Genitourinary Oncology

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Key Words

Oncology, Wilms Tumor, Renal Tumor, Testicular Tumor, Germ Cell Tumor, Rhabdomyosarcoma

Wilms Tumor

1. Introduction

Wilms Tumor (**WT**) or **Nephroblastoma is the most common renal tumor of childhood**. It is an embryonal tumor developing from the remnants of the immature kidney. **The classic pathologic findi stromal, and epithelial.** Over the last few decades, work performed by cooperative groups such as the National Wilms Tumor Study (NWTS) and the International Society of Paediatric Oncology (SIOP) Currently, treatment for WT in North America is based largely on protocols from the Children's Oncology Group (COG), Renal Tumors Committee. **Patients are stratified into risk groups based on curr that include surgery, chemotherapy and sometimes radiotherapy.** Increasing recognition of the late effects of treatment has driven the recent focus on minimizing therapy for those in low-risk groups

References: 1-2-3-4-5-6-7-8-9-10-11-12-13-14-15-16-17-18-19-20-21-22-23-24-25-26-27-28-29-30-31-32-33-34-35-36-37-38-39-40-41-42-43-44-45-46-47-48-49-50-51-52-53-54-55-56-57-58-59-60-61-62-63-64-65-66-67-68-69-70-71-72-73-74-75-76-77-78-79-80-81-82-83-84-85-86-87-8

2. Epidemiology

WT accounts for 6-7% of all childhood cancers. There are roughly 500 new cases per annum in the U.S., and the incidence is roughly 7.6 cases/million children under the age of 15 years. WT typically is equal. Most cases are diagnosed before 5 years of age and WT is rare in the neonatal period. In patients older than 10 years of age presenting with a renal mass, or in younger patients presenting with **malignancies, renal abscess, or segmental pyelonephritis.**

3. Risk Factors and Pathophysiology

While WT is most commonly sporadic, approximately 10% of children with WT have an associated congenital malformation syndrome.[2] These syndromes can be divided into those with features of somati overgrowth include isolated hemihypertrophy, Beckwith-Wiedemann syndrome (BWS), Perlman syndrome, Sotos syndrome, and Simpson-Golabi-Behmel Syndrome. **BWS** (**macroglossia, macrosomia imprinting abnormalities.**

Syndromes with an increased risk of WT without somatic overgrowth are almost invariably related to abnormalities of the WT1 gene on chromosome 11p13 and include Denys-Drash syndrome (DDS – ur mental retardation), among others.

ng is a triphasic pattern which includes varying proportions of three cell types: blastemal,
has led to dramatic improvement in survival, which approaches 90% for all patients collectively.
ent clinical and molecular staging paradigms and assigned into various treatment protocols
and developing new agents and strategies for those at highest risk.

89 90 91 92 93 94 95 96 97 98 99 100 101 102 103 104 105 106 107 108 109 110 111 112 113 114 115 116 117 118 119 120

occurs in young children, with a median age of 3.5 years at presentation. Male/female distribution
unusual symptoms such as fever or pain, other causes should be entertained, **such as different**

c overgrowth and those without. Syndromes with an increased risk of WT associated with somatic
, midline defects, ear creases, neonatal hypoglycemia) **is associated with chromosome 11p15**

nder-virilization, renal mesangial sclerosis, and WT), WAGR (WT, aniridia, genital anomalies, and

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%

Table 1 lists the various syndromes and the associated WT risk.[3-4-5-6-7-8-9] **Screening for high-risk children is recommended, with abdominal ultrasonography every three months until the age of eight years.** [10-11]

In addition to the above syndromes and associated genetic anomalies, prognostic molecular biomarkers have been identified. **Loss of heterozygosity** (**LOH**) **at chromosomes 16q** (**present in 20% of all WT**) **or 1p** (**seen in 10% of tumors**) **prognosis and have been incorporated into the risk stratification criteria**.[12] The gene *WTX*, located on the X chromosome at Xq11.1, was found to be altered in 15%-20% of WT cases.[13] MYCN copy number gain has been observed in appr anaplastic histology.[14] Gain of 1q, present in almost 30% of unilateral, favorable histology WT has recently been confirmed as a marker of poorer prognosis and will be incorporated into the risk stratification scheme in future protocols.[107]

Histopathology of the tumor remains an important predictor of outcome. **Tumors harboring anaplasia** (**cellular features characterized by large nuclei, abnormal mitotic figures, and hyperchromasia**) **identify patients at higher risk for re "unfavorable histology." Anaplasia is found in ~10% of patients and is the single most important histologic predictor of response and survival in patients with WT**.[15-16-17] Focal anaplasia is differentiated from diffuse anaplasia, which show mutations in the *TP53* tumor suppressor gene, which may be useful as an unfavorable prognostic marker.[18-19] Tumors in older patients (aged 10 to 16 years) have a higher incidence of anaplastic histology.[20]

Nephrogenic rests are abnormally retained embryonic kidney precursor cells arranged in clusters, and they are recognized as potential precursor lesions of WT that may also involute spontaneously. It is estimated that rests are ha WT patients, and in 1% of unselected infants identified on post-mortem exam. It is believed that only 1% of rests will go on to become WT.[21-22-23] **Two types of rests are commonly recognized. Perilobar nephrogenic rests** (**PLNR**) **are found nephrogenesis.** PLNR are associated with BWS and hemihypertrophy and may harbor 1p15 abnormalities. **Intralobar nephrogenic rests** (**ILNR**) are found within the renal lobe, develop earlier in nephrogenesis, and are associated with DDS between the two major types of rests. **Diffuse hyperplastic perilobar nephrogenic rests** (**DPLNR**) **are a unique category of rest in which the majority of the cortical surface of one or both kidneys is replaced by rests, and it is consid** WT and DPLNR can be challenging, and it is critical to examine the juncture between the lesion and the surrounding renal parenchyma.[24]

have emerged as important markers of worse
oximately 13% of WT cases, more commonly in those with

lapse or death. This feature defines patients with
carries a worse prognosis. The majority of anaplastic WT

rbored in 35% of unilateral WT patients, 100% of bilateral
in the periphery of the kidney and develop later in
and WAGR syndromes. **Table 2** describes the differences
ered a preneoplastic condition. Distinguishing between

Table 2. Nephrogenic Rests and Known Associations

	ILNR	PLNR
Associated Syndromes	WAGR Denys-Drash	BWS, Hemihypertrophy Perlman
Median Age of Wilms Tumor Development (months)	23	36
Wilms Tumor Histology	Stromal/Blastemal predominant	Blastemal/Epithelial pre

dominant

4. Diagnosis and Evaluation

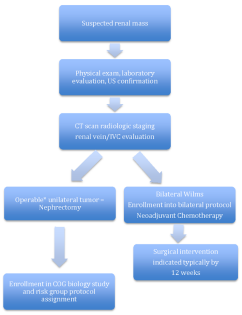

Figure 1. Diagnostic/treatment algorithm

The most common presentation is that of an asymptomatic abdominal mass noted by the parents or other caregivers. Less commonly, children will present with abdominal pain or gross hematuria. Hypertension related to high plasma re

Physical examination should evaluate for syndromic features such as aniridia, hemihypertrophy, and genitourinary abnormalities. A palpable mass in the flank is the norm. Laboratory evaluation should include complete blood count, liver function advisable to obtain a coagulation panel to determine the potential for acquired von Willebrand disease (4%-8% of patients with WT).[121] While ultrasonography is frequently the first-line imaging study, cross-sectional imaging is necessary **to defir evaluate the contralateral kidney and the presence of metastatic disease, with the lungs being the most common site.** Computerized tomography (CT) is used in most centers but magnetic resonance imaging (MRI) is also acceptable. C of IVC extension.[108]

A sequential diagnostic/treatment algorithm is presented in Figure 1.

5. Treatment

5.1 Surgery

For the majority of patients with unilateral lesions, nephrectomy with regional retroperitoneal lymph node sampling is the first therapeutic step according to current COG protocols. In COG protocols, surgical staging and evaluation central to risk stratification and therapy assignment. **Surgeons should be cognizant of the propensity for tumor rupture in WT, as intraoperative tumor spillage results in upstaging and requires treatment with abdominal radiation**. A r (AREN03B2 – biology and banking study open to all newly diagnosed pediatric renal tumors) described a 10% intraoperative spill rate in patients with unilateral WT; spillage was more common in tumors > 12 cm and located on the right side.[109] the SIOP approach, which is based on preoperative chemotherapy for every newly diagnosed case of WT followed by nephrectomy. Surgical staging criteria are found in **Table 3**.

nin levels may be present.[25]

tests, renal function panel, and urinalysis. It is also
ıe location, size, and local extension of the tumor, to
ſ of the abdomen is sufficient to evaluate for the presence

of tumor biology prior to chemotherapy exposure are
ɔcent study using data from the current COG biology study
Conversely, outside of North America most centers follow

Table 3. Staging System for Wilms tumor

Stage	Findings
I	• 43% of patients • The tumor is limited to the kidney and was completely excised. • The renal capsule has an intact outer surface. • 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. • All lymph nodes sampled are negative.
II	• 20% of patients • The tumor extends beyond the kidney, but was completely excised. • There must be no evidence of tumor at or beyond the margins of resection. • There may be regional extension of tumor (penetration of the renal capsule or extensive invasion of the renal sinus or invasion into adrenal gland). • The blood vessels outside the renal parenchyma, including those of the renal sinus, may contain tumor. • Vascular extension of tumor is considered stage II only if it is completely removed en bloc in the nephrectomy specimen. • All lymph nodes sampled are negative.

III	• 21% of patients
	• Residual non-hematogenous tumor is present, and confined to the abdomen. Any one of the following may occur:
	  • Lymph nodes within the abdomen or pelvis are found to be involved by tumor - renal hilar, para-aortic, or beyond. (Lymph node involvement in the thorax or other extra-abdominal sites would be 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 occurs either before or during surgery.
	  • Any biopsy is performed, regardless of type- Tru-cut biopsy, open biopsy, or fine-needle aspiration- before the tumor is removed.
	  • The tumor is resected in more than one piece. For example, if the adrenal gland is involved with tumor but resected separately from the kidney it would be considered stage III.
	  • Extension of the primary tumor in the vena cava into the thoracic vena cava and heart is considered stage III, rather than stage IV, even though outside the abdomen. Of note, lower levels of IVC thrombus extension c
	  nephrectomy specimen.

IV	• 11% of patients • Hematogenous metastases (lung, liver, bone, brain), or lymph node metastases outside the abdominopelvic region are present. • Tumor thrombi which embolize to the pulmonary vasculature are considered stage IV and specifically a site of extra-pulmonary metastatic disease. • Presence of tumor within the adrenal gland is not interpreted as metastasis.
V	• 5% of patients • Bilateral renal involvement is present at diagnosis.

'.)

:an be stage II if completely resected en bloc with the

Patients with unilateral WT, stages I-IV, proceed to nephrectomy through a generous transverse abdominal or thoracoabdominal incision in order to avoid intraoperative tumor rupture and to facilitate intra-abdominal inspection and rena node assessment. Extraperitoneal flank incisions are not recommended. The importance of LN sampling cannot be underestimated for WT and all pediatric renal malignancies yet its omission is a common protocol violation. While formal LN disse sampling of inter-aortocaval LNs in addition to para-aortic LNs for left sided tumors and para-caval LNs for right sided tumors should be done as these are the primary landing zones. There is no minimum LN yield necessary, but data suggest at l of missing occult metastatic disease[122]

In rare cases, patients with large tumors may be deemed "inoperable." (**Table 4**). **Intraoperative tumor rupture or initial biopsy requires abdominal radiotherapy and chemotherapy intensification for treatment. The adrenal gland can be exists (or venous thrombus),** and the ureter should be taken as low as conveniently possible. **Intra-operative assessment of the contralateral kidney is not necessary if appropriate preoperative imaging has been obtained**. Palpation o tumor thrombus. Pathologic and radiologic staging will determine risk group assignment and chemoradiation protocols.

al hilar, periaortic, pericaval and inter-aorto-caval lymph
ection is not mandated, recent data suggest careful
least 6-10 LNs should be removed to minimize the chance

left in place unless an upper pole or abutting tumor
of the renal vein and IVC should be performed to exclude

Table 4. Criteria For Inoperability
Extension of tumor thrombus at or above the level of the hepatic veins
Tumor involves contiguous structures whereby the only means of removing the tumor requires removal of the other structure (spleen, pancreas, colon but excluding the adrenal gland)
Unnecessary morbidity/mortality, diffuse tumor spill or residual tumor
Pulmonary compromise due to extensive pulmonary metastases

Preoperative or intraoperative biopsy is generally contraindicated and should be performed only in unique circumstances. In the rare situation where biopsy is indicated, it should be performed from a posterior or flank approach to avoid biopsy is considered a “tumor spill” and mandates stage III designation and the administration of radiotherapy.

Traditionally, nephrectomy for WT has been performed through an open trans-abdominal approach. However, there have been reports of laparoscopic nephrectomy for WT, which seems to be a viable alternative in selected cases, specifically for

Since patients with bilateral WT, predisposition syndromes and solitary kidneys are at higher risk for long-term renal dysfunction, they are treated with upfront chemotherapy in an attempt to reduce tumor burden and facilitate p generally avoided.

5.2 Chemotherapy and Radiation Therapy

Risk assignment based on surgical/pathologic and biologic criteria determine treatment stratification into the various COG protocols. Multi-agent chemotherapy with or without radiation therapy is standard. Current chemotherapy regimens used fo duration of treatment is variable based on risk stratification, which in turn considers, histology (favorable vs. anaplastic), molecular features (presence of loss of heterozygosity 1p and 16q) and staging.

contamination of the abdomen. In COG protocols, tumor

smaller tumors or after preoperative chemotherapy.[110,111]

artial nephrectomy. Biopsy before treatment is

r the treatment of WT are summarized on **Table 5**. The

Table 5: Treatment regimens used for WT in the last set of COG studies

Regimen Name	Regimen Description
Regimen EE-4A	Vincristine, dactinomycin
Regimen DD-4A	Vincristine, dactinomycin, doxorubicin
Regimen M	Vincristine, dactinomycin, doxorubicin, cyclophosphamide, etoposide
Regimen UH-1	Vincristine, doxorubicin, cyclophosphamide, carboplatin, etoposide
Regimen UH-2	UH-1 + vincristine / irinotecan (VI) window

Table 6 gives an overview of recently completed and ongoing renal tumor studies and outcomes; current protocols are in the design stage. **Surgeons can access current COG protocols through their institutional primary investigator. The S information for urologic representatives familiar with treatment protocols.**

Some key conclusions from the most recently closed COG studies are summarized below:

- AREN 0532 - There is a subset of very low risk WT patients that can be treated with surgery alone; currently, candidates for this approach are children younger than 2 years of age with a favorable histology lesion that weighs less than 550 expand those criteria for future studies.
- AREN 0533 – Patients with favorable histology WT and loss of heterozygosity for both chromosomes 1p and 16q received augmented therapy with improved survival; stages I/II WT were treated with DD4-A and stages III / IV with regimen M IV compared to 74.9% and 65.9% in NWTS5, respectively.[113]
- AREN 0533 – Patients with favorable histology WT and lung metastases have been treated with chemotherapy and lung irradiation. In this study, radiation to the lungs was omitted for stage IV patients who experienced complete lung respo Complete response was observed in 39% of the patients enrolled. 4-year EFS and OS were 78% and 95%, respectively, suggesting that there is a subset of patients with stage IV WT that can be safely spared from chest radiation![114]
- AREN 0534 – Patients with bilateral lesions were treated with 3-drug chemotherapy (VAD) upfront without a biopsy. Re-evaluation was undertaken after 6-12 weeks and surgery offered then, with the goal of attempting a nephron-sparing ap deemed too large, further chemotherapy was given. Surgery was not to be postponed past week 12. This approach was associated with event-free survival (EFS) and overall survival (OS) of 80.97% and 94.16%, respectively, with 39% of p treatment. [115] Also, patients with syndromic predisposition and unilateral lesions were similarly treated with 6-12 weeks of chemotherapy (EE-4A) in attempt to enable nephron sparing surgery. This was successful with 65% of patients bei 4-year EFS and OS rates were 94% (95% CI, 85.2%-100%) and 100%, respectively.[123]
- AREN 0321 – Patients with diffuse anaplastic WT stages II-IV were treated with regimen UH-1; dosages had to be adjusted mid-study due to toxicity. Nonetheless,3-year EFS for all patients was 69%, which was superior to 55% seen in NW Furthermore, patients with stage IV disease were exposed to a window of vincristine / irinotecan (VI) and if response was observed, VI was added to the UH-1 regimen (UH-2). Patients exposed to the VI window had a 57% EFS compared t

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grams.[112] The new generation of COG protocols will

M. EFS was 83.9% for stages I/II and 91.5% for stages III /

nse with DD4-A based on CT reassessment at 6 weeks.

proach whenever possible. If the tumor burden was still
atients retaining portions of both kidneys after
ng able to undergo nephron sparing surgery and the

/TS5. Outcomes by stage are detailed on the table.
o 33% for those who did not receive it. [124·125]

Table 6: Completed Wilms tumor treatment trials and associated survival

Stage	Histology / LOH Status	Treatment
I	FH, <24 mos, tumor wt <550 g Very low risk WT	Surgery only
I	FH, >24 mos, tumor wt >550 g No LOH 1p / 16q	Nephrectomy + lymph node sampling followed by regimen EE-4A
I	FA or DA	Nephrectomy + lymph node sampling followed by abdominal XRT (10.8 Gy) and regimen DD4-A
II	FH No LOH 1p / 16q	Nephrectomy + lymph node sampling followed by regimen EE-4A
II	FA	Nephrectomy + lymph node sampling followed by abdominal XRT (10.8 Gy) and regimen DD4-A
II	DA	Nephrectomy + lymph node sampling followed by abdominal XRT (10.8 Gy) and regimen UH-1
I or II	FH LOH 1p and 16q	Nephrectomy + lymph node sampling followed by regimen DD4-A
III	FH No LOH 1p and 16q	Nephrectomy + lymph node sampling followed by abdominal XRT (10.8 Gy) and regimen DD-4A
III	FA	Nephrectomy + lymph node sampling followed by abdominal XRT (10.8 Gy) and DD4-A
III	DA	Nephrectomy + lymph node sampling followed by abdominal XRT (20 Gy) and regimen UH-1
IV	FH No LOH 1p and 16q Complete response of lung metastases to chemo after 6 weeks	Nephrectomy + lymph node sampling, followed by abdominal XRT if surgical stage III, no lung radiation, and regimen DD-4A
IV	FH No LOH 1p and 16q Incomplete response of lung metastases to chemo after 6 weeks	Nephrectomy + lymph node sampling, followed by abdominal XRT if surgical stage III, lung XRT (12Gy), and regimen DD-4A initially. Once incomplete response of lung metastases diagnos
III or IV	FH LOH 1p and 16q	Nephrectomy + lymph node sampling, followed by abdominal XRT (10.8 Gy), lung XRT (12 Gy), and regimen M
IV	FA	Nephrectomy + lymph node sampling followed by abdominal XRT (10.8 Gy), lung XRT (12 Gy) and regimen UH-1
IV	DA	Nephrectomy + lymph node sampling followed by abdominal XRT (10.8 Gy), lung XRT (12 Gy) and regimen UH-1 / UH-2 for some
V	Bilateral WT	Preoperative chemotherapy with vincristine, dactinomycin, and doxorubicin. Treatment response is assessed after 4-8 weeks of chemotherapy with repeat imaging. At this point, patients wit nephrectomy should undergo surgery, while patients with poor treatment response (less than 50% reduction in tumor size) should undergo bilateral open biopsies. Additional chemotherapy attempt at resection or biopsy of apparently unresectable tumor is undertaken no later than 12 weeks from diagnosis.

FH=Favorable histology, FA=Focal anaplasia, DA=Diffuse anaplasia, OS=Overall survival, EFS=Event-free survival, RFS=Relapse-free survival

	4 yr Survival
	100% OS, 89.7% RFS
	98% OS, 94% RFS
	100% OS, 100% EFS
	98% OS, 86% RFS
	100% OS, 100% EFS
	84% EFS, 84% OS
	83.9% RFS
	94% OS, 87% RFS
	Data not available
	82% EFS, 91% OS
	78% RFS, 96% OS
ed, switched to regimen M	88.5% EFS, 95.4% OS
	91.5% RFS, 96.1% OS
	42% EFS, 49% OS
h tumors amenable to partial may be administered. Planned	81% EFS, 94% OS

6. Role of Partial Nephrectomy

COG protocol AREN0534 allowed for nephron sparing surgery (NSS) after neoadjuvant chemotherapy in children with bilateral disease, WT in a solitary kidney, or patients with unilateral WT and tumor predisposing syndromes.[29] The study is clos
analysis of 4,021 patients enrolled in the COG biology study (but not on AREN0534) revealed that 39 (1%) received a partial nephrectomy for unilateral WT. In those treated with partial nephrectomy, there was greater than expected intraoperativ

Despite allowing nephron sparing surgery at the discretion of the surgeon after preoperative chemotherapy, the SIOP WT-2001 study registered only 91/2800 (3%) patients receiving such modality; while outcomes were comparable to total nephr
consideration of risks and benefits given the possible increased risk of positive margins and upstaging.[118] While not currently entertained by COG treatment protocols, recent consideration has been given to expanding the role of NSS to include
WT. Much of the enthusiasm for expanding the role of NSS in children stems from adult literature that demonstrates improved long-term renal function and equivalent oncologic outcomes in patients treated with NSS for renal cell carcinoma. Long
recommendations can be extrapolated to the pediatric population. The relative rarity of WT, especially those amenable to upfront partial nephrectomy, presents a challenge to conducting controlled trials[89].

7. Late Effects

Late effects of therapy have emerged as a major long-term concern for survivors of childhood cancers, with up to 60% being affected. **Late effects seen in WT survivors include musculoskeletal effects related to radiation, cardiotoxicity a
reproductive health problems, renal dysfunction, and secondary malignancies**.

Non-WT Renal Tumors

1. Renal Cell Carcinoma

Renal cell carcinoma (RCC) is the second most common renal tumor in children and is usually discovered postoperatively on pathology. There are several clues preoperatively however that may suggest this diagnosis, such as age >12y, prior ch
syndromes (See **Table 7**).[126]

Table 7. Genetic syndromes associated with RCC

Genetic Predisposition Syndrome	Gene	Presentation
Von Hippel Lindau	*VHL* (3p)	Clear cell RCC Retinal and CNS hemangioblastomas Pheochromocytomas Pancreatic cysts/tumors Epididymal cystadenomas
Tuberous Sclerosis	*TSC1 or TSC2*	AMLs Clear cell RCC Seizures Mental retardation Facial angiofibromas Hamartomas
Hereditary Papillary RCC	*MET*	Low grade type 1 papillary RCC
Birt-Hogg-Dubé	*FLCN*	Chromophobe RCC Fibrofolliculomas Lung cysts and blebs
Hereditary Leiomyomatosis and RCC	*FH*	High grade type 2 papillary RCC Uterine fibroids at young age
Succinate Dehydrogenase RCC	*SDH*	Different RCCs Paragangliomas pheochromocytomas
Sickle hemoglobinopathy	*Hemoglobin-Beta (11p)*	Medullary RCC

Generally, work up and initial treatment is the same as for WT, with US, cross sectional imaging, followed by radical nephrectomy with LN sampling. Staging, however, is per adult RCC staging. While generally approached similar to adult RCC, th children, with RCC generally being more aggressive in pediatric patients.

In adults, clear cell RCC is the most common RCC subtype, but in children, the most common histology is translocation RCC (50%). These tumors have activating mutations of *TFE3* on Xp11.2 causing continuous tyrosine kinase activity and dow proliferation. Despite these tumors often being smaller than their WT counterparts, they are aggressive and associated with locally advanced or metastatic disease in 63% of children[126]

While NSS and minimally invasive approaches for adult RCC are considered standard of care, their role in pediatric RCC is less clear. This is likely because the pathology is not known preoperatively and COG WT surgical protocols emphasize o suspected renal malignancy. Unlike WT, but like adult RCC, surgery is the mainstay of treatment. Surgical treatment revolves around radical nephrectomy vs. NSS, with careful consideration for laparoscopy. LN sampling is also imperative for tra imaging has low sensitivity (57%) for identifying the high rate (48%) of LN involvement for cT1 tumors. More recent COG data from AREN0321 suggest that complete surgical resection of disease, including all metastatic sites, and therefore presu advantage, highlighting the importance of careful surgical planning and adherence to current protocols![126]

5y overall survival is generally excellent for those with pT1-3 disease, but drops to 55% for patients with LN metastases and just 8% for those with distant disease.[127] Directly correlated to the high prevalence of tRCC in this population, overall su compared to adults. Data using traditional adjuvant therapy for adults are limited in children, further emphasizing the important of surgical resection of all disease sites. AREN 1721, a newer COG study, is currently examining the benefit of immun another treatment option for patients with more widespread disease.

2. Other rare renal tumors

While WT and RCC comprise the vast majority of all renal tumors seen in the pediatric population, there are several other rare tumors that are important (**Table 8**).

Table 8

Clear Cell Sarcoma of the Kidney (CCSK)	Age of onset: 1-4yo M:F= 2:1 Associated with skeletal and brain metastasis Genetics: No known familial predisposition syndromes or cases of bilateral CCSK. Eval and Treatment: Radical nephrectomy with regional lymph node sampling. Adjuvant therapy includes radiation and chemotherapy (vincristine, doxorubicin, cyclopl Survival: 80-90% 5yr survival
Rhabdoid Tumor of the Kidney (RTK)	Age of onset: 80% <2yo Genetics: Germline mutations in INI-1 on chromosome 22. Associated with CNS metastasis Eval and Treatment: MRI of brain should be included in evaluation. Radical nephrectomy with lymphadenectomy is the primary treatment modality as RTK is chemo- a Survival: 20% 5-year overall survival; CNS involvement is nearly universally fatal.
Congenital Mesoblastic Nephroma (CMN)	Age of onset: Most common renal tumor in infants <6 months of age; Often seen on prenatal ultrasound and is associated with polyhydramnios and preterm birth Eval and Treatment: Although originally described as a benign tumor, CT scan of the chest, abdomen and pelvis should be performed. Radical nephrectomy with LN s Survival: Excellent prognosis, especially with surgery within the first 6 months of life. Metastasis and recurrence can occur, therefore serial abdominal ultrasonography
Renal medullary carcinoma (RMC)	Genetics: sickle cell trait or disease; strong African-American predominance Eval and Treatment: Complete cross-sectional staging imaging is necessary. >90% will have advanced/metastatic disease on presentation. Radical nephrectomy is th chemoradiation. Survival: Very poor prognosis; average overall survival between 4-16 months.
Angiomyolipoma (AML)	AML composed of three histologic components: blood vessels, muscle and adipose. Often present with spontaneous retroperitoneal hemorrhage. Genetics: Associated with Tuberous Sclerosis Complex (TSC) Eval and Treatment: Annual monitoring with ultrasonography or MRI for size and stability. Nephron-sparing interventions should be prioritized if necessary, especially i recurrent tumors. mTOR inhibitor therapy (Everolimus) has been shown to reduce the size and slow progression of TSC related AMLs. TSC patients are also at an inc considered in fat-poor lesions
Cystic Tumor Variants: Multilocular Cystic Nephroma (MCN), Cystic Partially differentiated Nephroblastoma (CPDN), Cystic WT	MCN and CPDN Age of onset: commonly in patients <2 years of age Genetics: MCN associated with DICER-1 mutation MCN have benign septae; CPDN have poorly differentiated tissue/blastemal cells in septae Eval and Treatment: Radical nephrectomy is considered curative in stage I tumors. If nephron-sparring approaches are undertaken, frozen section analysis to confirm vincristine and actinomycin chemotherapy Cystic WT Age of onset: more common 3-5yo Exhibit more solid strictures between the cysts with stromal, mesenchymal or epithelial components. Eval and Treatment: Radical nephrectomy with lymph node sampling. Adjuvant therapy based on stage-dependent WT guidelines

Primary Testis Tumor in Pediatrics

1. Definition

Primary pediatric testicular tumors refer to either a **non-germ cell tumor (i.e. stromal tumor such as leydig cell tumor or sertoli cell tumor) or germ cell tumor** that arises from the celomic epithelium or primordial germ cells. Germ cell tumor patients of all ages. However, in contrast to adults, **benign tumors represent the majority of primary testicular tumors in children**.

Pubertal status is very important in patients with testis tumors. Pre-pubertal patients typically have a benign diagnosis and consideration should be given to partial orchiectomy with intraoperative frozen section. Any malignancies in the age group post-pubertal patients are likely to have a malignant diagnosis and radical orchiectomy is generally the treatment of choice. While COG protocols do exist for post-pubertal patients, recent data suggest that outcomes are inferior for post-pubertal r COG studies have incorporated adult regimens to address this issue.

2. Risk Factors and Pathophysiology

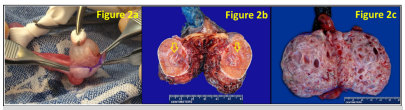

Figure 2 Representative gross specimen images of a variety of pediatric testicular tumors. 1a) Gross photograph of a teratoma in an infant during a partial orchiectomy. 1b) Gross photograph of a pure embryonal carcinoma (non-seminoma) in a peri-pubertal male (yellow arrows indicate the tumor). 1c) Gross photograph of a mixed non-seminoma germ cell tumor in a pubertal male.

There are four well-established risk factors for testicular germ cell tumors in adults: cryptorchidism, family history of testicular cancer, personal history of prior testicular cancer, and germ cell neoplasia in situ (GCNIS, formerly intratubular germ ce relative risk of cancer increases with age at time of orchidopexy, with the greatest risk for those undergoing orchidopexy after puberty.[80]

In children, **patients with disorders of sex development (DSD) have an increased incidence of gonadal tumors. Patients with hypovirilization and gonadal dysgenesis are at the highest risk. The risk of tumor formation in gonadal present, with the incidence of tumor development approximately 10% by age 20 years**[81] **GCNIS has been noted in 6% of children with DSD, with a higher incidence after puberty**.[82] No cases of carcinoma in situ were found before pub insensitivity.[83]

In children, germ cell tumors are the most common pediatric testicular tumors. Mature teratoma, which is classically benign, is the **most common benign tumor in pre-pubertal children**.[84] A teratoma is typically well encapsulated with multiple teratoma is composed of elements of more than one germ cell layer: endoderm, ectoderm, and mesoderm, and microscopically the appearance can vary because of the relative contribution of the different germ cell layers and the extent of their m are only composed of one germ cell layer. They occur within the testicular parenchyma and are filled with keratinous debris. Immature teratomas have a gross appearance similar to that of mature teratomas, but they contain various immature tiss

Yolk sac tumor (YST) is the **most common malignant testicular tumor in pre-pubertal boys**.[84] Grossly, the tumor is firm and yellow-white on cross section, and hemorrhage is unusual. The microscopic appearance shows a mixture of epitheli pattern. Eosinophilic cytoplasmic inclusions are common, and specialized staining techniques demonstrate the presence of α-fetoprotein (AFP). **The characteristic histologic finding in yolk sac tumors is Schiller-Duval bodies**.[85] YST is clas non-seminoma germ cell tumors include embryonal carcinoma, choriocarcinoma and teratoma in a post-pubertal patient. Often these are clinically found as a heterogenous mix of tumor histologies and are termed a mixed non-seminoma. In contr histology alone, such pure testicular seminomas are very rare in the pre-pubertal population.

Non-germ cell tumors, such as Leydig, Sertoli, and Granulosa cell tumors, have a common embryologic origin from a mesenchymal stem cell. Pathologic diagnosis can be difficult due to incomplete differentiation.[86] Leydig cell tumors are well-enc production by the tumor, which can compress the adjacent testicular tissue. Microscopically, they are similar to adrenal rests. The pathognomonic histologic feature of Leydig cell tumor, **Reinke crystals**, is present in only about 40% of tumors. F Leydig cell tumors.[105]

Sertoli cell tumors are solid, usually without hemorrhage or necrosis, and are white to yellow and lobulated in appearance. Microscopically there are large polygonal cells with eosinophilic cytoplasm. Large cell Sertoli cell tumors can be confused by cells with abundant eosinophilic cytoplasm.[86]

Gonadoblastomas are potentially pre-malignant tumors found in patients with gonadal dysgenesis. They are similar to GCNIS but found in an ovarian type tissue background. They are bilateral in up to one third of cases. The tumors are compose derivatives resembling immature granulosa and Sertoli cells, and occasionally stromal elements. When these become invasive germ cell tumors, they are termed dysgerminomas.

GCNIS is commonly found in adult patients and is a risk for factor for the development of a germ cell tumor. **The incidence of GCNIS is 1.7% in adults who have previously undergone orchidopexy**.[87] GCNIS has been detected in adolescent pre-pubertal children with YST of the testis. [88] GCNIS is also frequently detected in patients with androgen-insensitivity disorders and dysgenetic gonads.[88] Although, there is an association between cryptorchidism and the development of GCNIS pre-pubertal cryptorchid testes.

3. Epidemiology

Pediatric testicular tumors represent 1-2% of all pediatric solid tumors. The overall incidence is uncommon (1:100,000 <15 years of age), with most occurring between 2-4 years of age.[89] There is a second increase in incidence at puberty. As con children and represent 38-74% of all the pediatric testicular tumors.[90-91-92] Primary pediatric testicular tumors are more common in Caucasians.[84] Overall, **teratoma is the most common pre-pubertal benign testicular tumor, and YST is the m**

4. Diagnosis and Staging

Patients typically present with a painless testicular mass. Occasionally a testicular tumor can be identified in the setting of other scrotal pathology (epididymitis, testicular torsion, hydrocele, undescended testicle, or hernia). All patients should be exam. If a testicular tumor is suspected, a scrotal US and laboratory analysis (LDH, AFP, β-hCG and hormone measurement, if a hormonally active tumor is suspected) are obtained.

4.1 Imaging

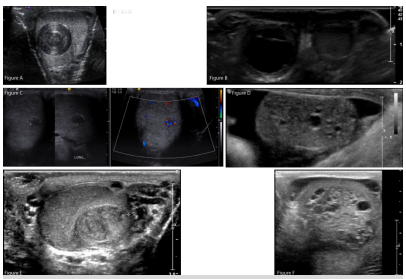

Figure 3 Representative sonographic images of a variety of pediatric testicular tumors. 3a) Sonographic image of epidermoid cyst in a pre-pubertal boy. 3b) Sonographic image of a teratoma in an infant. 3c) Sonographic image of a testicular leydig cell tumor in a peri-pubertal male. 3d) Sonographic image of a testicular granulosa cell tumor in an infant. 3e) Sonographic image of a pure embryonal carcinoma (non-seminoma) in a peri-pubertal male. 3f) Sonographic image of a mixed non-seminoma germ cell tumor in a pubertal male.

Imaging of testicular masses should be performed with color Doppler ultrasound (US)[93] (**Figure 3**). **US cannot reliably distinguish benign and malignant tumors, but the finding of anechoic cystic lesions can suggest a benign lesion, su** Epidermoid cysts have the unique US appearance of a heterogeneous intra-testicular mass with concentric rings of alternating hypo and hyperechoic layers ("onion-skin appearance"), which corresponds to the multiple layers of keratin debris. Lik flow in the surrounding tissue[94] For those children with testicular masses concerning for malignant disease, CT of the retroperitoneum and chest are required to exclude metastatic disease. The timing of the CT (prior to or after resection of the pri

4.2 Serum Markers

AFP is a single-polypeptide chain amino acid produced by the fetal yolk sac, liver and gastrointestinal tract. **YSTs invariably produce AFP, and all AFP-positive tumors are considered to contain yolk sac elements**.[95] **Teratomas and other** synthesis continues after birth, and elevated levels of AFP are normal until approximately 8 months of age (<10 mg/mL)[96] The half-life of AFP is 5 days and can be used as a tumor marker in children with YST tumors.

Human chorionic gonadotropin-β (β-hCG) is a glycoprotein produced by embryonal carcinoma and mixed teratomas and has a half-life of 24 hours. **β-hCG is rarely elevated in pre-pubertal testicular tumors.**

The combination of benign appearing lesion on Color Doppler US and negative AFP and β-hCG levels warrant consideration of a testis sparing procedure.[97] After primary removal, pediatric testicular tumors are staged according to pathologic finc tumor markers (**Table 9**). For those with "marker-positive" tumors, AFP and β-hCG levels are monitored after radical inguinal orchiectomy to determine if there is an appropriate half-life decline.

Table 9: Children's Oncology Group (COG) Staging for Pediatric Primary Testicular Tumors

Stage	EXTENT OF DISEASE
I	Tumor is limited to the testis, completely resected by high inguinal orchiectomy. No clinical, radiographic, or histologic evidence of disease beyond the testes. If scrotal orchiectomy has been performed, all margins are negative a of the internal inguinal ring. Tumor markers are negative after appropriate half-life decline. If radiographic studies demonstrate retroperitoneal lymph nodes greater than 2 cm and patients have normal or unknown tumor markers retroperitoneal node sampling to be considered to have stage I disease
II	Microscopic residual disease is present in the scrotum or high in spermatic cord. Tumor markers remain elevated after appropriate half-life interval. Tumor rupture or scrotal biopsy prior to complete orchiectomy.
III	Retroperitoneal lymph node involvement. Lymph nodes greater than 4 cm by CT are considered metastases. Lymph nodes greater than 2 cm and less than 4 cm need biopsy to document nodal metastases.
IV	Distant metastatic deposits.

5. Tumor Specific Treatment

5.1 Germ Cell Tumors

5.1.1 Teratoma

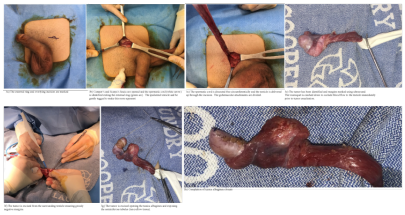

Figure 4: Partial orchiectomy step by step. 4a) The external ring and overlying incision are marked. 4b) Camper's and Scarpa's fascia are opened and the spermatic cord is identified exiting the external ring. The ipsilateral testicle and be gently tugged to make this more apparent. 4c) The spermatic cord is dissected free circumferentially and the testicle is delivered up through the incision. The gubernacular attachments are divided. 4d) A ¼ inch Penrose is used to create a tourniquet but not cinched down until tumor excision is about to begin. 4e) The tumor has been identified and margins marked using ultrasound. The tourniquet is cinched down to occlude blood flow to the testicle immediately prior to tumor enucleation. 4f) The tumor is excised from the surrounding testicle ensuring grossly negative margins. 4g) The tumor is excised opening the tunica albuginea and exposing the seminiferous tubules (tan-yellow tissue). 4h) Completion of tunica albuginea closure.

Teratoma is the most common tumor (40% of all pre-pubertal tumors) and is typically **benign in pre-pubertal patients**. Ultrasound demonstrates anechoic or complex cystic lesions surrounded by highly echogenic signals. Blood work is negative a partial orchiectomy if serum tumor markers are normal and benign pathology is confirmed by frozen section. In the pre-pubertal setting, excision alone is sufficient and no further oncologic evaluation or follow up in needed.[106] In post-pubertal pa treated accordingly. **Figure 4** outlines the steps of a testis-sparing surgery for a testicular tumor.

5.1.2 Yolk Sac Tumor and Other Non-Seminoma Germ Cell Tumors

Yolk Sac Tumor (YST) is the second most common pediatric germ cell tumor, but the most common malignant tumor of infants and young boys (<2 years of age). **AFP is usually elevated**. Treatment is radical orchiectomy, which is typically cura complete staging. 90% of pre-pubertal YST are Stage I. If AFP is elevated, appropriate decrease to normal levels should be expected after orchiectomy if there is no metastatic disease. RPLND and or chemotherapy is not indicated in the pre-pub undergone a scrotal biopsy prior to resection are Stage II. However, delayed scrotal resection is generally not required as stage II patients are treated with systemic chemotherapy (3 cycles of cisplatin, etoposide and bleomycin).

After orchiectomy for a Stage I tumor, standard follow up consists of a chest X-ray, and contrast-enhanced CT or MRI of the retroperitoneum at increasing intervals (every month x 3, every 3 months x 1 year, then every 6 months until 36 months). frequently. Relapses while on surveillance for Stage I disease should undergo biopsy to confirm diagnosis.

Additional therapy is considered for those with higher stage disease. For those with evidence of lymphadenopathy but normal tumor markers, lymph node sampling or biopsy should be considered to determine if this represents metastatic disease markers are considered Stage III and should receive systemic chemotherapy (cisplatin, etoposide and bleomycin). Similarly, patients with Stage IV disease and should receive systemic chemotherapy (cisplatin, etoposide and bleomycin). For pre- chemotherapy, biopsy or local excision (not formal RPLND) is indicated to confirm histologic diagnosis and guide adjuvant chemotherapy selection.

5.1.3 Immature Teratoma

This is less common and often benign in children unless associated with malignant cells. Treatment is resection with observation.

5.1.4 Epidermoid cysts

These are intra-testicular cysts filled with keratinous debris. US can have a classic onion skin appearance. A testis sparing procedure is indicated.

5.1.5 Seminoma

This is uncommon in childhood except in the presence of a disorder of sexual differentiation (DSD). Treatment of seminoma should follow guidelines for adults with testicular seminoma.

5.2 Gonadal Stromal Tumors

These are the most common non-germ cell tumor of the testis and are typically benign but may be hormone secreting.

5.2.1 Leydig Cell Tumor

This is the most common gonadal stromal tumor and is typically **benign** in pre-pubertal boys (peak incidence 4-5 years). It can produce testosterone and children may present with precocious puberty that may not resolve after primary therapy.[99] nature in pre-pubertal children, partial orchiectomy has been reported if confirmed by frozen.[100]

5.2.2 Sertoli Cell Tumor

This is the second most common gonadal stromal tumor in children. Therapy is a radical inguinal orchiectomy. Metastatic disease is uncommon. Partial orchiectomy can be considered in pre-pubertal children if confirmed by frozen.[101]

5.2.3 Gonadoblastoma

This is similar to GCNIS but in a ovarian background rather than a testis. These are most commonly associated with DSD in the presence of a Y chromosome. Mixed gonadal dysgenesis has a 25% risk of this tumor that increases with age. The g into seminoma/dysgerminoma and non-seminoma/non-dysgerminoma. The issue of gonadal removal in the setting of DSD and an undescended gonad is controversial and the treatment decision should be personalized after an informed discussi patient/family's tolerance for risk.

5.3 Other Tumors

5.3.1 Leukemia and Lymphoma

These are the most common childhood malignancy to spread to testes. There is a 20% incidence of testicular relapse in children with bulky **acute lymphoblastic leukemia** (ALL). Routine biopsy is no longer recommended. However, in those wh should be considered to document recurrence.

5.3.2 Testicular Microlithiasis

This is present in up to 5% of healthy men. Routine screening, other than routine testicular self-exam, is not needed in asymptomatic children with no significant history that increases their risk for testicular cancer.[103·104]

Genitourinary Rhabdomyosarcoma

1. Definition

Rhabdomyosarcoma (RMS) is an aggressive soft tissue sarcoma **derived from embryonic mesenchymal tissue, specifically striated muscle**. These tumors can arise from multiple locations, including the head and neck, extremities, and the

Although three histological subtypes are recognized by the Intergroup RMS Study Group (IRSG)/Children's Oncology Group (COG), only two classically occur within genitourinary organs: Embryonal RMS (ERMS) and Alveolar RMS (ARMS). Mor stratification based on risk categories as explained below.

2. Risk Factors and Pathophysiology

Table 10. Factors that increase or diminish the risk of development of Rhabdomyosarcoma

Risk Factors	Protective Factors
Maternal age >35 yrs[34]	Asthma[36]
Birth weight >4000 g[34]	Eczema[36]
Large for gestational age (>90th percentile)[34]	Allergic reactions in childhood[36]
Maternal drug use[79]	
Radiation exposure in utero[35]	
Li Fraumeni syndrome[37]	
Neurofibromatosis Type 1[38]	
Basal cell nevus syndrome[41]	
Costello syndrome[41]	
Noonan syndrome[40]	
Multiple endocrine neoplasia Type 2A[42]	
Beckwith-Wiedemann syndrome[41]	

RMS can arise in any location derived from embryonic mesenchyme. The majority of RMS affects the extremities and trunk; **20% arise in the genitourinary system.**[31] **The most common sites are prostate, bladder, pelvic, and paratesticula** infiltration with spread to regional lymph nodes is common, and distant metastases are present in approximately 16% (lung 6%, bone 5%, bone marrow 6%) of newly-diagnosed cases.[32]

Approximately 80% of ARMS exhibit a chromosomal translocation between either *PAX3* (chromosome 2) or *PAX7* (chromosome 1) and *FOXO1* (chromosome 13) resulting in a fusion gene that has become a useful prognostic factor. **Expressior conveys worse event-free and overall survival.** The remaining 20% of ARMS that are fusion-negative behave similarly to ERMS.[33] The current intermediate risk RMS protocol utilizes fusion status rather than histology to group patients, becau outcome. **In other words, fusion status appears to be more clinically relevant than histology.**

The **majority of RMS cases are sporadic**, but an increasingly recognized percentage are associated with known genetic disorders such as Li-Fraumeni Syndrome, DICER 1 mutations[129,130], and Neurofibromatosis Type 1.[37,38,39,40,41,42] These malformations.[43,44]

3. Epidemiology

The incidence of RMS in the U.S. is **4.5 cases per million** children and adolescents per year. In North America, approximately 350 children develop RMS annually. There is a **slight male predominance**, with a rate ratio of 1.37 (incidence 5.2 v occur in the first decade of life, and **a bimodal age distribution exists, with a peak incidence during the first two years of life and then again during adolescence.**[31,45,46] ERMS occurs more frequently and is more common in younger child children and adolescents. Approximately 70% of ERMS occur in children younger than ten years of age, compared to ARMS which has a more equal age distribution (50%).[45]

4. Diagnosis and Evaluation

Traditionally, the metastatic work-up for all patients included (*i*) imaging of the primary mass and retroperitoneum via magnetic resonance imaging (MRI) or computerized tomography (CT), (*ii*) chest CT to assess lung metastasis, (*iii*) bone scan, a 1,687 RMS patients helped to clarify specific risk factors for metastasis in an effort to avoid potentially unnecessary and expensive testing. Patients with **stage T1 and embryonal (or fusion-negative) histology were unlikely to have either bor lymph node disease, and fusion-positive alveolar histology were highly predictive of distant metastases**. In low-risk patients (T1, N0, embryonal histology), bone scan and bone marrow biopsy may be safely omitted. Lung involvement wa group (<1%), and chest radiograph can safely substitute for chest CT.[32] Some data suggest a role for functional imaging, such as with [F-18]-fluorodeoxy-D-glucose (FDG) positron emission tomography (PET), in staging of RMS; however, this has

5. Prognostic Factors

Several robust prognostic factors have been identified, including: patient age, tumor histology, anatomic site of origin, tumor burden (size and/or volume) and stage, the extent of initial surgical resection, and fusion gene status. Other pathologic fa affect survival in some subsets of patients.[49] These prognostic factors have led to a **risk stratification system that drives individually tailored therapy** to minimize overtreatment resulting in treatment-related morbidity and mortality. (**Tables 11-**

Vaginal and paratesticular primaries are more favorable sites than those arising from the bladder or prostate. In current algorithms, the negative influence on survival incurred by *PAX-FOXO1* fusion suggest that it may be the driving force histology; as a result, for prognostic reasons fusion status is considered rather than histology.[33,50,51]

Patient age is another independent risk factor, although it should be noted that ERMS primarily afflicts younger patients. In multiple studies, patients who were <1 or ≥ 10 years of age fared worse than 1-9 year old patients.[52]

Table 11. Pretreatment Staging System*

Stage	Site	T (invasion)	Size	Nodes
1	Genitourinary, except bladder or prostate	T1 or T2	Any Size	N0, N1, Nx
2	Bladder/Prostate	T1 or T2	< 5cm	N0 or Nx
3	Bladder/Prostate	T1 or T2	< 5cm	N1
3	Bladder/Prostate	T1 or T2	≥5cm	N0, N1, Nx
4	Any	T1 or T2	Any Size	N0, N1, Nx

T1: confined to anatomic site of origin, **T2:** extension and/or fixation to surrounding tissue; T2a: ≤ 5 cm; T2b: ≥ 5 cm in maximum diameter

N0: absence of nodal spread; **N1:** presence of regional nodal spread beyond primary site; **Nx**: unknown N status

M0: absence of metastatic spread; **M1:** presence of metastatic spread beyond primary site and regional lymph nodes

* see reference 66

Table 12. IRS/COG Clinical Group Classification*

Group	Definition
I	Localized disease, *completely* resected
II	Total *gross* resection; evidence of regional spread
IIA	*Grossly* resected tumor, evidence of microscopic residual disease
IIB	Involved regional nodes *completely* resected, NO microscopic residual disease
IIC	Involved regional nodes *grossly* resected, evidence of microscopic regional disease
III	Biopsy only, or incomplete resection with *gross* residual disease
IV	Distant metastatic disease (excludes regional nodes and adjacent organ infiltration)

* see reference 66

Table 13. COG Risk Stratification (Adapted from Malempati 2011, data from IRS-III and IRS-IV)*

Risk	Histology	Stage	Group
Low, subset 1	EMB	1 or 2 1	I or II III (orbit)
Low, subset 2	EMB	1 3	III (non-orbit) I or II
Intermediate	EMB	2 or 3	III
Intermediate	ALV	1, 2, or 3	I, II, or III
High	EMB or ALV	4	IV

EMB: embryonal histological type

ALV: alveolar histological type

* see reference 66

6. Treatment

The treatment of RMS has evolved over the years from primarily surgical to **multi-modal therapy** incorporating chemotherapy and radiotherapy. Overall survival has improved dramatically for non-metastatic disease since the adoption of multi-a risk-stratified therapy, leading to a shift in focus toward organ preservation and minimization of treatment-associated morbidity.[53,54,55]

6.1 General Principles of Surgery

Complete resection of pelvic RMS (excluding paratesticular RMS) should only be attempted if organ preservation is possible; otherwise, the initial surgical approach should be limited to a biopsy for diagnostic purposes. Local fa

Pretreatment Re-excision (PRE) is defined as a wide local excision that is performed BEFORE initiation of chemotherapy. PRE has been shown to improve survival in children with GU RMS and should be performed when there is tumor that is positive margins, or uncertainty of margins.

Delayed Primary Excision (DPE) is defined as a wide local excision that is performed AFTER initiation of chemotherapy. DPE has not been shown to improve survival in children with GU RMS, although it has been shown to improve survival in if an R0 resection (i.e., negative resection margin) is reasonably expected and if it is possible without organ compromise. DPE may allow for radiation dose reduction.

6.1.1 Gynecological RMS

Initial biopsy can be obtained in the lithotomy position, and if necessary, complete excision can be accomplished via a perineal approach. Pelvic lymph node dissection is typically not recommended, as regional lymph node spread is uncommon fi should be avoided if at all possible[131] **IRS/COG protocols have relied mainly on primary chemotherapy with surgical excision and/or radiation for local control**. In the combined cohort of IRS I through IV, five-year overall survival was 82% MMT84 and MMT89) demonstrated that primary chemotherapy could achieve cure without local control via surgery or radiotherapy in only 44%[57] Today the current trend is to biopsy and rely on chemo/radiation, either by external beam or brachy demonstrated good results using brachytherapy (see below). For uterine tumors the same general principles stated above apply. In those rare patients that require hysterectomy the distal vagina and ovaries are usually preserved. In cervical lesic cases ovarian preservation is recommended unless the ovaries are grossly involved.

6.1.2 Bladder/Prostate RMS

Initial biopsy can be performed cystoscopically. If adequate tissue for diagnosis cannot be obtained with an endoscopic approach, COG protocols allow for open biopsy with pelvic and para-aortic lymph node sampling.[31] A perineal biopsy approa staging of regional nodes should be performed. (**Table 13 for RMS lymph node basins**). A residual mass after completion of definitive chemotherapy and radiation for local control does not typically represent viable tumor, since tumor cells may surrounding stroma. Tumor cells may also differentiate into mature rhabdomyoblasts that may be observed and do not require radical resection.[18-30] Resection of residual, post-treatment masses has not been shown to improve survival.[132] Indica rare, and the rationale should be carefully documented and ideally vetted by COG Sarcoma Committee members.

In high-risk patients with viable tumor and no evidence of distant metastasis after chemotherapy and radiation, pelvic exenteration can be considered.[31] Partial cystectomy can be performed in patients with locoregional disease after completing ch treatment failure if a sufficient margin can safely be obtained without unduly compromising bladder capacity and function.[31-47] The rates of radical cystoprostatectomy and pelvic exenteration as primary therapy are in decline. In the 1970s, all pati exenteration/cystoprostatectomy versus only 13% in IRS IV.[59] Despite this trend toward bladder preservation, **overall survival (78-83%) has remained relatively constant over the same time period.**[58-60-61-62-63-64-65]

Despite the improvement in bladder preservation rates, only 40% of patients who retained their bladder in IRS IV had normal bladder function.[65-66] Few studies have used objective measures such as validated questionnaires and urodynamic stud and the true incidence of bladder dysfunction in these patients is unknown. Two small series incorporating urodynamic testing suggest that at least 50% of these patients experience significantly decreased capacity as measured by urodynamics.

Anticholinergic therapy may be useful for patients with urinary frequency, urgency, and incontinence. In patients with intractable symptoms, bladder augmentation with or without bladder neck reconstruction and catheterizable channel should be c as treatment for RMS may affect sphincteric function[69]

6.1.3 Paratesticular RMS

Suspected paratesticular RMS should be initially treated with radical orchiectomy via inguinal approach, as a scrotal approach can result in tumor seeding.[133,134] If a scrotal approach is used, then the remainder of the cord should be exc (PRE) prior to chemotherapy administration. Hemiscrotectomy or scrotal radiation have not been shown to improve outcomes in this situation, however.[134]

Nerve-sparing staging ipsilateral retroperitoneal lymph node dissection (RPLND) is recommended in children with paratesticular primaries who are ten years of age and older, or in patients of any age with retroperitoneal lympha based on studies demonstrating that patients ten years of age and older were much more likely to have retroperitoneal disease,[71] and that CT scanning may have a very high false negative rate in the detection of retroperitoneal lymph node involv chemotherapy and radiotherapy and a subsequent decrease in survival in IRS IV versus IRS III (86% versus 92%, respectively) as well as in more recent COG studies.[134,71] Of note, in patients <10 years old with evidence of retroperitoneal sprea

6.2 Chemotherapy

Table 14. Lymph node drainage based on primary tumor site for RMS	
Extremity	
Lower extremity	Inguinal, femoral, popliteal nodes (rarely involved)
Upper extremity	Axillary, brachial, epitrochlear, infraclavicular
Genitourinary	
Bladder/prostate	Pelvic, retroperitoneal nodes at renal artery level or below
Cervix and Uterus	Pelvic, retroperitoneal nodes at renal artery level or below
Paratesticular	Pelvic, retroperitoneal nodes at renal artery level or below
Vagina	Pelvic, retroperitoneal nodes at or below common iliacs
Vulva	Inguinal nodes
Head and Neck	
Head/neck	Ipsilateral cervical, jugular, preauricular, occipital, supraclavicular nodes, may be bilateral with centrally placed tumors
Orbit/Eyelid	Ipsilateral jugular, preauricular, cervical nodes
Intrathoracic	Internal mammary, mediastinal nodes
Retroperitoneum/pelvis	Pelvic, retroperitoneal nodes
Trunk	
Abdominal wall	Inguinal, femoral nodes
Chest wall	Axillary, internal mammary, infraclavicular nodes
Note: any tumor with involved node other than listed above signifies distant metastasis (stage 4/Group IV)	

The addition of active multi-agent chemotherapy in the 1970s resulted in an overall increased survival from <25% up to 71%.[53-54-55] The backbone of most chemotherapeutic regimens is **Vincristine, D-Actinomycin, and Cyclophospha** limit acute toxicities and long-term morbidity. **The dose and duration of therapy is dictated by clinical risk group.** The currently open intermediate risk study ARST1431 compares VAC alternating with vincristine & irinotecan (VI) to VAC/VI + t rapamycin (mTOR) inhibitor. mTOR is a serine /threonine kinase the regulates multiple intracellular tumor promoting pathways. Xenograft models have demonstrated synergistic effect of mTOR inhibitors with VAC.

6.3 Radiation Therapy

Radiation dosage and timing of therapy depend upon the histology, stage, clinical risk group, and anatomic location of the primary tumor and fusion status. Radiotherapy has been shown to be effective for local control, as local recurr receiving radiation.[73-74] **Tumor size > 5 cm at diagnosis has been associated with local failure,** thus in the current intermediate risk study these patients will receive an increased RT dose at the primary site. When dealing with very young chil effects.

6.3.1 Gynecological RMS

In girls with RMS of the genital tract, several promising reports demonstrate excellent survival combining chemotherapy and radiation with only limited or no radical surgical resection. Martelli *et al.* reported 91% five-year overall survival, 78% five rate of 88%. In this small series, 44% of these children were cured with chemotherapy alone.[57] Magne *et al.* also reported excellent five-year overall survival (87%) with primary chemotherapy to shrink the tumor followed by brachytherapy, and als 85% experiencing normal menses which was attributed to pre-brachytherapy oophoropexy to minimize ovarian radiation exposure[75] Brachytherapy is currently recommended for vaginal tumors when its use is feasible. For uterine tumors the sam reserved for patients with recurrent or progressive tumors. [131]

6.3.2 Bladder/Prostate RMS

Bladder/Prostate RMS is considered an unfavorable site. The most currently completed COG trial for intermediate-risk RMS (ARST0531) advocated radiotherapy beginning at week four, based on several reports of poorer overall survival (64 versus 63-70%),[76-135] and 25-30% worse ten-year failure-free survival rates in those who did not receive radiotherapy.[73]

6.3.3 Paratesticular RMS

Paratesticular RMS carries an excellent prognosis and is primarily treated with chemotherapy and surgery (radical inguinal orchiectomy ± ipsilateral RPLND in older children older than age 10 or in those with N1 nodal involvement). Radiation lymphatic disease. The usual dose is to the para-aortic chain, with the inclusion of the ipsilateral pelvic nodes depending on the extent of disease.[77]

7. Long-Term Complications of Therapy

RMS survivors experience frequent and often severe therapy-related complications, including secondary malignancies, renal and urinary dysfunction, hormonal disturbance, infertility and sexual dysfunction, bowel complications, and psychologica chemotherapeutic agents are well-known: **vincristine** (**neuropathy**), **doxorubicin** (**heart failure**), **and cyclophosphamide** (**myelosuppression and hemorrhagic cystitis**). Spunt *et al.* reported that 88% of female long-term survivors of pelvic the majority experiencing a median of three severe late sequelae. Radiotherapy in particular has been implicated as a causative factor, with an almost ten-fold increase in adverse sequelae compared to those who did not receive radiotherapy[78] C and decreased bladder capacity following “bladder preservation” therapy as well.[65-66-67-68] Despite significant improvement in survival, the burden of therapy remains high for these patients. Future studies are underway with the goal of achieving t sequelae without sacrificing oncologic outcomes.

Videos

Removal of Wilms Tumor

Laparoscopic Radical Nephrectomy

Partial Nephrectomy for Multifocal Unilateral Wilms Tumor

Advanced Testicular Cancer in a Teenager--Tips and Tricks for Radical Orchiectomy

Presentations

WILM'S TUMOR Presentation 1

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