Pediatric Urologic Oncology

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Disclosures

- None

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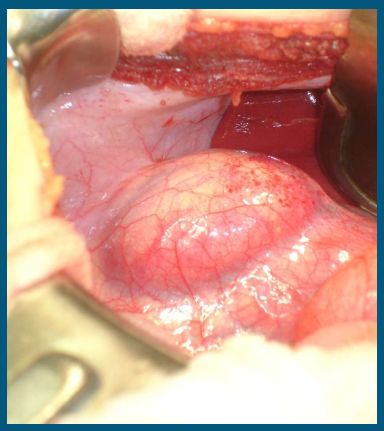
Wilms tumor



- Most common primary **renal** malignant neoplasm in childhood
- 95% of **kidney** cancers in children <10 years old
- Success over last 50y due to cooperative pediatric oncology groups in North America and Europe
- NWTS contributed to cure rates of children with Wilms tumor to now >90%

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Neoplasm	Age Range	Peak Age
Mesoblastic nephroma	0-1 yr	1-3 mo
Wilms tumor - Unilateral - Bilateral	 1-11 yr 2 mo - 2 yr	 3.5 yr 15 mo
Rhabdoid tumor	6 mo - 9 yr	6-12 mo
Nephroblastomatosis	Any age	6-18 mo
Multilocular cystic nephroma - Cystic nephroma (MLCN) - Cystic partially differentiated nephroblastoma (CPDN)	 5th-6th dec, F 3 mo - 4 yr	 5th-6th dec, F 1-2 yr
Clear cell tumor	1-4 yr	2 yr
Renal cell carcinoma	6 mo - 60 yr	10-20 yr

Abbreviation: yr = year; mo = month; dec = decade; F = female
Reference: RadioGraphics 2000;20:1583-1603.

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80% present before 5 years old

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Reference: RadioGraphics 2000;20:1583-1603.

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Wilms Tumor

- *Most common renal tumor of childhood*
  - *~500 cases per year in USA, 95% of renal tumors under 15 yrs*
- Median age 3.5 years
  - Most before age 5, rare in neonatal period, 90% prior to 8 years
- Classic pathologic pattern = *triphasic pattern*
  - *Blastemal*
  - *Stromal*
  - *Epithelial*
- Collaborations -> Dramatic improvement in survival -> ~90%

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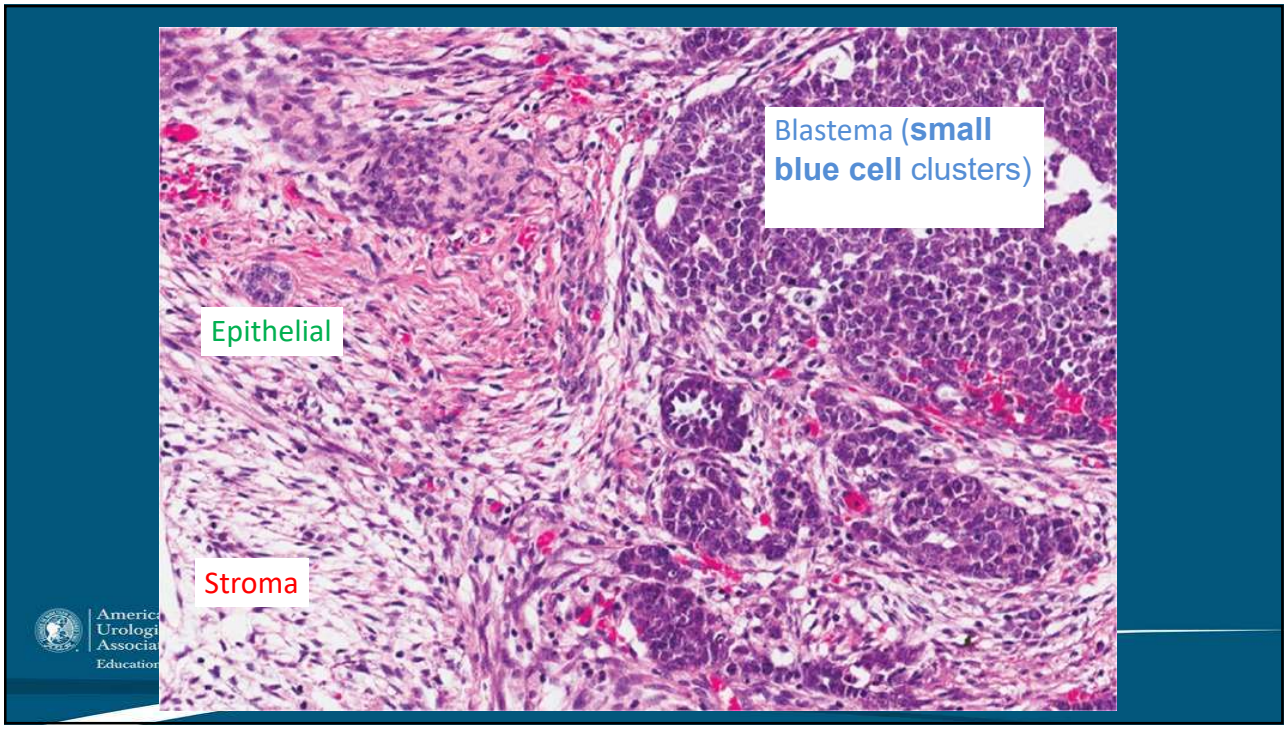

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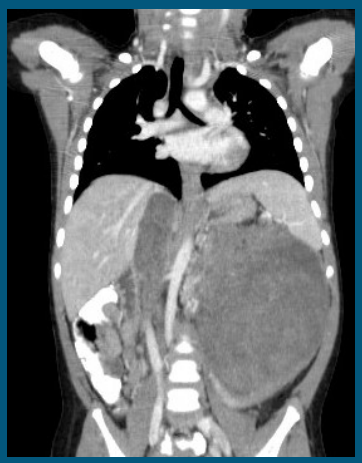
Clinical presentation

- Painless palpable abdominal mass in healthy appearing child
- <15% hematuria
- Hypertension
- Screening (Predisposition syndrome)



Workup:

- Ultrasound → CT c/a/p
- Basic Labs
- No biopsy (will upstage the cancer; minimal benefit)

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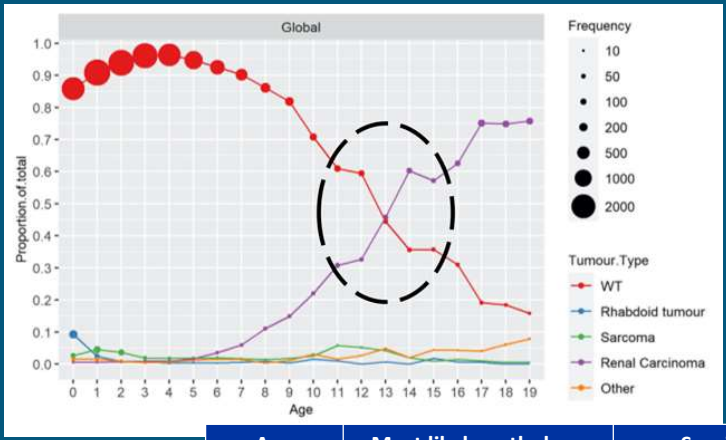
Renal Masses and Age



- Surgical guidelines are the same, regardless of pathology!
- Biopsy rarely changes management

Age	Most likely pathology	Surgical recommendation
0-6 mos	CMN	Radical Nx with LN sampling
7 mos-12y	Wilms Tumor	
>12y	RCC	

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Nakata *et al. Int J Cancer 2020*

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Wilms Tumor Genetics

Table 1. Wilms Tumor Risk In Associated Syndromes

Syndrome	Tumor Risk
BWS / isolated hemihypertrophy	5-10%
Perlman	30-60%
Simpson-Golabi-Behmel	7.5%
Denys-Drash	90%
WAGR	30-50%

- *WT1 gene on chromosome 11p13*
- *11p15 imprinting genes*
- Most commonly sporadic
- **10% of children have syndrome**

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Wilms tumor syndromes: WT1 11p13

- WAGR (Wilms tumor, Aniridia, Genital anomalies, mental Retardation)
  - Gene for aniridia is close to WT1 gene
  - *30-50% risk of Wilms tumor*
- Denys-Drash
  - Undervirilized male (46 XY DSD), renal sclerosis -> ESRD, Wilms tumor
  - Very high risk of Wilms tumor, ~90%
  - *Also increased risk for gonadoblastoma!*
  - *Bilateral nephrectomy if ESRD and unilateral renal mass*

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Wilms tumor syndromes: 11p15

- 11p15 = cluster of imprinted genes
  - Loss of imprinting -> Wilms tumor
- Overgrowth syndromes
  - *Beckwith-Wiedemann Syndrome = 5-10% Wilms risk*
  - *Hemihypertrophy*
  - Perlman
  - Soto
  - Simpson-Golabi-Behmel

Congenital Anomalies

•High risk (>20%)

- WT1 **deletions** (including **WAGR syndrome**)
- Truncating and pathogenic missense WT1 mutations (including **Denys-Drash syndrome**)
- Familial Wilms tumour
- **Perlman syndrome**
- Mosaic variegated aneuploidy
- **Fanconi anaemia** D1/Biallelic BRCA2 mutations

•Moderate risk (5–20%)

- WT1 intron 9 splice mutations (Frasier syndrome)
- **Beckwith-Wiedemann syndrome**
- **Simpson-Golabi-Behmel syndrome** caused by GPC3 mutations/deletions

•Low risk (<5%)

- Isolated hemihypertrophy
- Bloom syndrome
- Li-Fraumeni syndrome

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Wilms Tumor Predisposition Syndromes

- *Screening with renal sonogram recommended*
  - Q3-4 months until 7-8 years
  - Tumors usually lower stage, nephron sparing more likely
  - Improved survival not proven

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Pathologic staging

STAGE	
I	Tumor confined to the kidney and completely resected. The renal capsule is intact and the tumor was not ruptured prior to removal. No renal sinus extension. There is no residual tumor.
II	Extracapsular penetration but is completely resected. Renal sinus extension or extrarenal vessels may contain tumor thrombus or be infiltrated by tumor.
III	Residual nonhematogenous tumor confined to the abdomen: lymph node involvement, any tumor spillage, peritoneal implants, tumor beyond surgical margin either grossly or microscopically, or tumor not completely removed. BIOPSY = STAGE III
IV	Hematogenous metastases to lung, liver, bone, brain, etc.
V	Bilateral renal involvement at diagnosis.

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Treatment: North America

- Children's Oncology Group (COG) protocols followed
- For unilateral and resectable
  - *Open nephrectomy and regional lymph node sampling*
- Intraoperative tumor spillage = upstaging
  - *Goes from stage 1 or 2 to stage 3 = radiation/more chemo*
- Bilateral, inoperable, solitary kidney, syndromes
  - *Preop chemotherapy, no biopsy, possible partial nephrectomy*
- *75% of all pediatric kidney cancer is favorable histology Wilms*

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Treatment: outside North America

- Societe Internationale D'oncologie Pediatrique (SIOP) protocols
- *Chemotherapy first then nephrectomy*
- Decreased risk of tumor rupture (33% to 4%)
  - Surgery easier
  - Possible increased role of partial nephrectomy
- Small risk chemotherapy for non-Wilms tumor or benign lesion
- *Similar overall survival to COG approach*

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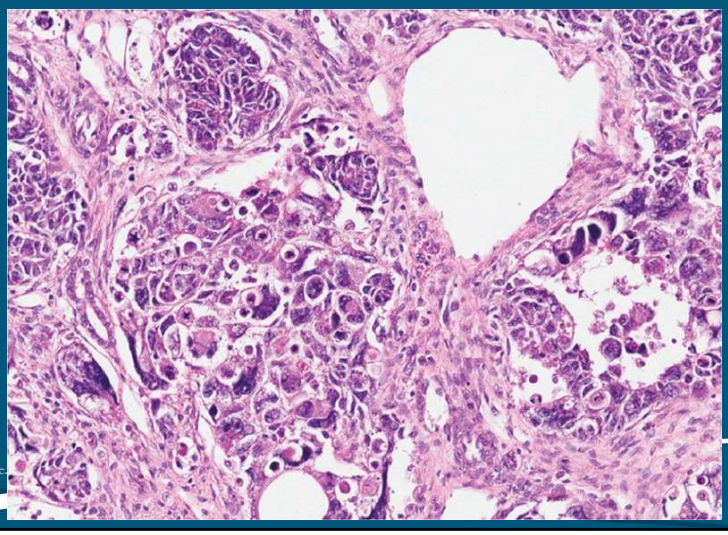
Anaplasia (unfavorable histology) = predictive of bad outcome, ~10% of cases



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- *LOH at 1p and 16q associated with poor outcome*
- *Seen in 10-20% of cases*
- *Independent predictor*

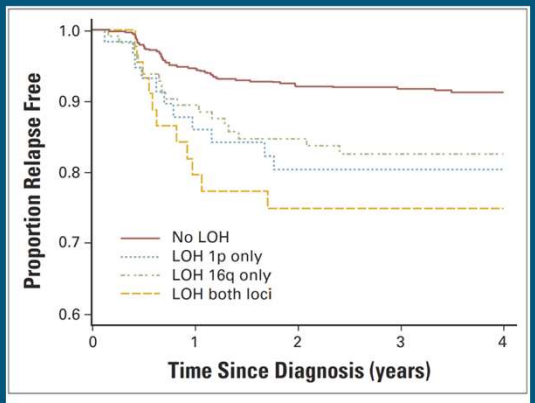

Fig 2. Relapse-free survival by joint loss of heterozygosity at chromosomes 1p and 16q for stage I/II favorable-histology Wilms tumor patients. LOH, loss of heterozygosity.

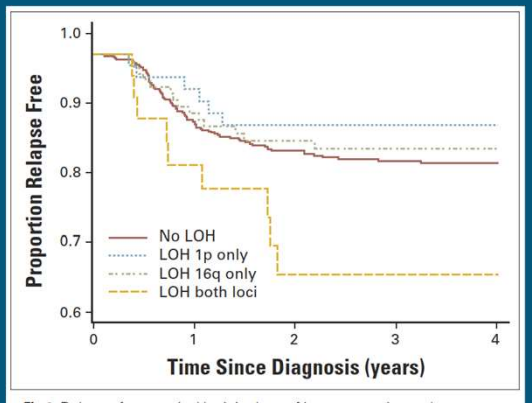

Fig 3. Relapse-free survival by joint loss of heterozygosity at chromosomes 1p and 16q for stage III/IV favorable-histology Wilms tumor patients. LOH, loss of heterozygosity.

J Clin Oncol. 2005 Oct 10;23(29):7312-21.

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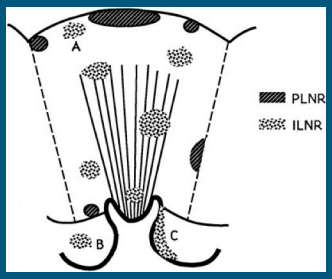
Nephrogenic rests



- Clusters of retained embryonic kidney precursor cells
- Potential Wilms precursors
  - Seen in ~1% infants -> 99% involute by 6 months
- Intralobar (ILNR) vs perilobar (PLNR)
  - PLNG assoc with overgrowth (BWS, hemihypertrohpy)
  - ILNR assoc with WAGR, Denys Drash
- *Unilateral Wilms ->35% have rests in kidney removed*
  - *Associated with contralateral recurrence, especially PLNR*
- Bilateral Wilms -> essentially 100% have them

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Med Pediatr Oncol 1993;21:158–168

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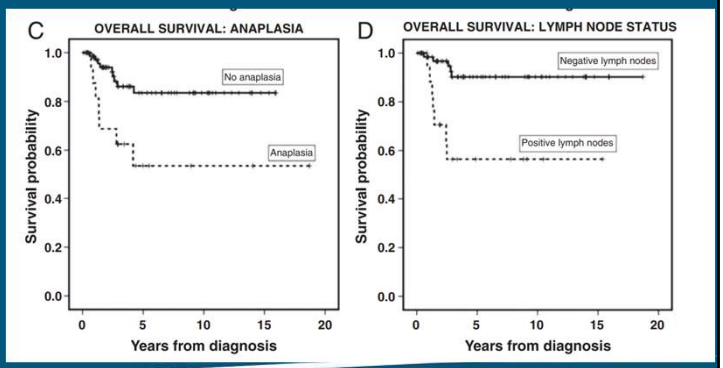
- *Stage III -> radiation*
  - *Tumor spillage, biopsy*
- *Anaplasia -> radiation*
  - *All stages*

- *Anaplasia and positive lymph nodes associated with poor survival*

	Local/locoregional disease		
	Stage I	Stage II	Stage III
Favorable histology	No RT	No RT	10.8 Gy
Focal anaplasia	10.8 Gy	10.8 Gy	10.8 Gy
Diffuse anaplasia	10.8 Gy	10.8 Gy	19.8 Gy



Wilms tumor. Pediatr Blood Cancer. 2021 May;68 Suppl 2:e28257.
Pediatr Surg. 2012 Jun;47(6):1228-33.

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Wilms tumor chemotherapy/XRT

- *Stage 1, no anaplasia, <550 grams -> no chemotherapy*
- *Stage 1, no anaplasia, -> dactinomycin, vincristine; if LOH 1p/16q add doxorubicin*
- Stage 1, +anaplasia -> *abd XRT,* dactinomycin, vincristine, doxorubicin
- Stage 2, no anaplasia -> dactinomycin, vincristine
- Stage 2, focal anaplasia -> *abd XRT*, dactinomycin, vincristine, doxorubicin
- Stage 2, diffuse anaplasia -> *abd XRT,* dactinomycin, vincristine, doxorubicin, etoposide, cyclophosphamide
- Stage 3&4, no anaplasia -> *abd XRT,* dactinomycin, vincristine, doxorubicin; no lung XRT if complete response for stage 4
- Stage 3&4, *LOH 1p/16q* -> similar to stage 2 diffuse anaplasia, *but add lung XRT*
- Stage 3, focal anaplasia -> *abd XRT,* dactinomycin, vincristine, doxorubicin
- Stage 3, diffuse anaplasia -> *abd XRT; carboplatin,* vincristine, doxorubicin, etoposide, cyclophosphamide
- Stage 4, focal anaplasia -> *abd and lung XRT; carboplatin,* vincristine, doxorubicin, etoposide, cyclophosphamide
- Stage 4, diffuse anaplasia -> *abd and lung XRT; carboplatin,* vincristine, doxorubicin, etoposide, cyclophosphamide
- Stage 5 -> preop chemo with dactinomycin, vincristine, doxorubicin. Assess after 6 weeks with repeat imaging then possible partial nephrectomy vs biopsy vs more chemotherapy

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Clear Cell Sarcoma of Kidney

- *2nd most common pediatric malignant renal tumor*
- *2-3 year age group (1-6 years old);* Male:Female = 2:1
- Locally advanced at presentation; mean 11 cm
  - Never bilateral
- Aggressive behavior and late relapses
- *"bone metastasizing renal tumor of childhood" (bone/brain)*
- Treated chemo/radiation similar to high risk Wilms
  - 5 year overall survival 86%, improved over time

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Arch Pathol Lab Med. 2020 Jan;144(1):119-123.

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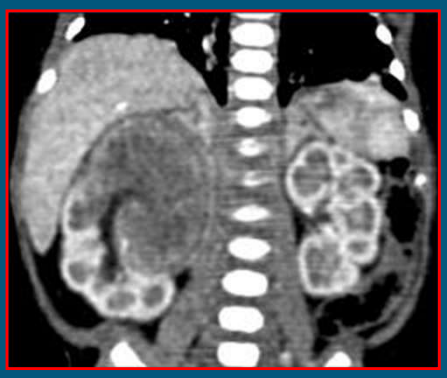
Congenital Mesoblastic Nephroma (CMN)



- Most common renal tumor < 6 months of age
- Abdominal mass, polyhydramnios, hypercalcemia
- Antenatal diagnosis common
- Histology/genetics = congenital fibrosarcoma
- Nephrectomy is curative

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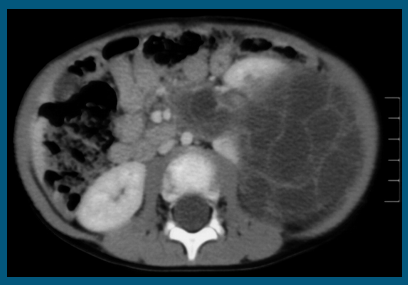
Multilocular cystic nephroma



- *Benign cystic tumor*
  - – Rare reports of malignancy, ? Correct diagnosis ?
- *Biphasic distribution*
  - – *Young male children (60% vs 40% female, <11)*
  - – *Young adult women (80% vs 20% male, >11)*
- Present with palpable mass, incidental, pain, hematuria
- Treatment = nephrectomy, curative
- 200 cases in literature, rare

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AJR Am J Roentgenol. 2015 Dec;205(6):1188-93.

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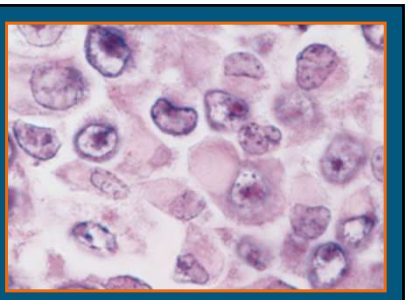
Rhabdoid tumor



- *Infants and young children*
  - – *Median 10 months*
- *Rare but most aggressive renal cancer in peds*
  - – *20-25% survival*
- *Hypercalcemia and brain mets*
  - – Advanced stage at presentation common
- Rare: 2-4% of pediatric renal tumors; 20-25 cases/year USA
- Treated chemo/radiation similar to high risk Wilms

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Renal cell carcinoma

- Incidence increases with age (adolescents/teenagers)
  - *Most common renal malignancy age 10-20*
- *Papillary*
- *Translocation tumors are predominant*
- *Hereditary syndromes*
  - *VHL; tuberous sclerosis; hereditary papillary*
- *Present with symptoms: abdominal pain, hematuria, mass*
- Treatment similar to adults
  - possible benefit to lymph node dissection; better survival than adults

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Curr Opin Urol. 2019 Sep;29(5):500-504.

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Lymphoma

- Kidney involvement secondary
- *Constitutional symptoms*
  - *Night sweats, fevers, weight loss*
- Generalized lymphadenopathy
- *Biopsy to confirm diagnosis, if suspected*
- Burkitt lymphoma most likely to involve kidney

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Angiomyolipoma

- *Usually seen with tuberous sclerosis*
  - They can also get cysts and RCC
- *Fat on CT scan*
  - Lipid poor -> biopsy to distinguish from RCC
- *Treatment, more likely to be needed if larger (>4 cm)*
  - *Embolization*
  - *Medical: mTOR inhibitors (everolimus, sirolimus)*
    - *Sustained reduction in size*

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Pediatric renal tumors by age

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Renal tumors done!

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Neuroblastoma

- Good news!

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Rhabdomyosarcoma

- Genitourinary ~ 15-20%
- Survival varies by site:
  - Favorable: Para-testicular, vagina, uterus
  - Unfavorable: Bladder/prostate
- Site and size (</> 5 cms.) of tumor are important

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Rhabdomyosacroma

- *Aggressive soft tissue sarcoma*
  - *Arise from embyronic mesenchymal tissue, striated muscle*
- Most sporadic, but some syndromes
  - Li-Fraumeni, DICER 1, neurofibromatosis 1, Costello syndrome
- 350 cases per year USA
- Bimodal: first 2 years and adolescence

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Bladder and prostate

- May be difficult to detect exact site of origin
- Obstructive Sx, hematuria common
- Bladder: Botryoid, trigone, intraluminal
- Prostate: Solid
- Transurethral Bx at time of cysto
- MOST not amenable to primary partial cystectomy or prostatectomy

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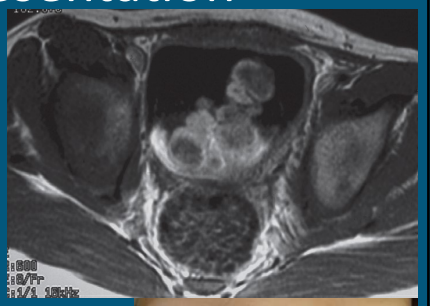
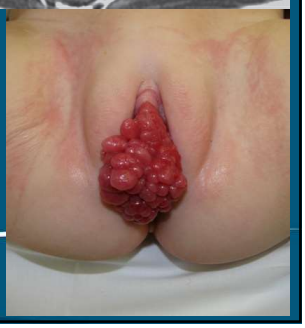
GU Rhabdomyosarcoma presentation

- Local spread/infiltration and lymph node spread common
- Distant mets 15-20% at presentation
- *Symptoms depend on location*
  - Prostate/bladder: hematuria, obstruction, LUTS
  - Vagina/uterus: bleeding, sarcoma botryoides (grape like mass)
  - Paratesticular: painless scrotal mass





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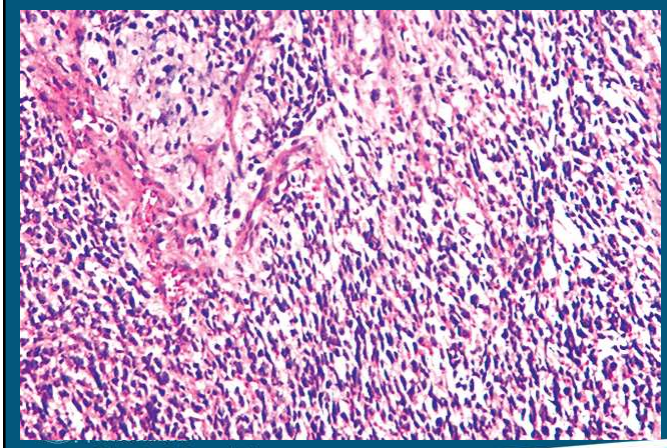
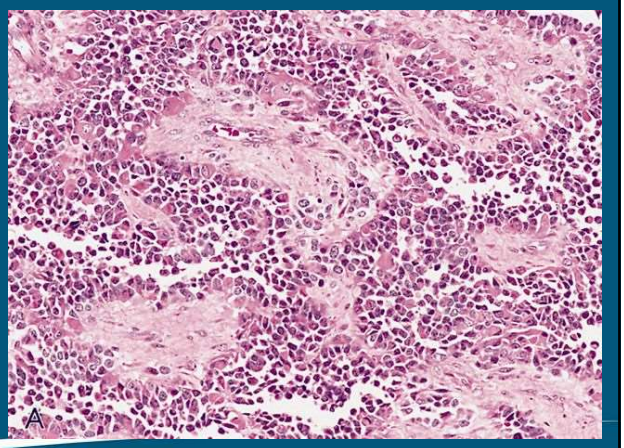
GU Rhabdomyosacroma

Embryonal



Alveolar (worse)



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GU rhabdomyosarcoma predictors

- *Embryonal better than alveolar*
- *Bladder/prostate unfavorable compared to other GU*
  - unfavorable site → **cannot** be stage I
  - Paratesticular and female genital tract is considered a favorable site → can **only** be stage I or IV
- *Translocation of PAX3 or PAX7 with FOXO1 unfavorable*
  - *"Fusion positive";* More important than histology in current protocols
- Tumor size > 5 cm unfavorable; metastasis unfavorable

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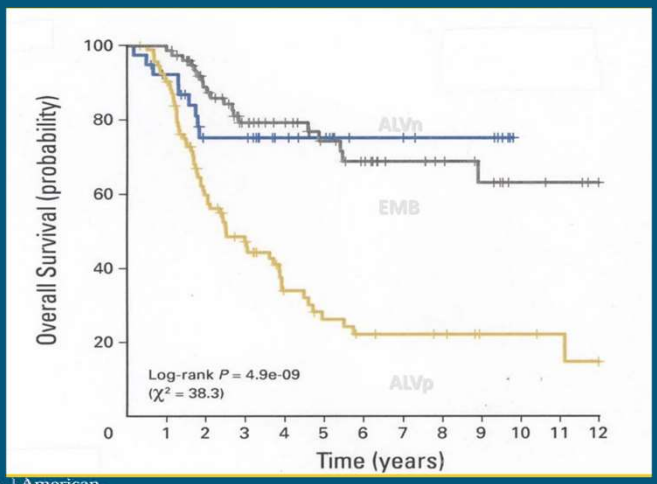
Fusion status important predictor



Alveolar/embryonal without fusion similar survival

Alveolar with fusion + much worse survival

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Williamson, JCO 2010

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GU rhabomyosarcoma treatment

- *Multimodal -> Biopsy, chemo/radiation, +/- surgery*
- Bladder/prostate
  - cystoscopic biopsy/TUR -> chemo/radiation
  - Selective complete excision of primary
  - If outlet obstruction, leave catheter or SP tube during treatment
- Vagina
  - Biopsy -> chemo/radiation
  - Selective complete excision of primary
- Paratesticular
  - Radical orchiectomy -> chemo, +/- RPLND, +/- radiation

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GU rhabdomyosarcoma surgery

- *Complete resection of primary only if organ preservation possible*
  - *Generally 1st step is biopsy*
  - *Exception: Paratesticular -> radical inguinal orchiectomy*
- Complete resection after biopsy
  - Pretreatment re-excision: before chemo; only if possible and organs spared
  - Delayed primary excision: after chemotherapy but before XRT, only if possible and organs spared

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GU Rhabdomyosarcoma radiation

- Important for local control
- *Cystectomy or prostatectomy generally not done for local control*
  - *Remember: surgery is just one part of multimodal therapy*
- Varies on histology, stage, risk group, location
- Long term effects common
  - Bladder: small capacity, LUTS, incontinence
  - Only 40% bladder/prostate cases have “normal” function
- Post treatment resection of residual masses generally not needed
  - Post treatment mass = stroma; not been shown to improve survival

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GU rhabdomyosarcoma chemo

- Chemo increased survival from <25% to over 70%
- Vincristine, Dactinomycin, Cyclophosphamide (VAC)
  - Vincristine -> neuropathy
  - Dactinomycin -> myelosupression, infertility, hair loss
  - Cyclophosphamide -> myelosuppression/hemorrhagic cystitis

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Paratesticular Rhabdomyosarcoma

- *Radical inguinal orchiectomy*
- *Ipsilateral RPLND*
  - *10 years or older regardless of CT findings*
  - *If <10 years, if CT scan positive*
  - *If nodes positive -> radiation*
- Chemotherapy regardless of node status
- Excellent prognosis
  - 60-80% stage 1, 90% embryonal, survival > 90%

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Pediatric testis tumors

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New scrotal tumor - Differential

Testicular

- Germ cell tumor
- Stromal Tumor
- Epidermoid Cyst
- Metastatic Lesion
  - Leukemia
  - Lymphoma
- Neuroendocrine tumor
- Fibrous tumors

Para-Testicular

- Rhabdomyosarcoma
- Other spermatic cord sarcomas
- Leiomyomas
- Adenomatoid Tumor
- Cystadenoma (VHL)
- Mesothelioma
- Spermatocele

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Pediatric Testis Tumors: concepts

- Postpubertal -> typical malignant germ cell tumors
- *Prepubertal → typically benign (75%)*
  - *1% of solid tumors; Peak incidence age 2*
  - *Peak incidence age 2*
  - *Testis-sparing surgery is standard of care (with frozen, intraop ultrasound, prepared for radical with an inguinal approach)*
  - *If malignant, more favorable course*
- *Differential for prepubertal*
  - *Germ cell tumors: yolk sac, teratoma (mature/immature)*
  - *Tumors of any other cells: Leydig, Sertoli, Stromal*

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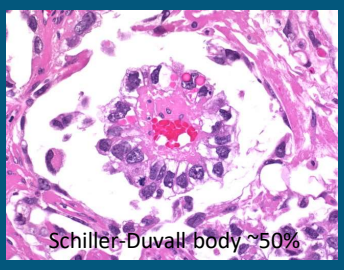
Yolk sac tumor

- *Most common malignant testis tumor in prepubertal*
  - ~15% of prepubertal testis masses
- Asymptomatic scrotal mass
- Scrotal US
- *AFP elevated in 90%*
  - T ½ = 5-7 days


Schiller-Duvall body ~50%

- *Radical ing orchiectomy + CT/MRI abd/pelvis-> 90% stage 1*
- Surveillance alone for stage 1, no RPLND or chemo
  - AFP & MRI/CT Q3 mo x 1 year -> Q6 mo x 2 years

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Yolk sac tumor: higher stage

- *Persistent elevated AFP with or without lymphadenopathy*
  - *Chemo first*
- RPLND if:
  - Lymphadenopathy but normal markers (prior to chemo)
  - Persistent lymphadenopathy after chemo
  - Persistent AFP elevated after chemo

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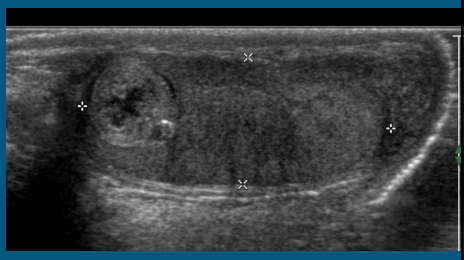
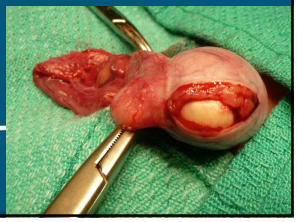
Teratoma

- Most common prepubertal testis mass
  - 40-50% of prepubertal testis masses
- *Benign*
  - *Mature and well-differentiated*
- *AFP level distinguish from Yolk Sac*
  - Exception: infants have normal elevated of AFP
- *US -> heterogeneous, cystic/solid areas, calcifications*
  - Yolk sac: usually homogeneous
- Treatment = partial orchiectomy/enucleation
  - Scrotal incision fine





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Teratoma

- Can be found at any age
  - Commonly mixed and immature in post-pubertal patients
  - Commonly mature in PRE-pubertal
- Behavior depends on age/pubertal status of patient
  - Benign in pre-pubertal (focal insult, no GCNIS)
  - Mets and malignant degeneration in post-pubertal (field effect, with GCNIS)
- Post-surgical management depends on pubertal status of patient
  - Post-pubertal patient with "pre-pubertal teratoma" on path report → malignant NSGCT

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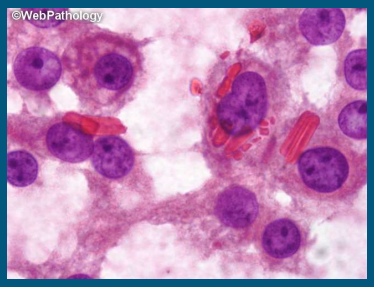
Leydig cell tumor



- Benign stromal tumor, usually unilateral
  - Peak age 4-5 years
- Leydig cells make testosterone
- *Presentation*
  - *Testis mass, precocious puberty, elevated testosterone*
  - *Low LH/FSH*
- Treatment: partial orchiectomy/enucleation, follow hormones
- Pathology: *40% Reinke crystals*

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Juvenile Gonadal Stromal Tumor (JGST)

- *Most common testis tumor in neonates*
- *Benign*
- *Stain negative for AFP*
- Treatment = radical orchiectomy if unsure diagnosis vs partial orchiectomy

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DSD and Gonadoblastoma

- Gonadoblastoma = benign tumor -> dysgerminoma
- Dysgerminoma = malignant tumor similar to seminoma
- Dysgenetic gonads with "Y" chromosome material have increased risk
  - The more abnormal the gonad and higher it is, the higher the risk
- *Treatment: gonadectomy in high risk patients*

Table 4 Risk of germ cell malignancy according to diagnosis

Risk group	Disorder	Malignancy risk (%)	Recommended action
High	GD[a] (+Y)[b] intra-abd.	15–35	Gonadectomy[c]
	PAIS non-scrotal	50	Gonadectomy[c]
	Frasier	60	Gonadectomy[c]
	Denys-Drash (+Y)	40	Gonadectomy[c]
Intermediate	Turner (+Y)	12	Gonadectomy[c]
	17β-HSD	28	Monitor
	GD (+Y)[b] scrotal	Unknown	Biopsy[d] and irrad.?
	PAIS scrotal gonad	Unknown	Biopsy[d] and irrad.?
Low	CAIS	2	Biopsy[d] and ???
	Ovotest DSD	3	Testis tissue removal ?
	Turner (−Y)	1	None
No (?)	5α-Reductase	0	Unresolved
	Leydig cell hypoplasia	0	Unresolved

Consensus statement on management of intersex disorders

I.A. Hughes [a,*], C. Houk [b], S.F. Ahmed [c], P.A. Lee [b], Lawson Wilkins Pediatric Endocrine Society (LWPES)/European Society for Paediatric Endocrinology (ESPE) Consensus Group[1]

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Undescended testis and testis cancer

- *Risk of testis cancer without surgery increased but still rare*
  - ~2% lifetime risk
  - Risk ratios: 2-18 times baseline risk
  - The higher the testis is, likely the higher the risk
- 10% of testis tumors arise in ones with history of UDT
- Seminoma most common

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- Large Swedish cohort 16,983 men who had orchiopexy
- 56 testis cancer cases
- *Prepubertal orchiopexy had about half the increased risk*
  - *RR 2.2 vs 5.4*
- *Oldest cohort (35-40 yrs old)*
  - *~2% had testis cancer*

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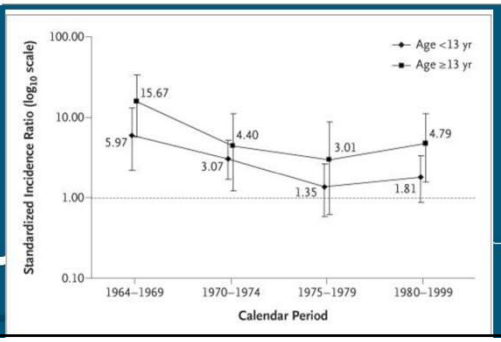
N Engl J Med. 2007 May 3;356(18):1835-41.

Table 2. Standardized Incidence Ratio for Testicular Cancer According to the Age at Orchiopexy among Men 15 to 55 Years of Age between 1965 and 2000.*

Age at Orchiopexy	No. of Men with Testicular Cancer	Standardized Incidence Ratio (95% CI)
All ages	56	2.75 (2.08–3.57)
0–6 yr	9	2.02 (0.93–3.84)
7–9 yr	14	2.35 (1.28–3.94)
10–12 yr	15	2.27 (1.27–3.74)
13–15 yr	12	5.06 (2.61–8.84)
16–19 yr	6	6.24 (2.29–13.58)
<13 yr	38	2.23 (1.58–3.06)
≥13 yr	18	5.40 (3.20–8.53)

* The Swedish general population was used as the comparison group.



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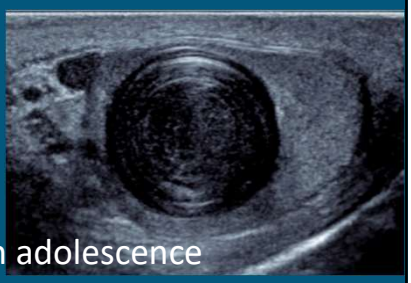
Epidermoid Cyst



- Benign
- Present as painless mass
- Typically in mid-adulthood but can be seen in adolescence

- Ultrasound:
  - "Onion-skin" or "whorled" appearance on ultrasound
  - Layers of keratinous debris lined with keratinizing squamous epithelium
  - Avascular

- Enucleation vs orchiectomy

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Hematuria in Pediatric Urology

- Infection is a frequent cause of both gross and microscopic hematuria
- **Malignancy is a rare cause of hematuria in children**
- Coexistent hypertension or proteinuria should prompt investigation for glomerular disease.
- The most common causes of persistent microscopic hematuria are not urological
  - Thin basement membrane nephropathy, immunoglobulin A nephropathy, or idiopathic hypercalciuria
  - Post-infectious glomerulonephritis
- Microscopic hematuria is often transient and work-up will not identify the cause
- Ultrasound is often enough to r/o neoplasms, stones, structural abnormalities
- (Gross hematuria in infant: Renal vein thrombosis, renal artery thrombosis, ATN of infancy)

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Some other odds and ends

- Multicystic Dysplastic Kidney (MCDK) is NOT a risk factor for cancer (disproven); nephrectomy not necessary if asx

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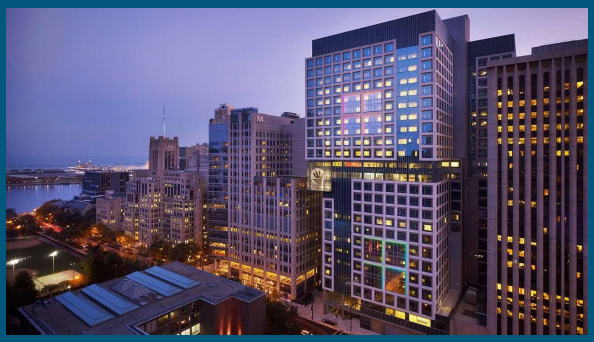
Thank you



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