Non-Wilms Pediatric Renal Tumors

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Disclosures: None.

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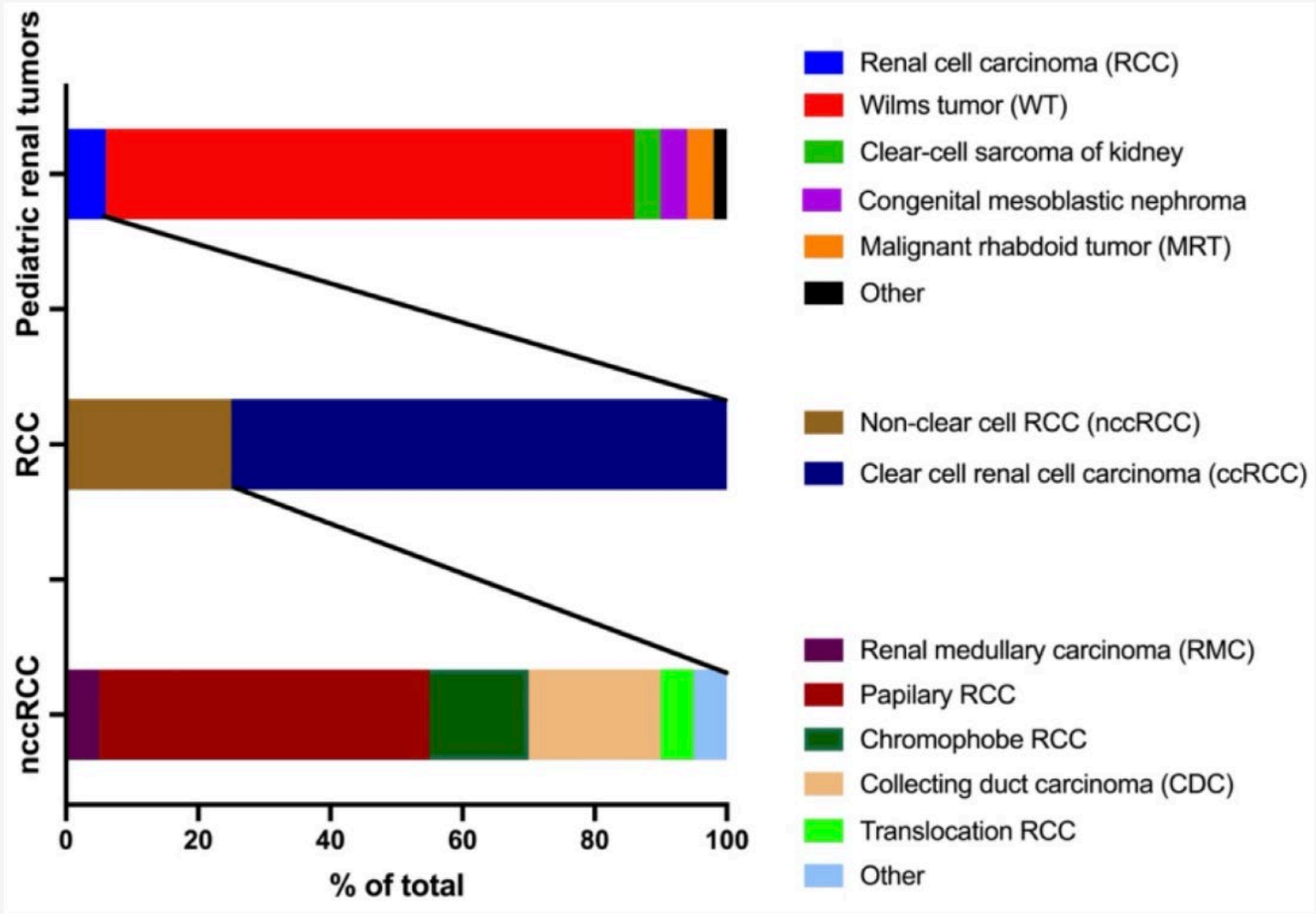
How Rare is Rare?

Figure 1. Subtypes of pediatric renal tumors and percentages.



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How Rare is Rare?

- Rare enough that the images and histology that I will show you here are (unless otherwise stated) from publicly-available websites
- I do not have the copyright to these pictures, but please see the links if you would like better resolution
- Understanding imaging and histology may help you diagnose someone with a rare cancer!
- Always consider a clinical trial for patients with rare (and generally bad) diseases

Non-Wilms Pediatric Renal Tumors (a short list)

- Renal cell carcinoma
- Renal medullary carcinoma
- Rhabdoid tumors of the kidney
- Clear cell sarcoma of the kidney
- Congenital mesoblastic nephroma
- Ewing sarcoma of the kidney
- Primary renal myoepithelial carcinoma
- Cystic partially differentiated nephroblastoma
- Multilocular cystic nephroma
- Primary renal synovial sarcoma
- Anaplastic sarcoma

Non-Wilms Pediatric Renal Tumors

- **Renal cell carcinoma**
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Renal Cell Carcinoma

- About 1 in 20 new pediatric renal tumors (4 cases/million children)
- Uncommon in children aged <15 years (but after that, about 2/3 of renal malignancies are RCC)
- Compared with young adults, children and adolescents are more likely to present with advanced disease

Table 2. *Logistic regression analysis of cancer variables*

	Age Group (yrs)				
	0–15	15–21	21–30	Total/Av	p Value
% Histology:					<0.0001
Clear cell	13.04	18.99	35	32.49	
RCC NOS	64.6	55.79	48.04	49.52	
Chromophobe	3.11	7.42	8.73	8.35	
Papillary	19.25	17.8	8.24	9.64	
% Analytic stage:					<0.0001
1	37.14	51.9	73.98	70.35	
2	17.14	20.57	11.18	12.31	
3	21.43	10.76	6.12	7.2	
4	24.29	16.77	8.72	10.13	
% Grade:					<0.0001
Well differentiated	14.43	15.23	19.4	18.87	
Moderately differentiated	30.93	46.09	55.42	53.77	
Poorly differentiated	43.3	34.98	21.5	23.42	
Undifferentiated	11.34	3.7	3.68	3.94	
Mean tumor length (cm)	6.86	6.93	5.07	5.33	<0.0001
% Laterality:					0.926
Unil	99.4	99.71	99.42	99.45	
Bilat	0.6	0.29	0.58	0.55	
% Margin status:					0.017
Neg	91.61	95.56	95.89	95.67	
Pos	8.39	4.44	4.11	4.33	
% Nodal status:					0.005
All neg	53.85	54.88	71.53	66.67	
1+ Node(s) pos	46.15	45.12	28.47	33.33	

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Akhavan 2015

Characteristics of RCC

- Translocation RCC is most common subtype (40-50%)
  - Usually *TFE3* gene on Xp11.2 (can combine with multiple other genes); less commonly *TFEB* gene; occasionally *ALK* gene
  - Poor survival associated with 9p loss, 17q gain, increased copy number repeats
  - Only known risk factor for translocation RCC is previous chemotherapy with alkylating agent or topoisomerase II inhibitor (4+ years after treatment)
- Histology is usually papillary or clear cell (but 25% unclear/mixed)
- Most important prognostic factors are nodal involvement and stage of disease (though improved survival for LN+ disease compared with adults)

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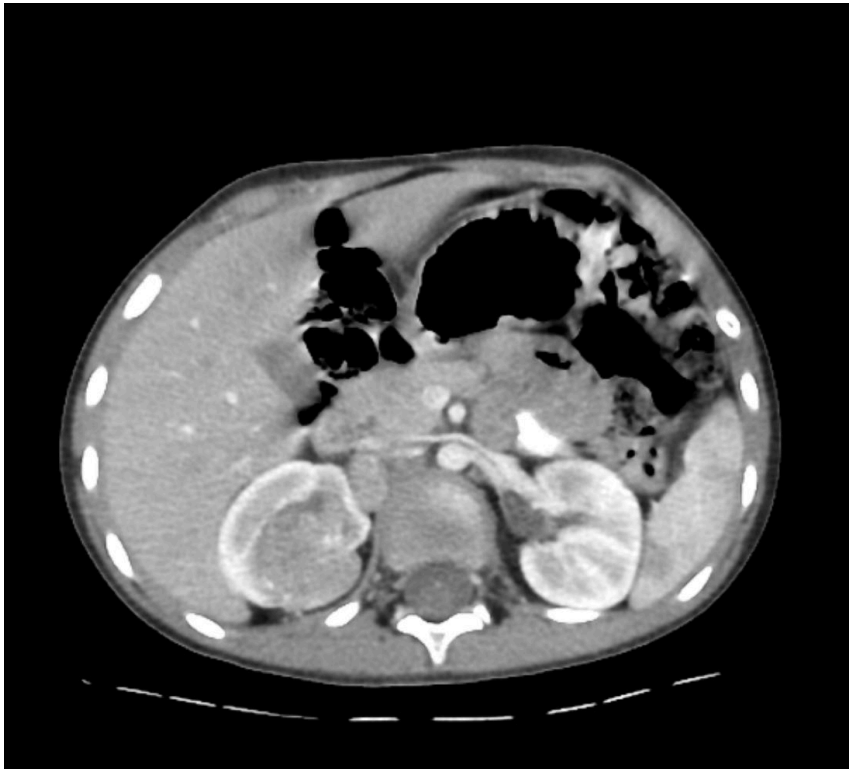
Geller 2004; van der Beek 2021

Translocation Renal Cell Carcinoma: Radiology and Pathology



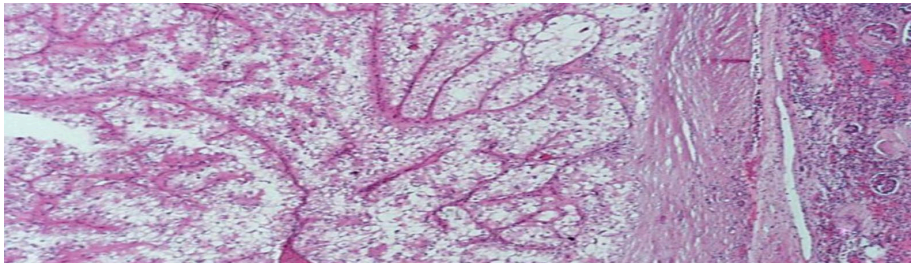


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Image: Radiopaedia; Pathology: JHU

Syndromes Associated with Pediatric RCC Development

- Von Hippel-Lindau
  - AD, chromosome 3, mutation of tumor suppressor gene
  - Annual screening with RBUS/MRI at 8-11 years
- Tuberous sclerosis
  - Need to rule out perivascular epithelioid cell tumor with smooth muscle and melanocyte markers
- Familial RCC
  - Associated with a translocation of chromosome 3
  - Mutations in Krebs cycle enzymes are common (SDHB, SDHC, SDHD) and are associated with pheochromocytoma and paraganglionoma (not seen with germline mutations)

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Ricketts 2008; Linehan 2010

Hereditary Leiomyomatosis and Renal Cell Carcinoma

- AD, chromosome 1q, mutations in the fumarate hydratase gene
- Usually presents in adulthood (40+ years) with leiomyomas on skin, in uterus
- 10-15% risk of RCC (usually type 2 papillary) development, and metastasize when small
- If family history, test for FH mutations, annual surveillance with MRI beginning at 9-10 years old

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Hol 202; Menko 2014; van Spaendonck-Swarts 2012

Genetic Testing for AYA with RCC

Table 8. Indications for Germline Genetic Analysis (Screening) of Children and Adolescents with RCC[a]

Indication for Testing	Tumor Histology	Gene Test	Related Syndrome
Multifocal RCC or VHL lesions	Clear cell	*VHL* gene	VHL syndrome
Family history of clear cell RCC or multifocal RCC with absent *VHL* mutation	Clear cell	Chromosome 3 gene translocations	Hereditary non-VHL clear cell RCC syndrome
Multifocal papillary RCC or family history of papillary RCC	Papillary	*MET* gene	Hereditary papillary RCC syndrome
Multifocal RCC or cutaneous fibrofolliculoma or pulmonary cysts or spontaneous pneumothorax	Chromophobe or oncocytic or clear cell	Germline sequence *BHD* gene	Birt-Hogg-Dubé syndrome
Personal or family history of early-onset uterine leiomyomata or cutaneous leiomyomata	Type 2 papillary or collecting duct carcinoma	*FH* gene	Hereditary leiomyomata/RCC syndrome
Multifocal RCC or early-onset RCC or presence of paraganglioma/pheochromocytoma or family history of paraganglioma/pheochromocytoma	Clear cell or chromophobe	*SDHB* gene, *SDHC* gene, *SDHD* gene	Hereditary paraganglioma/pheochromocytoma syndrome

RCC = renal cell carcinoma; VHL = von Hippel-Lindau.

[a]Adapted from Linehan et al.[31]

Genomics of RCC

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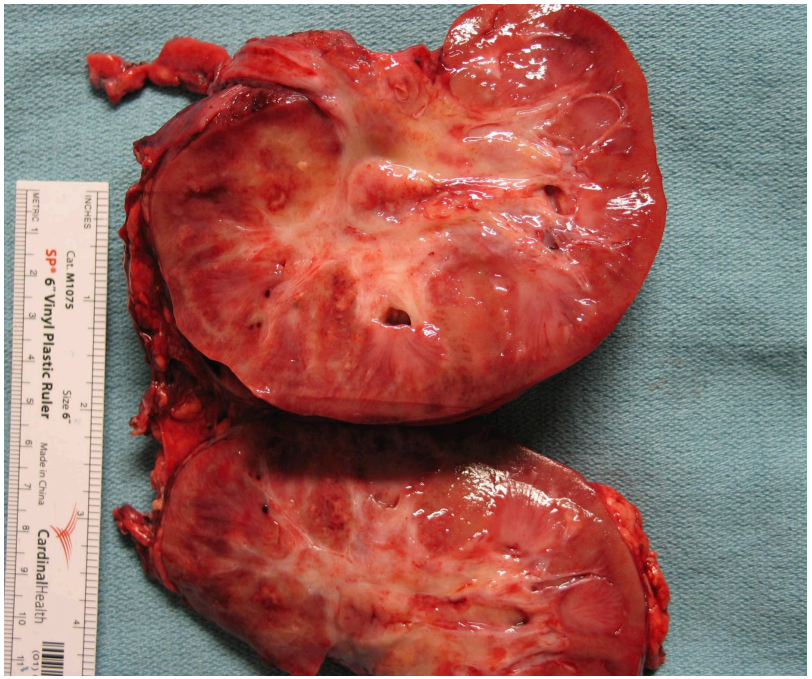
PDQ Cancer Information Summaries, published May 2023

Renal Medullary Carcinoma

- Typically seen in patients with sickle cell disease
  - Presentation: fever, hematuria, weight loss, flank pain
- Associated with *SMARCB1* deficiency (with resultant *INI1* loss) on chromosome 22q
- Usually widely metastatic at diagnosis
- Poorly responsive to chemotherapy and radiotherapy (median survival 4 months)



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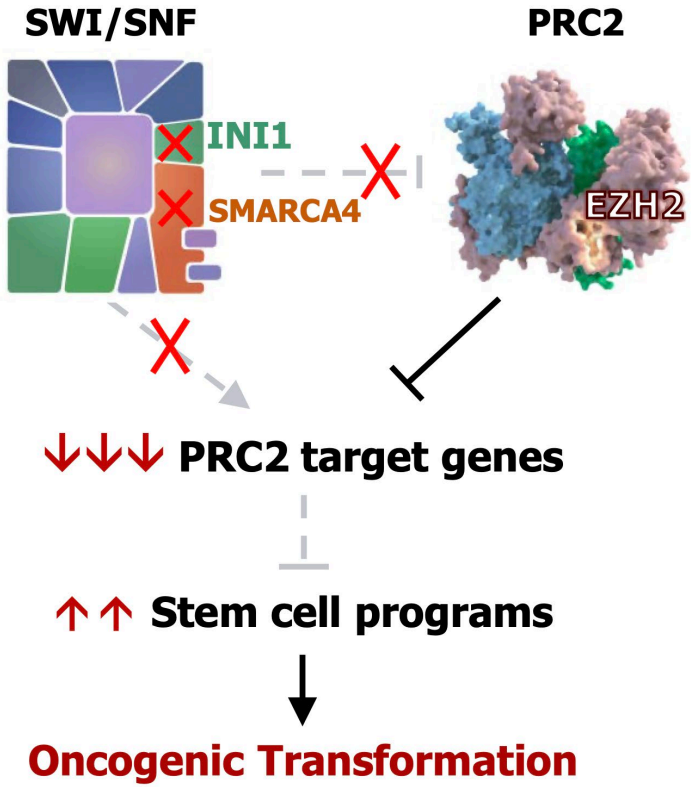
Agaimy 2021; Hong 2019; image from pathologyoutlines.com

Rhabdoid Tumor of the Kidney

- Associated with *SMARCB1* mutation (*INI* gene) on chromosome 22q
  - Less commonly *SMARCA4* mutation
  - 1/3 of patients have germline mutations (worse prognosis)
  - For children with this known mutation, surveillance is recommended with brain MRI every 3 months until 5 years old and abdominal ultrasound every 3 months



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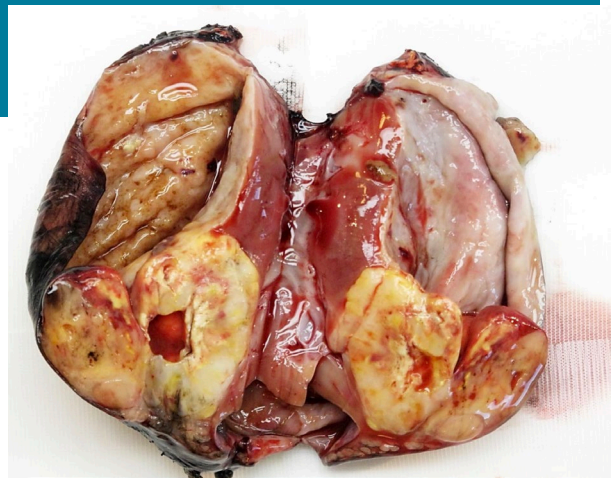
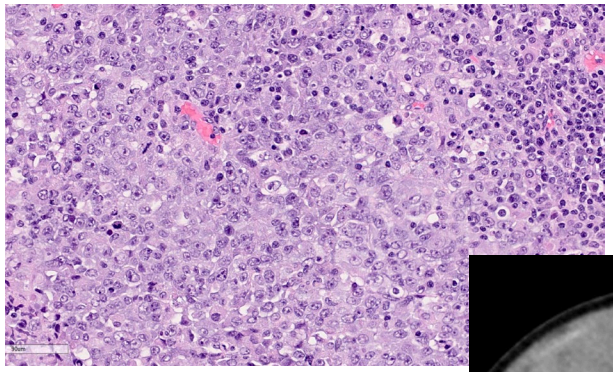
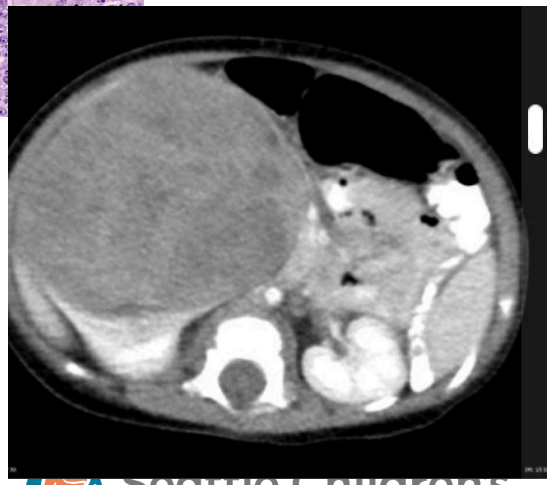
Tomlinson 2005; Janson 2006; image from fda.gov

Rhabdoid Tumor of the Kidney



- Typically occur in infants <11 months of age, usually with advanced disease
  - May be bilateral
  - Most commonly metastasize to lungs and brain (10-15%)





- Present with fever and hematuria

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Tomlinson 2005; Janson 2006; images from pathologyoutlines.com and radiopaedia.org

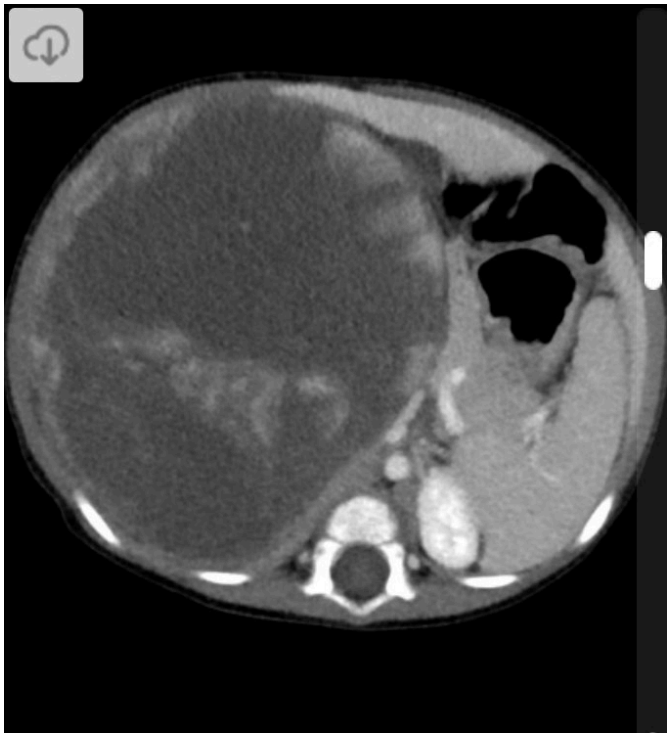
Rhabdoid Tumor of the Kidney

- Survival is dismal (2-year EFS 37% and OS 38%)
- Earlier surgical resection rather than upfront chemotherapy?
- Progression-free survival is higher in patients with Stage II and III disease if radiotherapy was received (67% vs. 15%)
- Optimal chemotherapy:
  - Doxorubicin appears to be active
  - Carboplatin/etoposide/cyclophosphamide arm of NWTS-5 closed early for poor outcomes
  - Some patients have done well with alkylator therapy and stem cell transplantation

Melchior 2020

Clear Cell Sarcoma of the Kidney

- About 1 in 20 pediatric renal tumors (usually <3 years old)
  - Worse prognosis if younger or higher stage disease at diagnosis
  - Stage 1: 100% EFS and OS; Stage 4: EFS 29%, OS 36%
  - Mutations in the *BCOR* gene (tandem duplications in exon 15)
- Classic metastatic pattern to brain, bone, soft tissue



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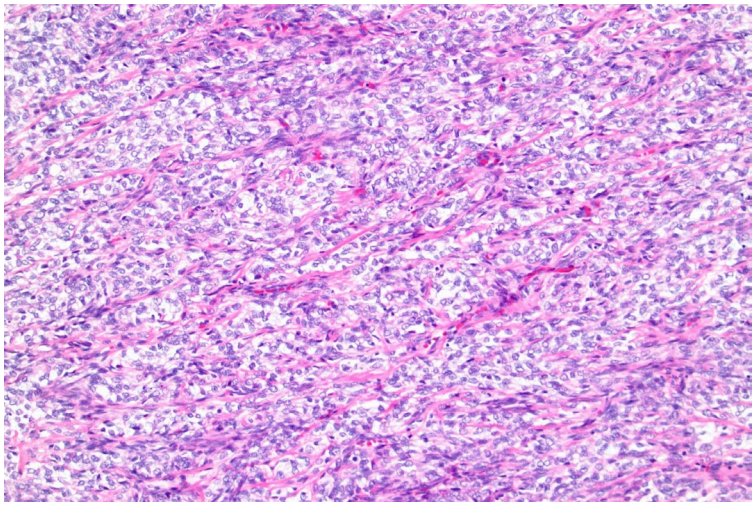
Singh 2021; Wong 2018; Seibel 2019; Gooskens 2014; image from radiopaedia.org

Clear Cell Sarcoma of the Kidney

- Treatment: multiagent chemotherapy (vincristine, doxorubicin, etoposide, cyclophosphamide) and radiation to the tumor bed after surgical excision



- Late relapses after chemotherapy previously common, now rare after 3 years
  - Most common site is brain

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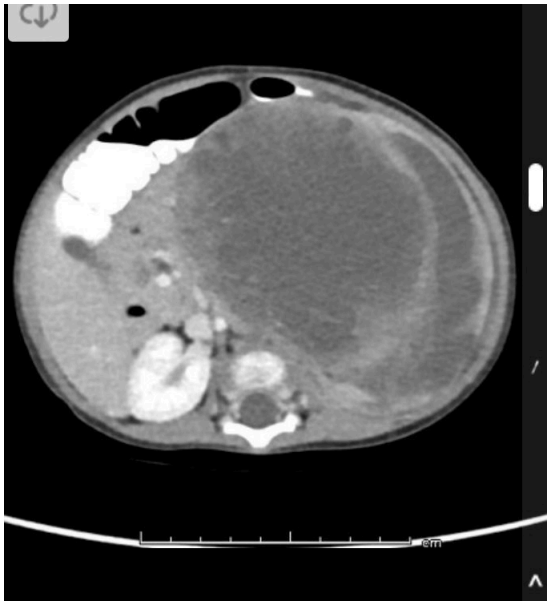
Singh 2021; Wong 2018; Seibel 2019; Gooskens 2014; image from pathologyoutlines.com

Congenital Mesoblastic Nephroma

- 3% of all pediatric renal tumors



- Can be seen prenatally (15% have polyhydramnios), very rare after age 2
  - Also presents with hypercalcemia (4%) and hyperreninemia (1%), both of which completely resolve after tumor excision
- Often not malignant, usually presents with local disease
  - Stage 3 disease in only 17%, usually because of + surgical margins or tumor rupture (often involve renal sinus, check medial margins)
  - Rare stage IV disease at presentation (bone)

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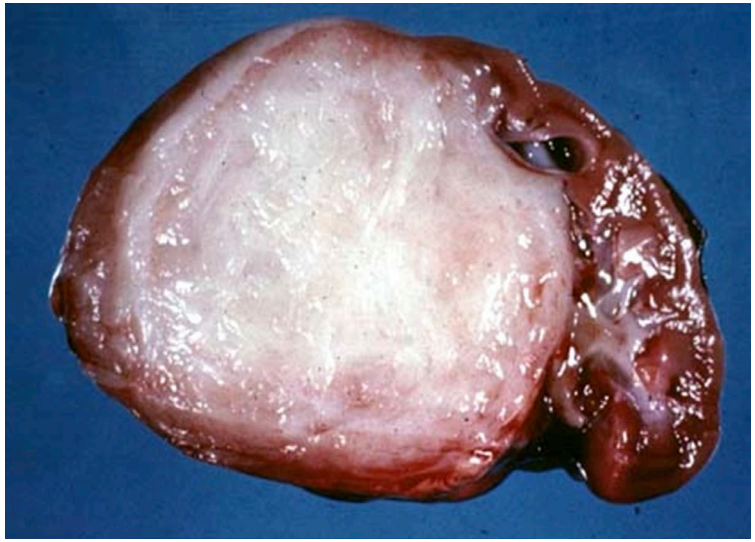
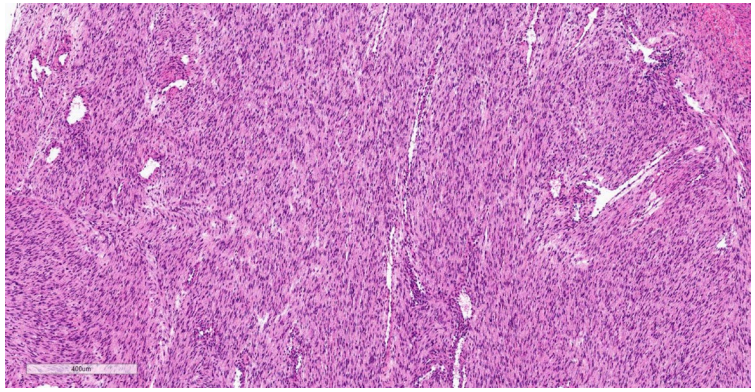
van den Heuvel-Eibrink 2008; England 2011

Congenital Mesoblastic Nephroma

- Three cellular types: classic (42%), cellular (39%), mixed (10%)



- Congenital anomalies are rare: GU anomalies, GI malformations, polydactyly, hydrocephalus, Beckwith-Wiedemann syndrome



- Associated with somatic trisomy 11 and a translocation of chromosomes 12;15 (*ETV6* and *NTRK3* genes)
  - Never seen in classic CMN

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Furtwaengler 2006; image from pathologyoutlines.com

Congenital Mesoblastic Nephroma

- Chemotherapy if Stage III or histology shows cellular subtype, otherwise can be managed with nephrectomy alone
- Chemotherapy is typically vincristine and dactinomycin, though doxorubicin, cyclophosphamide, ifosfamide have been used
- Low mortality (12%), split evenly between disease and treatment (if latter, usually infants)
- Rare relapse (4%), usually local or in brain or bone
  - More common with cellular subtype and stage III disease

Summary

- Renal tumors are only about 7% of solid organ tumors in children
- Rare pediatric renal tumors are very rare
- Maintain a high index of suspicion
- Consider clinical trials and COG enrollment to optimize outcomes

Thank You! Questions?