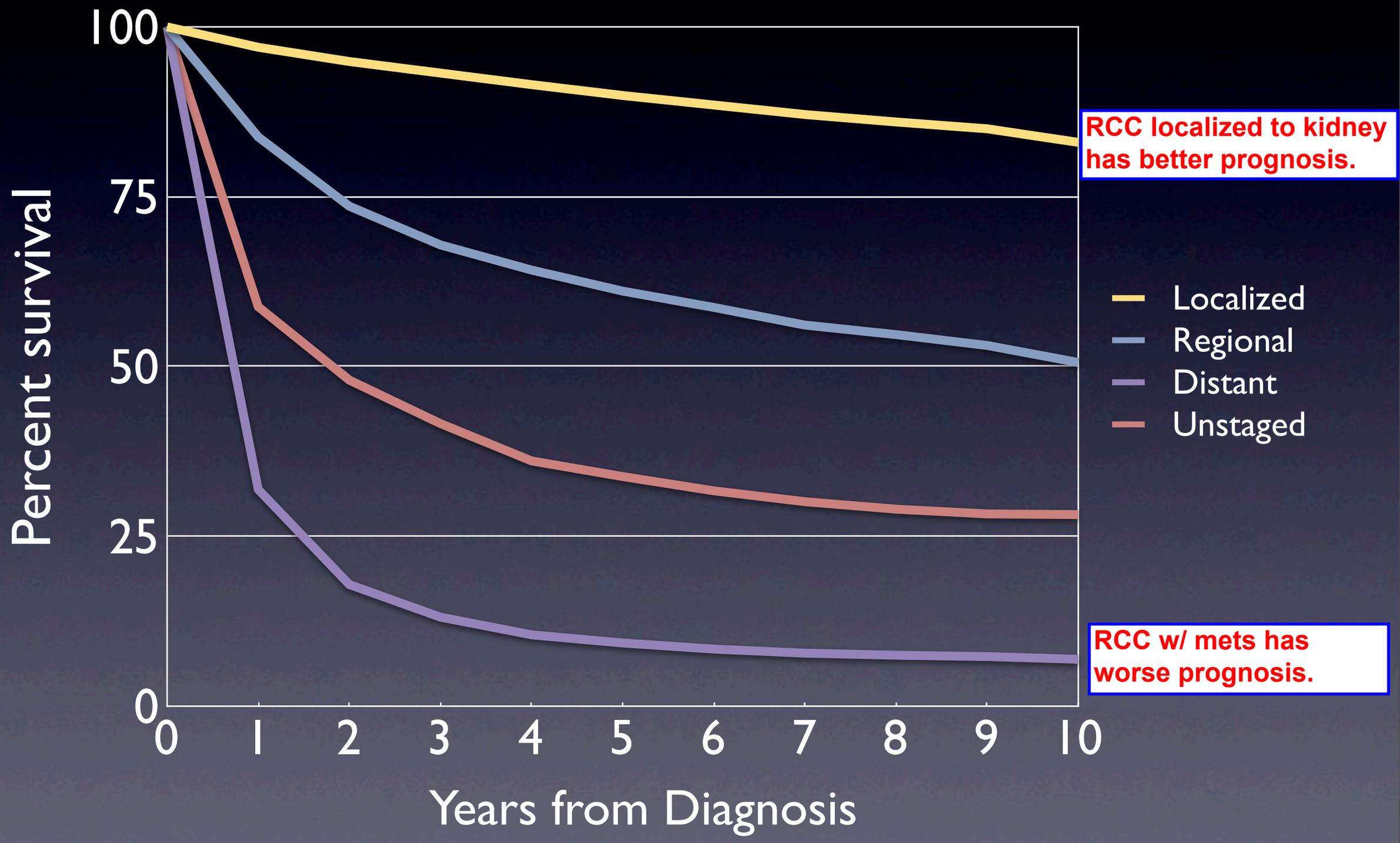
RCC Staging

- Stage I: Localized to kidney, <7 cm
- Stage II: Localized to kidney, <10 cm
- Stage III: Compartmental invasion and/or nodal metastasis (including vena cava)
- Stage IV: Extracompartmenal invasion (adrenal, retroperitoneum) and/or distant metastasis

RCC Stage Distribution in USA



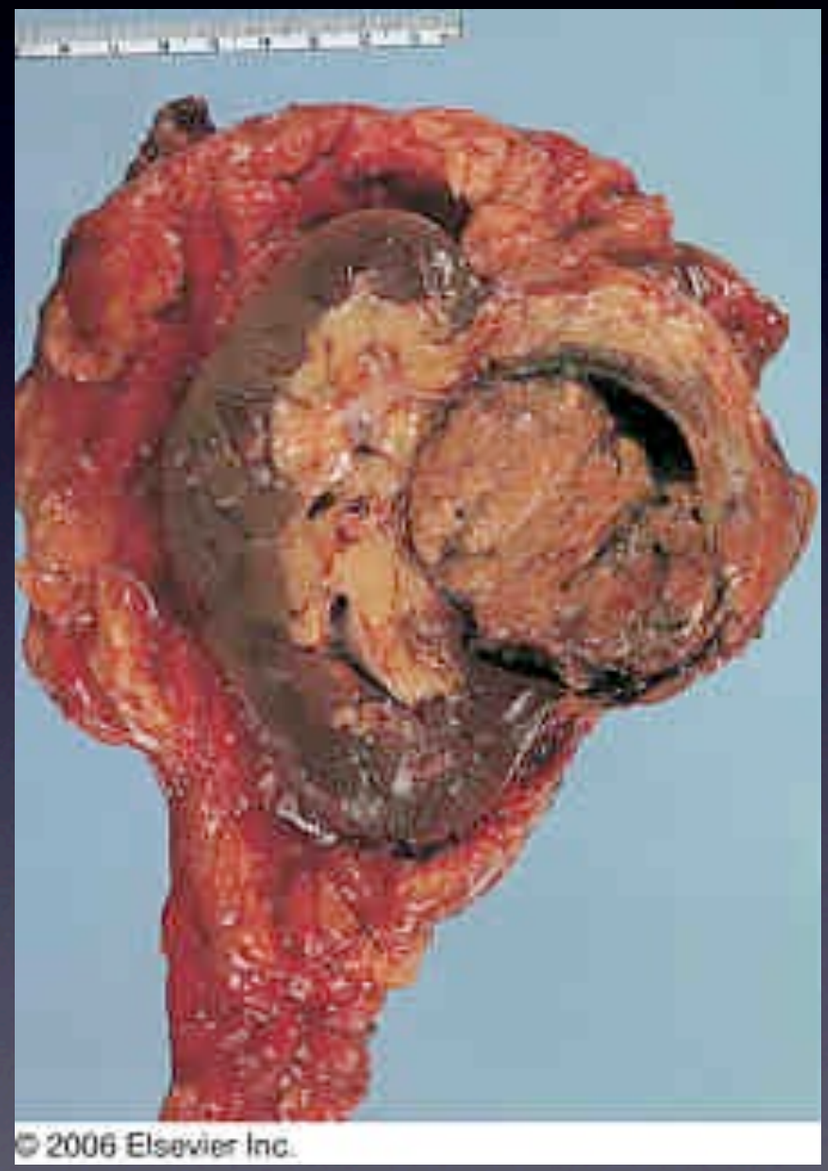
RCC survival (1988-2002)



- Not considered part of RCC classification.
- **Occurs ONLY in young Pts w/ sickle cell disease or sickle cell trait.**
- **Very high grade tumor that is usually fatal.**

Renal medullary carcinoma

- "Seventh sickle nephropathy"
- Almost exclusively in patients with sickle cell disease/trait
- Males > females
- Age ~20



Nephroblastoma (Wilms' Tumor)

- Recapitulates structures of embryonic kidney
- #1 renal cancer of childhood
- #3 solid cancer of childhood
  - 6% of childhood cancer
  - About 500 U.S. cases/year
  - >90% of pediatric renal tumors
- Males~females, average age ~3 years
  - Rare before 6 mos or after 10 yrs

- **Most common renal cancer of childhood!**
- Doesn't present as a congenital tumor.
- **Very rarely presents in adulthood.**
- Like RCC, it also **has a tendency to creep out the renal vein.**

Nephroblastoma Clinical

- 85% abdominal mass

Classic Wilm's story:
Mom bathing kiddo and finds a mass in his belly.

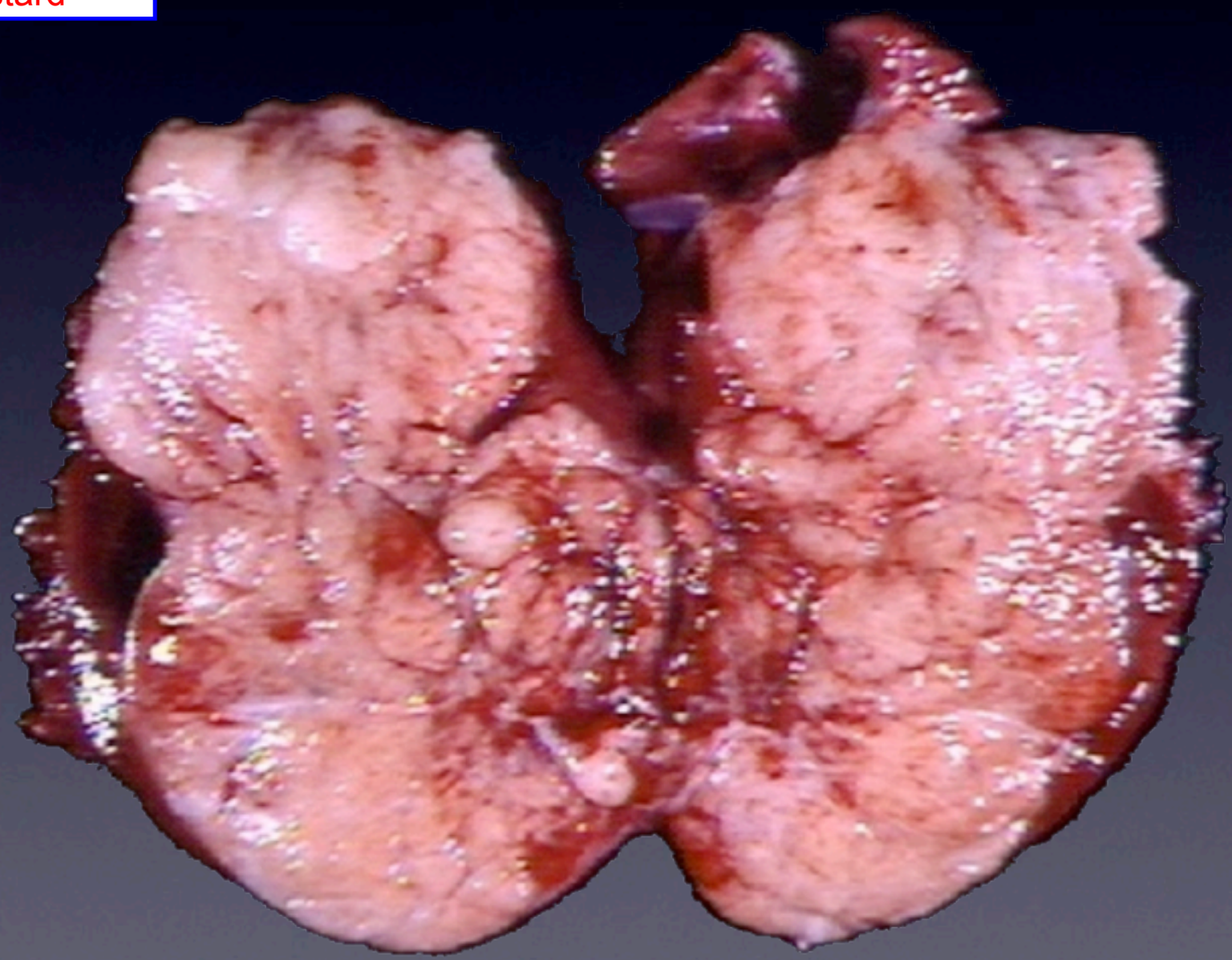
- 40% pain
- 60% hypertension
- 5% coexisting urogenital anomalies

These Pts are at higher risk of getting Wilm's tumor.

- 5% bilateral

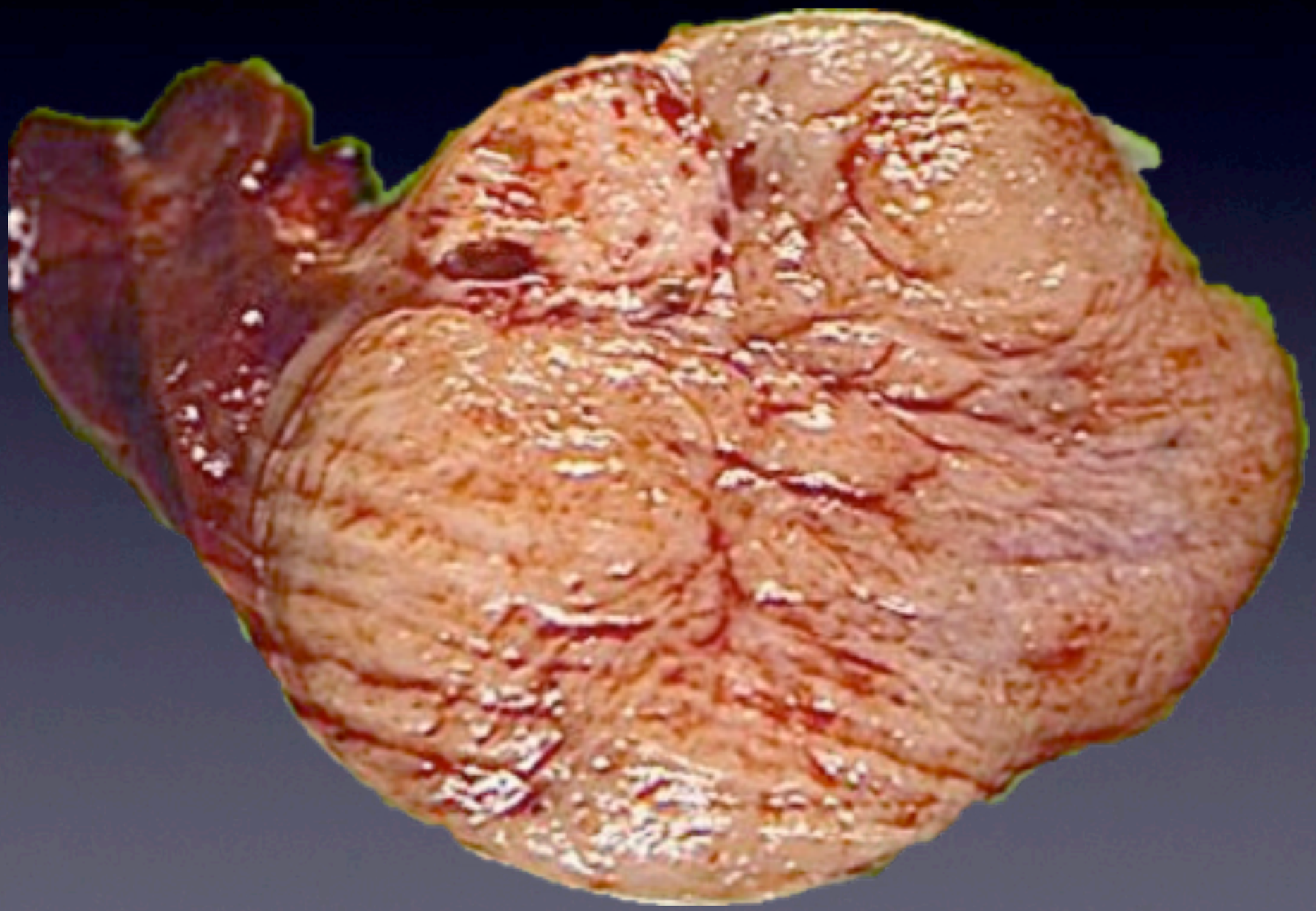
Fleshy, friable mass replacing entire kidney

almost like cutting into custard



Since tumor is so friable, they are usually not biopsied because it upstages them.

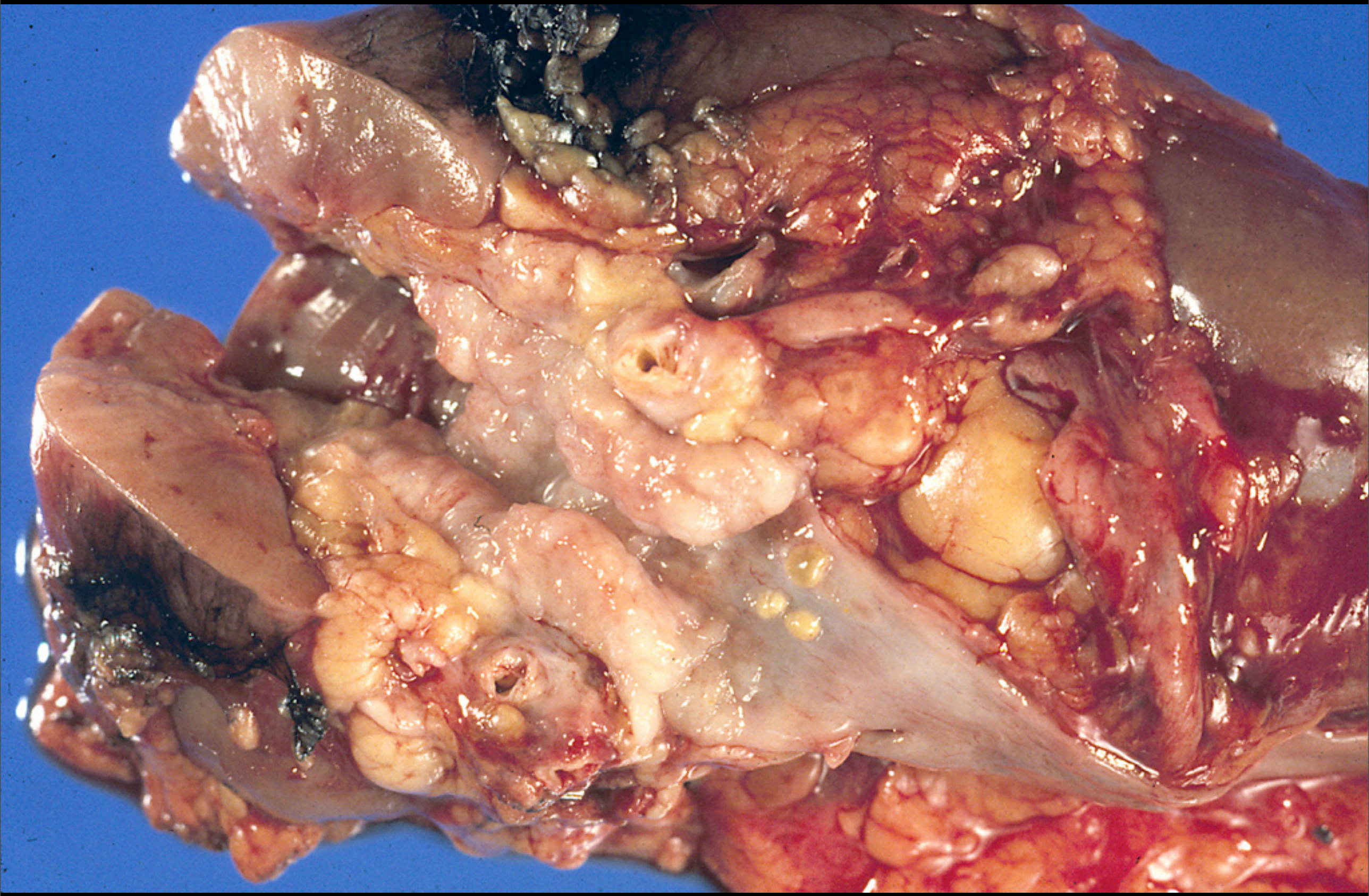
Soft, friable texture easily



- **Triphasic tumor.**
- Recapitulates stages of embryonic development of the kidney.
- **<u>3 components of the tumor:</u>**
1) **blastema**
2) **epithelium**
3) **stroma**

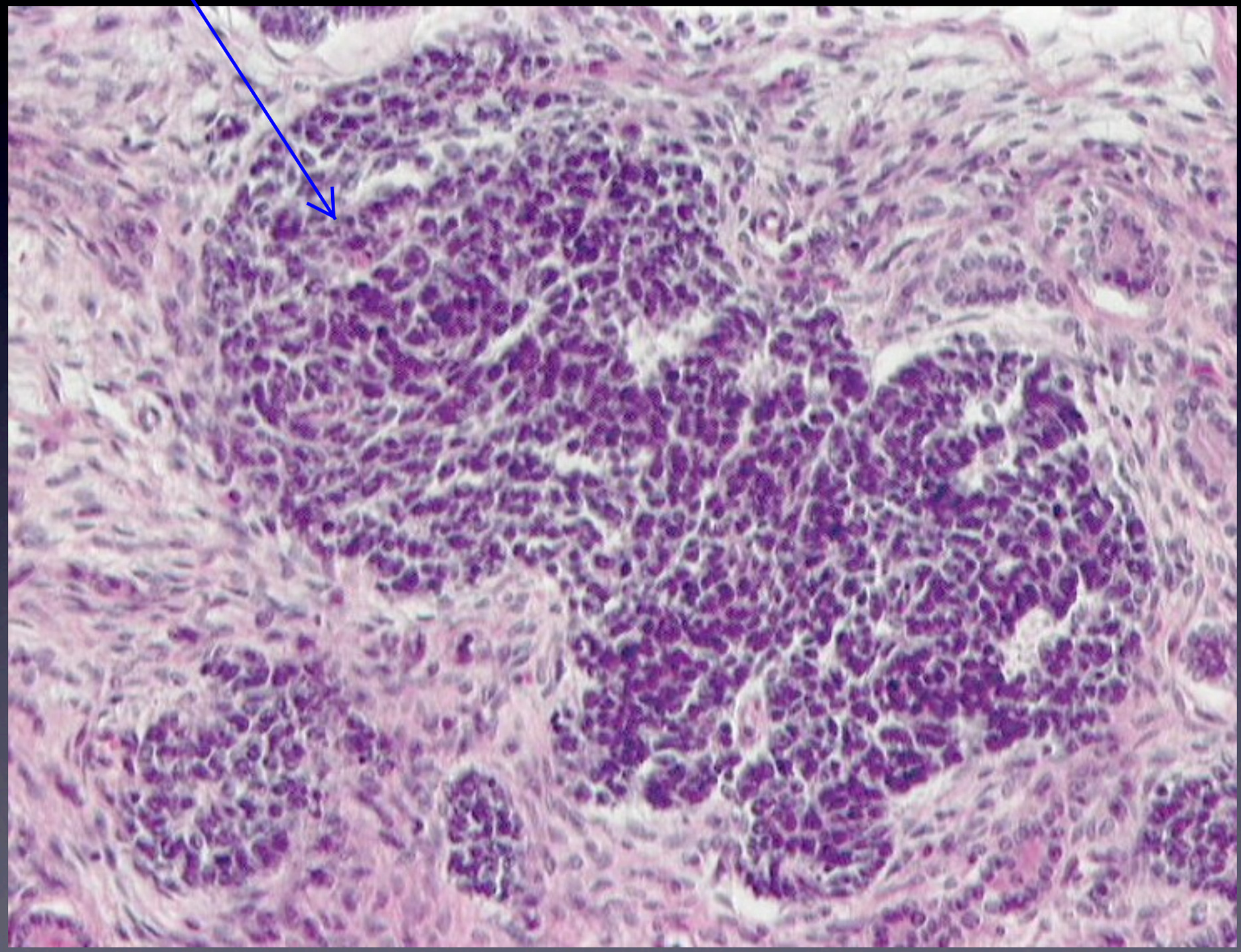
Components of nephroblastoma

- Blastema
- Epithelium
- Stroma



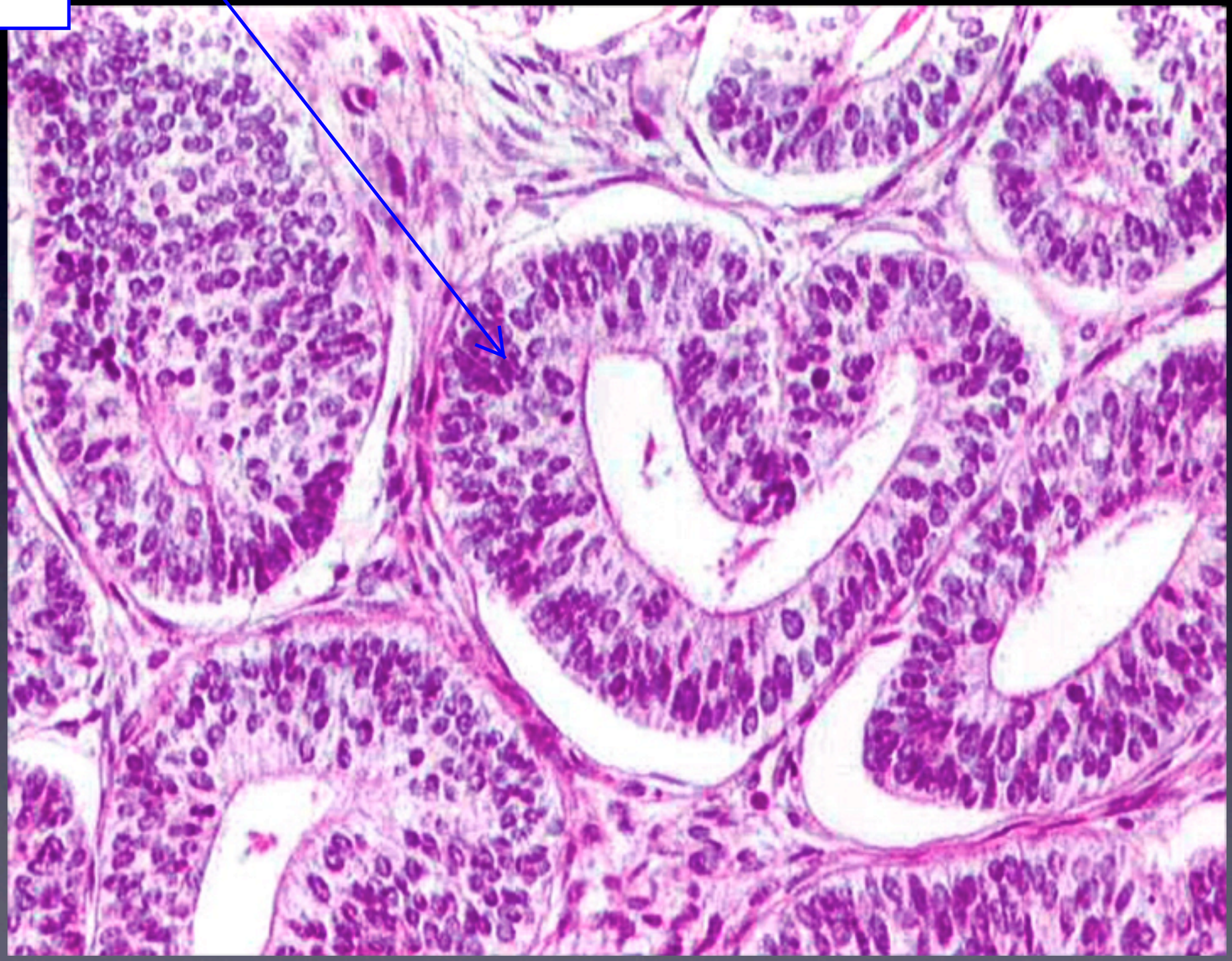
Blastema

Undifferentiated cells seen in nests or lakes.

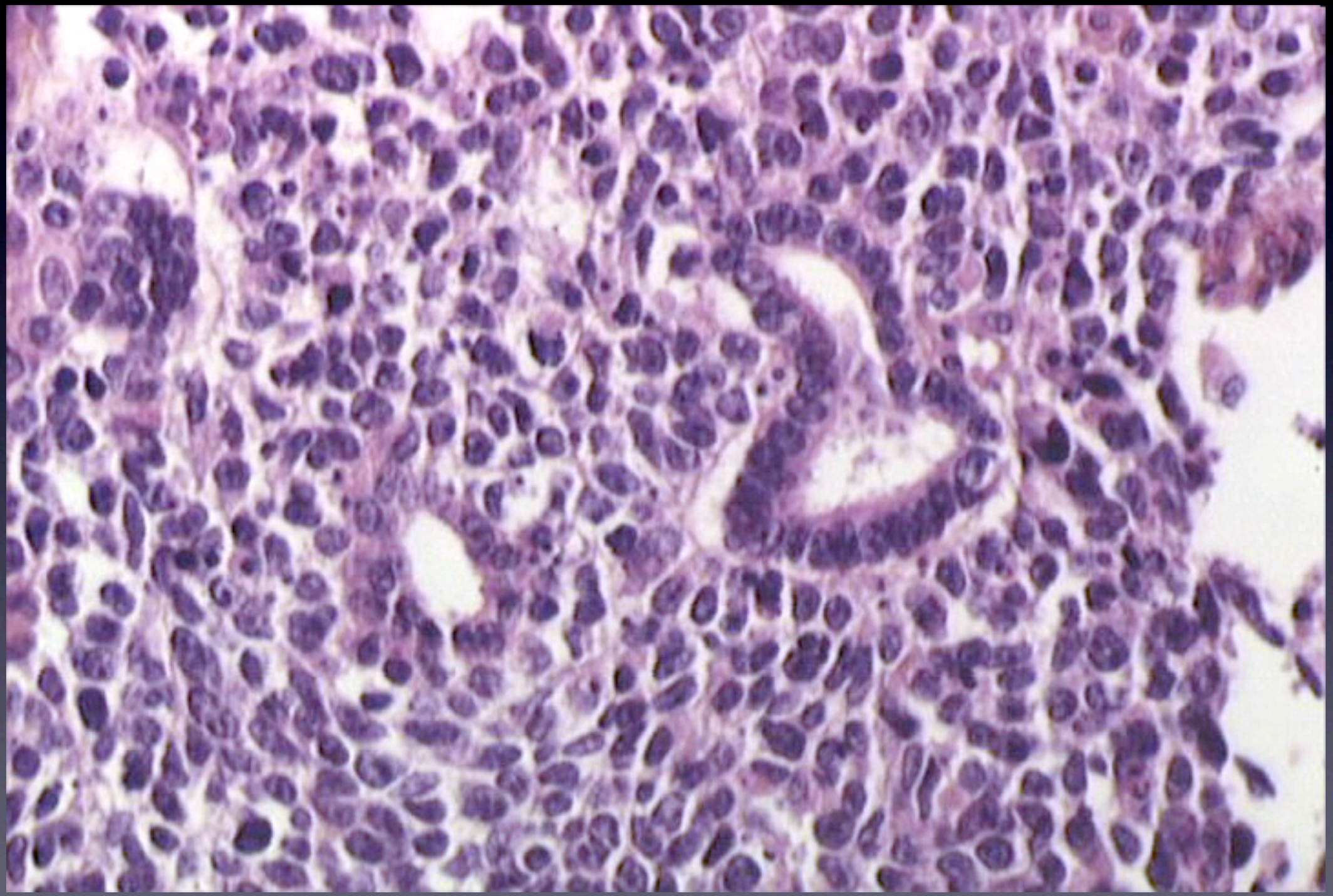


Epithelium

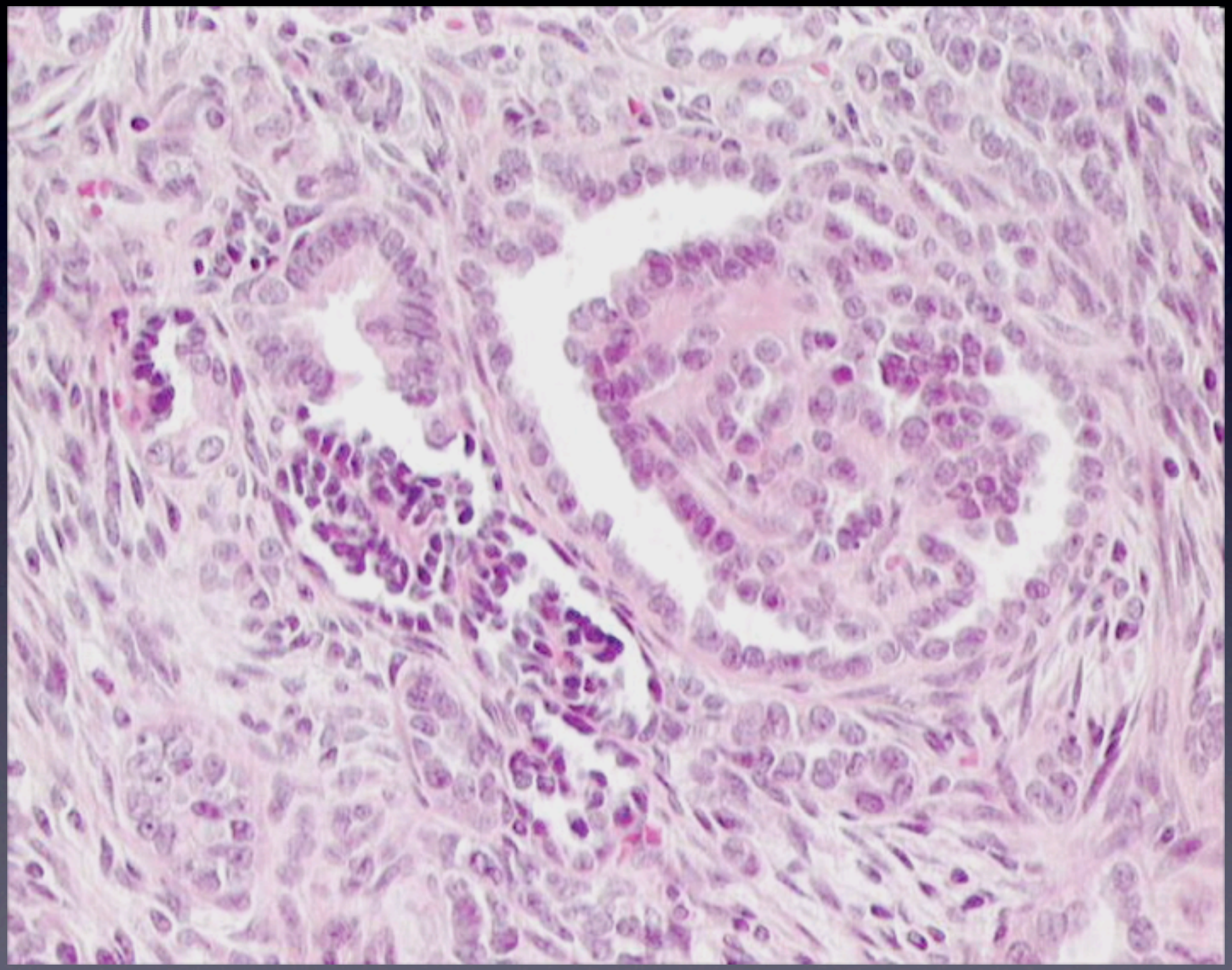
Epithelial structures trying to look like renal tubules or Bowman's or glomeruli, but don't quite get there.



Epithelium

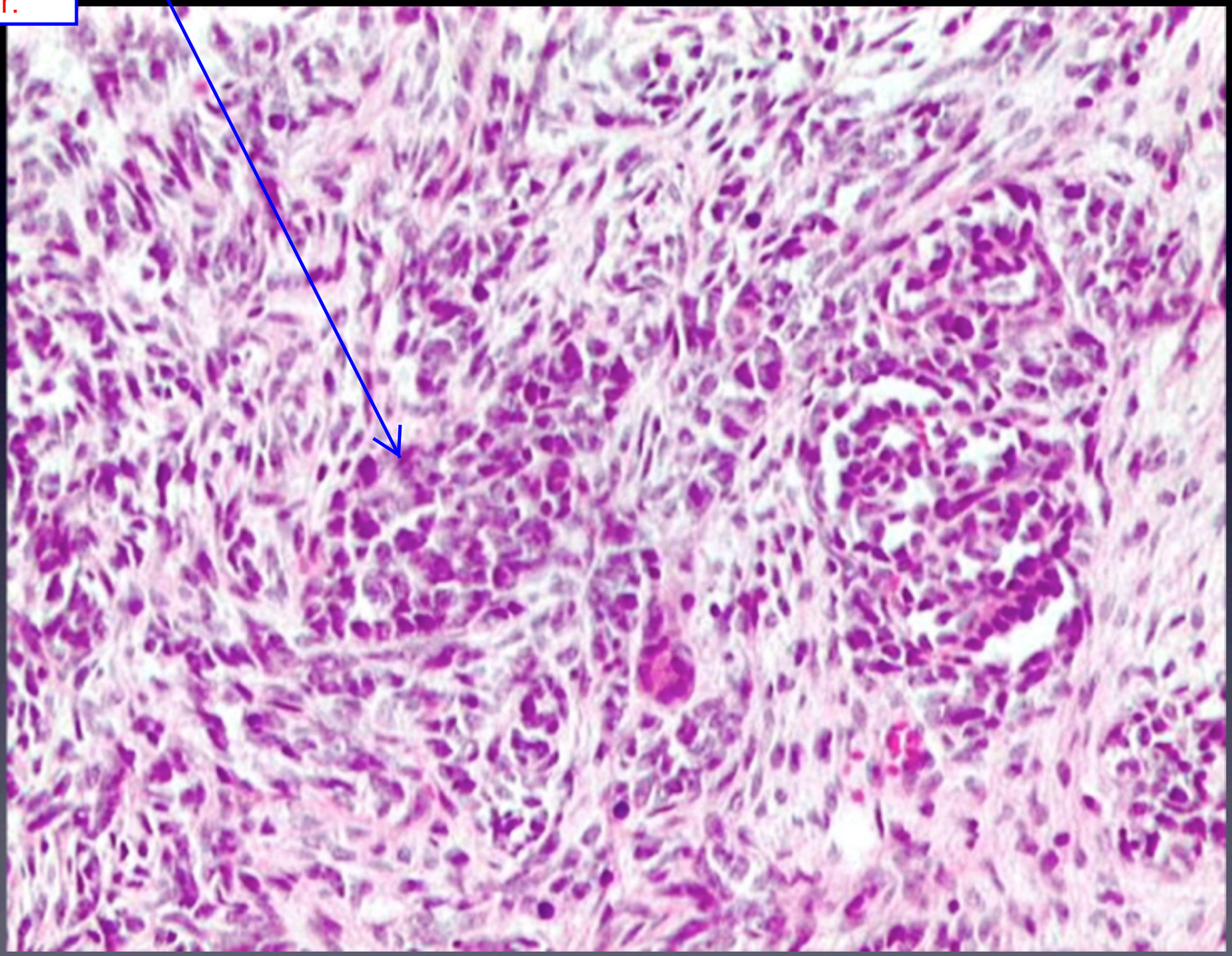


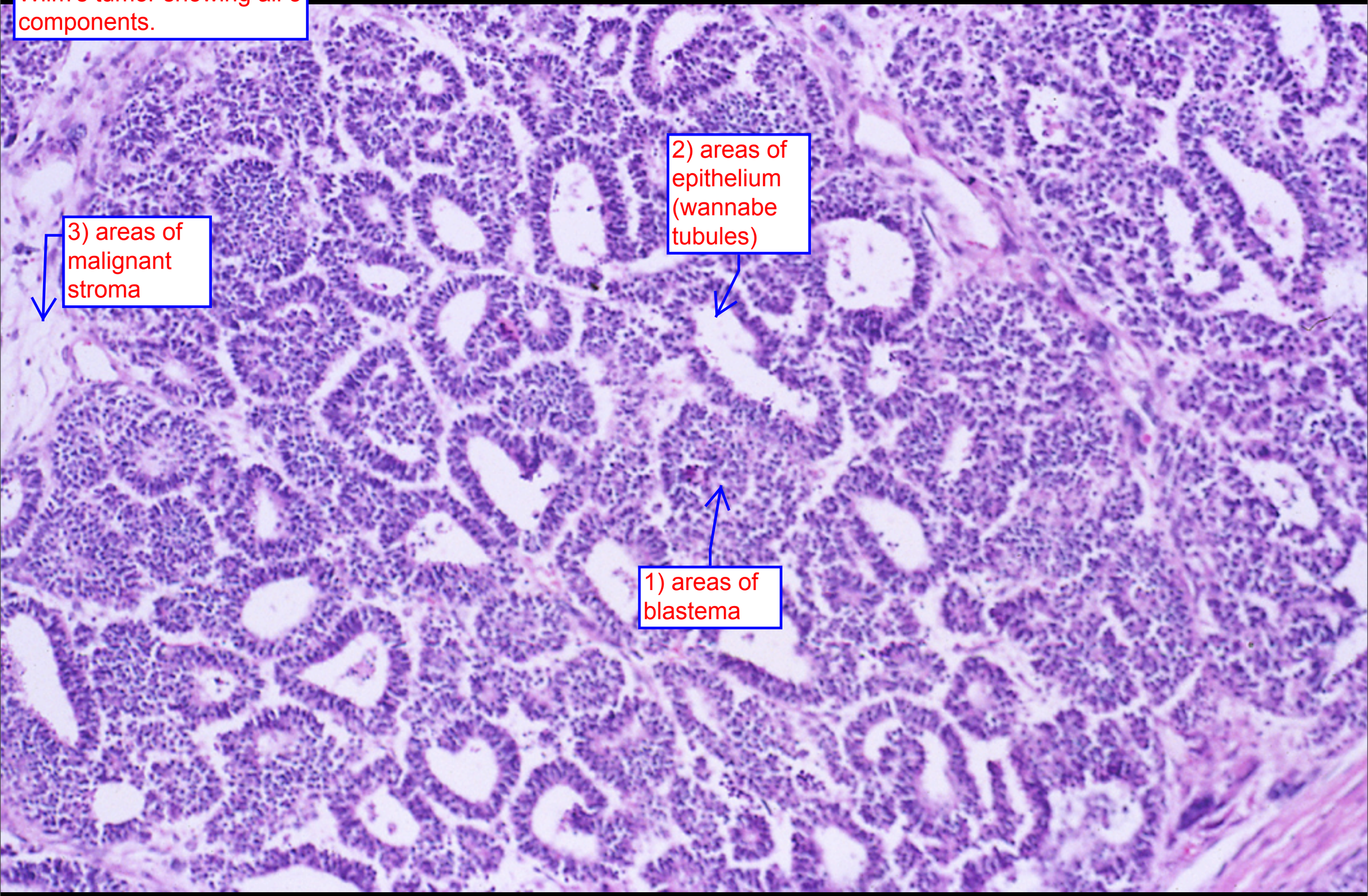
Glomeruloid structure



Stroma

Can have fibroblasts, muscle cells, cartilage and other components: triphasic tumor.




Low power histo pic of Wilm's tumor showing all 3 components.
3) areas of malignant stroma
2) areas of epithelium (wannabe tubules)
1) areas of blastema

Nephroblastoma Cytogenetics

- WT1 Tumor Suppressor Gene (11p13)
  - LOH in one-third of NB
  - DNA-binding protein
  - Normally extremely tissue- and developmentally-restricted expression
  - Transcriptional regulation
- WT2 Tumor Suppressor Gene (11p15)
  - Beckwith-Weidemann Syndrome
- WT3 (16q)
  - Poor prognosis

- **About 1/3 of Wilm's tumor Pts have loss of heterozygocity of this gene.**
- Normally not expressed after definitive development of the kidney, but Wilm's tumor Pts keep expressing it.

Wilm's tumor
- Fairly well characterized.
- **Problematic genes can be found on**
1) **chromosome 11**
2) **chromosome 16**

- **Therapeutic course is generally**
1) **definitive resection**
2) **chemotherapy**
- **How much post-op treatment influenced by whether histo is 'favorable' or 'unfavorable.'**
- 'favorable' or 'unfavorable' discrimination **has to do w/ tumor grading and age of the Pt.**

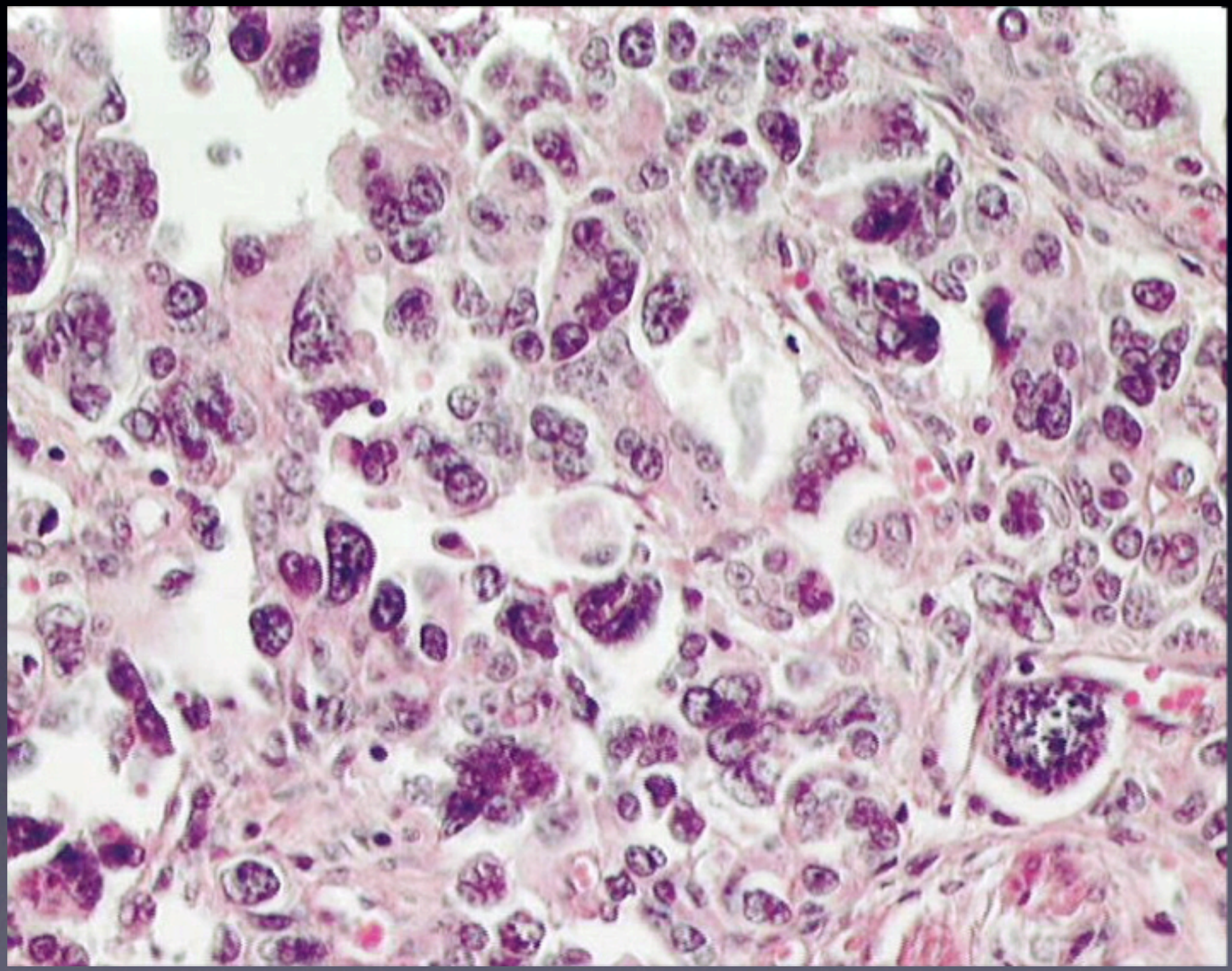
Nephroblastoma grading

- "Favorable histology" (95%)
  - Without anaplasia
  - Focal anaplasia
- "Unfavorable histology" (5%)
  - Diffuse anaplasia

worse prognosis

Pic of anaplastic Wilm's tumor.

Anaplasia



Nephroblastoma staging

has to do w/ extent of disease

- Stage I — Limited to kidney, completely excised
- Stage II — Extends beyond kidney, but completely excised
- Stage III — Residual tumor confined to abdomen
- Stage IV — Distant (hematogenous) metastasis
- Stage V — Bilateral renal involvement at diagnosis

Important prognostic factors

- Age at detection (older = worse)
- Stage
- Unfavorable histology

Typical therapy

- Favorable, Stage I-II or Unfavorable, Stage I
  - Light chemo and surgery
- Favorable, Stage III-IV or Unfavorable, Stage II-IV
  - Chemo, radiation, surgery

Big deal, because **Pts in this category invariably end up w/ radiation-induced scoliosis.**

NB treatment outcome

Stage	Histology	Survival
I-III	Favorable	>95%
IV	Favorable	90%
II-IV	Unfavorable	82%

Irrespective about stage and histo, **survival is in the 80%s,** which is great.