# Pediatric Renal Tumors

# 58

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## Overview

Renal tumors in children occur at an incidence of almost 8 per 1,000,000 representing approximately 7 % of all childhood cancers [1]. The vast majority (>90 %) of these are Wilms' tumors (WTs), but many other histological types of renal tumors also occur in children (Table 1). The incidence of each type of renal tumor is tightly correlated to the age of the patient. WT, most common in children under age 5, is much less often diagnosed in adolescents and young adults. An adolescent over 15 years of age with a renal tumor is more likely to have renal cell carcinoma than WT. Rhabdoid tumor of the kidney (RTK) and congenital mesoblastic nephroma (CMN) are seen almost exclusively in infants less than a year, and clear cell sarcoma almost always occurs in children less than 4 years old. With current multimodality therapy, curative therapy can be provided for the majority of children with a diagnosis of favorable-histology Wilms' tumor; however, the cure rates for children with relapsed or anaplastic WT and RTK remain unacceptably low.

**Table 1** Pediatric renal tumors

| | |
|---|---|
| Nephroblastomic tumors | Nephroblastoma (Wilms' tumor) |
| | Favorable histology |
| | Anaplasia (diffuse, focal) |
| | Nephrogenic rests and nephroblastomatosis |
| | Cystic nephroma and cystic partially differentiated nephroblastoma |
| | Metanephic tumors |
| | Metanephic adenoma |
| | Metanephic adenofibroma |
| | Metanephic stromal tumor |
| | Favorable histology |
| Mesoblastic nephroma | Cellular, classic, mixed |
| Clear cell sarcoma | |
| Rhabdoid tumor | |
| Renal epithelioid tumors of childhood | Papillary renal cell carcinoma |
| | Renal medullary carcinoma |
| | Renal tumors associated with Xp11.2 translocations |
| | Oncocytic renal neoplasms following neuroblastoma |
| Angiolipoma | |
| Ossisfying renal tumor of infancy | |

A wide variety of histological types of renal tumors occur in children; the overwhelming majority (>90 %) are Wilms' tumors

This chapter will touch on several pediatric renal tumors but, given the overwhelming prevalence, will focus largely on WTs. The principles of the diagnostic evaluation, surgical management, and the use of appropriate chemotherapy and radiotherapy used in WT can be generalized to some of the other less common renal tumors.

Although preserved specimens of bilateral kidney tumors from a child, later identified as nephroblastoma, date from the 1700s, the most common renal tumor of childhood became inexorably tied with the name of Max Wilms, a Professor of Surgery, when in 1899, he wrote a detailed monograph describing seven children suffering from renal "mixed tumors" [2, 3]. He provided a meticulous description of the triphasic morphology of this tumor, comprised of three defining components: epithelium, blastema, and stroma (Fig. 1). Also termed as nephroblastoma, the tumor became widely known as "Wilms'" tumor. It has become well recognized that WTs can have great histological diversity. Cell types seen in normal developing kidney can be present, as well as diverse elements such as adipose tissue, cartilage, skeletal muscle, and neuroglial tissue. These elements appear to arise from stromal differentiation. Epithelial differentiation can be seen with the presence of renal tubules, glomeruli, or comma and S-bodies. Tumors can be triphasic, with all three components; monophasic, with epithelial differentiation only; or biphasic, containing exclusively blastemal and stromal cells. Max Wilms also offered the important insight that all of these tumor components developed from a common undifferentiated germ cell. Along with the observation that the morphology of WT correlates with phases of normal renal development, this has helped build an understanding into the link between organogenesis and tumorogenesis in the kidney [4]. Study of this relationship has fostered understanding of the correlation between WT and a variety of renal abnormalities. It has

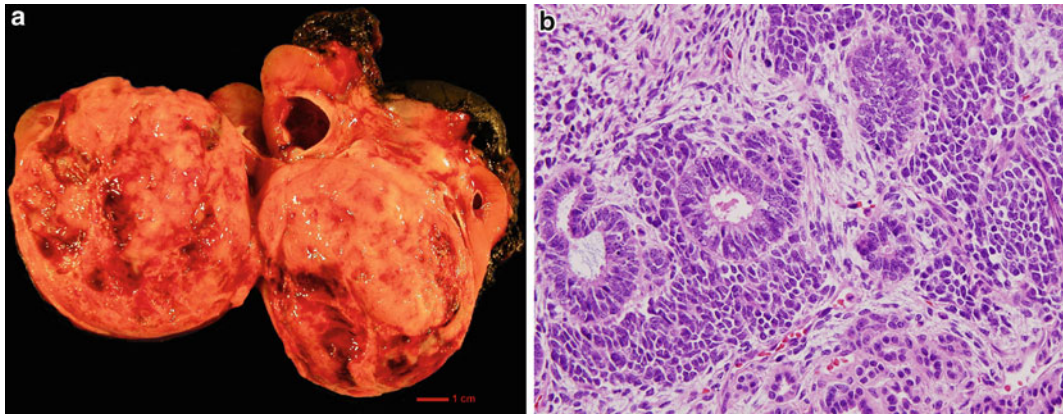


**Fig. 1** Gross and microscopic images of favorable histology Wilms' tumor. (**a**) Gross pathologic specimen, demonstrating typical friability, pink and variegated coloration, cystic changes, and area of hemorrhage and necrosis. (**b**) Classic microscopic triphasic histology of Wilms' tumor, containing blastemal, stromal and epithelial elements

also helped elucidate the connection between the persistence of embryonic renal tissue (termed nephrogenic rests) and risk for the development of WT. The expanding knowledge of the genetics of WT has added both answers and new questions into this link.

## Genetics of Wilms' Tumors and the Two-Hit Hypothesis

Over 90 % of Wilms' tumors are unilateral and sporadic. Wilms' tumors are derived from the nephrogenic mesenchyme, a tissue that is only present in the fetal kidney. As such, Wilms' tumor presentations are almost always restricted to young children, either at birth or during the first few years of life [5]. Because the nephrogenic mesenchyme is only present in fetal kidneys, the tumor is most likely initiated before birth. "Wilms' tumor" is in actuality a group of neoplasms that are all derived from the fetal kidney but that display variation in their histology and response to treatment. The classification of Wilms' tumors has undergone several rounds of revisions. A recent study based on mutational analysis, transcriptional profiling, and histology of over 200 Wilms' tumors found 4 (and possibly 5) major subtypes [6]. The primary distinguishing criteria for Wilms' tumors include determination of whether the histology is mainly epithelial or stromal (or mixed) and whether there are mutations or altered gene expression of the Wilms' tumor-1 (*WT1*), β-catenin, and/or insulin-like growth factor 2 (*IGF2*) genes.

Although most Wilms' tumors are sporadic and unilateral, there exist a subset that are bilateral [7, 8]. This duality is also a feature of retinoblastoma, a childhood tumor of the eye [9]. Bilateral Wilms' tumors or retinoblastomas are typically found earlier in life than unilateral tumors. This difference led Knudsen and Strong to suggest that a "two-hit" model may explain the relatively earlier occurrence of bilateral tumors, such that children with bilateral tumors were hypothesized to have a constitutional inherited or germline mutation and an additional mutation or "hit" at the remaining functional allele will produce the tumor [10]. In contrast, the more common sporadic unilateral tumors must result from both alleles being mutated somatically, a sequence that takes longer to occur during fetal or postnatal life.

The Knudsen/Strong two-hit theory has been borne out by a long history of genetic and molecular studies [10] and provides the basis for the modern concept of tumor suppressor genes. *RB1* was identified as the tumor suppressor gene for retinoblastoma, and Wilms' tumor-1 (*WT1*) gene was similarly identified for Wilms' tumor [11, 12]. However, Wilms' tumor is genetically remarkably more complicated; the *WT1* gene is

lost in a minority (~10–15 %) of Wilms' tumors [13–15]. This observation has led to a decades-long search for additional tumor suppressor genes for Wilms' tumor. Recently, these studies identified an X chromosome gene, WTX, as a tumor suppressor gene for Wilms' tumor [16, 17]. Although a long history of cytogenetic and other studies suggest the presence of an additional tumor suppressor gene at the 11p15 locus, a classic tumor suppressor gene has not yet been identified at this locus [18–20].

## The Identification of the Wilms' Tumor-1 Gene

Although most Wilms' tumors are sporadic and are not accompanied by extrarenal manifestations; the study of syndromic Wilms' tumor provided an avenue to identifying the *WT1* gene. A large number of chromosomal deletions were identified on chromosome 11 in individuals with the WAGR syndrome (Wilms' tumor, aniridia, genitourinary malformations, and mental retardation); this eventually led to the delimitation of a locus on chromosome 11p13 harboring a tumor suppressor gene for Wilms' tumor [19, 21]. Consistent with the "two-hit theory," constitutional hemizygosity for a tumor suppressor gene at 11p13 would predispose an individual to Wilms' tumor, and somatic LOH (loss of heterozygosity) at 11p13 in the nephrogenic mesenchyme would result in the initiation of an oncogenic process leading to a Wilms' tumor. Additionally, LOH at 11p13 was also apparent in individuals with sporadic Wilms' tumor [22, 23]. These studies identified a minimal 30 kb region on 11p13 that received the moniker *WT1* and as a presumptive tumor suppressor gene [24, 25]. Soon afterward, the *WT1* gene was positionally cloned and sequenced independently by two groups by mapping small regions of overlap among chromosomal deletions in germline and sporadic tumors [11, 12]. Additional mutations in *WT1* were then found in individuals with sporadic Wilms' tumor [26].

## The Structure of WT1

The mammalian *WT1* gene contains 10 exons and encodes a 55-kDa protein, the major structural features of which are four zinc fingers (Fig. 1) [27]. These zinc fingers are able to bind both DNA and RNA, and in addition to its well-studied role as a transcription factor, WT1 has also been studied as a protein that may affect RNA splicing [28]. Four major splice forms of WT1 have been characterized, produced by two major alternative splicing events: one that inserts a 15 amino acid exon 5 and the other that inserts three additional amino acids (lysine-threonine-serine; or KTS) at the end of the third zinc finger. Most tissues that express WT1 express all four splice forms though at characteristically distinct ratios [29]. Alternative translational start sites are also thought to contribute to the heterogeneity of WT1 peptides, but the functional importance of alternative start sites is unknown [30, 31]. Moreover, the functional significance of exon 5 remains unclear. Even though exon 5 s conserved among higher vertebrates, there was no apparent phenotype resulting from the derivation of mice in which this exon was deleted [32]. Despite the surprising absence of a phenotype in exon 5 deleted mice, isoforms of WT1 containing exon 5 are over-expressed in Wilms' tumor and other malignancies [33], and studies in vitro suggest a potential role in the regulation of cell survival and proliferation [34]. However, both the + KTS and –KTS forms of WT1 are required for normal development; mice able to express only the + KTS or –KTS, but not both, exhibit abnormal kidney and gonadal development [35].

## Molecular Studies on the Function of WT1 in the Nephrogenic Mesenchyme

The *WT1* gene has been subject to extensive genetic analysis in humans. Many mutations have been found, including a large number that affect the zinc finger region. The third zinc finger region appears to represent a "hot spot" for mutations that result in significant phneotypes [13]. Mutations in *WT1* are associated with two human syndromes. Denys-Drash syndrome (DDS) includes severe glomerular and gonadal dysgenesis and Wilms' tumor [36]. Frasier syndrome is caused by an inability to splice in the KTS segment [37]; this syndrome also includes gonadal dysgenesis but not Wilms' tumor.

It remains a mystery why DDS includes Wilms' tumor and Frasier syndrome does not. Perhaps this relates to the degree to which the respective causative mutations cause loss of WT1 function in kidney progenitor cells.

The zinc fingers of WT1 bear homology to other Kruppel family zinc finger proteins [12], especially one named early growth response-1 (EGR1), that binds GC-rich sequences that are commonly found in the 5′ regions of many genes. Therefore, most early studies that identified transcriptional targets of WT1 focused on genes that had these GC-rich elements in their promoter region (reviewed in [38]). These studies variously reported transcriptional activating or repressing functions of WT1, but many of the putative target genes were not expressed in the developing kidney and therefore of questionable relevance to the role of WT1 in the kidney.

Recent studies have shed more light on the role of WT1 in kidney progenitor cells and their differentiation into nephrons. These studies may also contribute to our understanding of the role of WT1 in the biogenesis of Wilms' tumor. A ChIP-Chip microarray approach was used by Hartwig et al. in which WT1-associated chromatin obtained by chromatin immunoprecipitation (ChIP) was used to probe the 5′ regions of all genes within the murine genome [39]. Hartwig et al. identified a consensus WT1 binding site and a target gene set that included many genes known to be important for kidney progenitor cells (e.g., *Pax2, Bmp7, VegfA*). Moreover, components of several of the most important signal transduction pathways in development (BMP, FGF, Notch, Shh, and others) were identified as WT1 target genes, such that WT1 may regulate the output of multiple signaling processes during nephrogenesis. Many novel WT1 target genes were also identified, among them genes involved in the epigenetic regulation of gene expression. A more recent WT1 ChIP-Seq study further identified several FGF genes as WT1 targets. As FGF signaling is well known to be crucial for progenitor cell self-renewal and survival, these studies brought additional understanding to requirement for WT1 in maintaining kidney progenitor cells in the embryonic kidney [40].

Additional mechanistic insight into the function of WT1 came from Essafi et al., whose work suggested a chromatin–switch model [41]. Wnt4, a gene essential to the mesenchymal-to-epithelial transformation (MET) in kidney development, was identified as a WT1 target gene. CTCF is a chromatin-binding protein that "insulates" or demarcates sections of chromosomes from regulatory influences outside the demarcated domain. WT1 maintained *Wnt4* expression in a CTCF-delimited domain. This was demonstrated by WT1-dependent recruitment of the transactivator p300 and WT1-dependent maintenance of histone modifications consistent with transcriptionally active chromatin. In contrast, in the epicardium of the heart, *Wnt4* is not expressed, despite the presence of *WT1*. However, unlike the kidney, in the epicardium WT1 associated with the Basp1 corepressor (instead of p300) at the Wnt4 locus. Thus, it appears that the activator versus repressor function for *WT1* is context dependent [41]. It remains unknown what mechanism determines whether WT1 confers transcriptional activation versus repression and associates with p300 versus Basp1 respectively. Whether WT1 can associate with both activating and repressive complexes in the same cells, or whether in any given cell or tissue it associates with one and not the other, is an important question that remains to be answered.

## Embryonic Expression of WT1 and Phenotypes of WT1 Mutant Mice

*WT1* expression begins in the intermediate mesoderm that gives rise to the entire urogenital system [42]. Its expression becomes localized to the mesonephric condensations and then to the metanephric mesenchyme [42–44]. As kidney development proceeds, *WT1* expression localizes to the nephron progenitor population and derivative structures, primarily those that become glomerular podocytes. Notably, *WT1* is expressed more broadly than *Six2*, a gene whose expression most clearly defines the self-renewing and committed progenitor population (see Fig. 2). Rather, *WT1* is also expressed in the stroma adjacent to the progenitors though at lower levels than in progenitors. As progenitors are induced to form nephrons, *WT1* expression continues in the pretubular

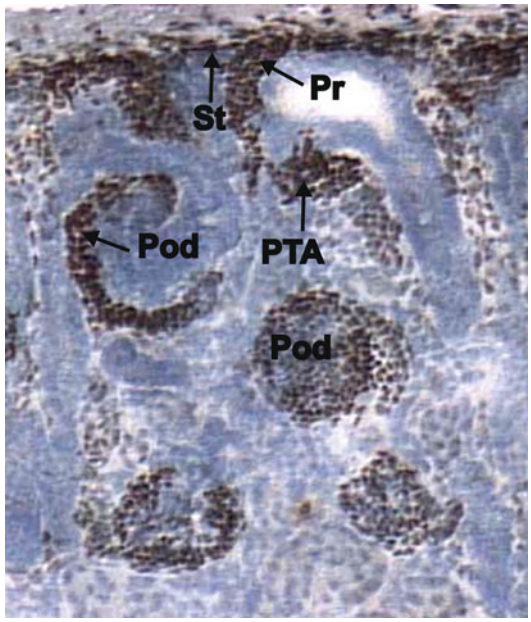


**Fig. 2** WT1 expression in human fetal kidney. WT1 protein is stained brown. Staining is present in the progenitor population (*Pr*) and adjacent stroma (*St*) and in pretubular aggregates (*PTA*) and early podocytes (*Pod*) (Courtesy of Dr. Valerie Schumacher)

aggregates and the renal vesicle, where its expression becomes restricted to cells that become the glomerulus [45]. *WT1* is particularly highly expressed in immature podocytes and in mature podocytes throughout life. In the adult kidney, WT1 expression is entirely restricted to podocytes [44].

Wt1 was among the first genes studied by gene targeting or "knockouts" in mice. Embryos unable to express *Wt1* exhibited complete kidney and gonadal dysgenesis [46] (see Fig. 3). These mutant embryos also displayed a thin myocardium, probably due to defective or absent epicardium. This latter aspect of the phenotype caused midgestational death and resorption of most homozygous mutant embryos. In *Wt1* homozygous mutant embryos the metanephric mesenchyme was transiently present at E11.5, when it first appears as a distinct structure, but apoptotic cells were already apparent, and by E12.5, the metanephric mesenchyme had entirely disappeared as a distinct structure. Therefore, *Wt1* does not appear to be required to specify the metanephric mesenchyme lineage [46]; rather other evidence suggests that this lineage specification involves the Eya1:Six1:Pax2 protein complex [47, 48]. Despite the initial appearance of a histologically distinct metanephric mesenchyme, the ureteric bud fails to grow out from the Wolffian duct in *Wt1* homozygous mutant embryos. This is similar to several other gene knockouts that affect the viability of the metanephric mesenchyme. Ureteric bud outgrowth is primarily mediated by glial cell line-derived neurotrophic factor (GDNF). However, GDNF was not identified as a WT1 target gene in aforementioned studies (GDNF is actually regulated by PAX2). As such, the failure of ureteric bud outgrowth is probably caused by insufficient expression of GDNF by apoptotic metanephric mesenchyme [46, 49].

Further studies on the role of WT1 in nephrogenesis made use of transgenic mice derived with YACs (yeast artificial chromosomes) containing the *Wt1* gene [50–52]. In the most successful YAC rescues, which were presumably those in which transgenes produced the highest levels of WT1, pretubular aggregates were present in transgenic kidneys, but these failed to undergo a successful MET to form nephrons, representing a partial rescue of nephrogenesis and suggesting that MET required higher levels of WT1 than is required to maintain viability of progenitor cells themselves [50–52]. A related phenotype was observed in conditional mutant mice, in which *Wt1* was inactivated in the progenitor (cap mesenchyme) population at E13.5 [53]. In these conditionally mutant embryos, *Six2*-expressing progenitors persisted, but they also failed to undergo MET.

How can the studies discussed above be formulated into a comprehensive model for WT1 function in the kidney progenitors and in MET? First, the identification of Pax2, VegfA, Bmp7, and other members of FGF and BMP/TGFβ

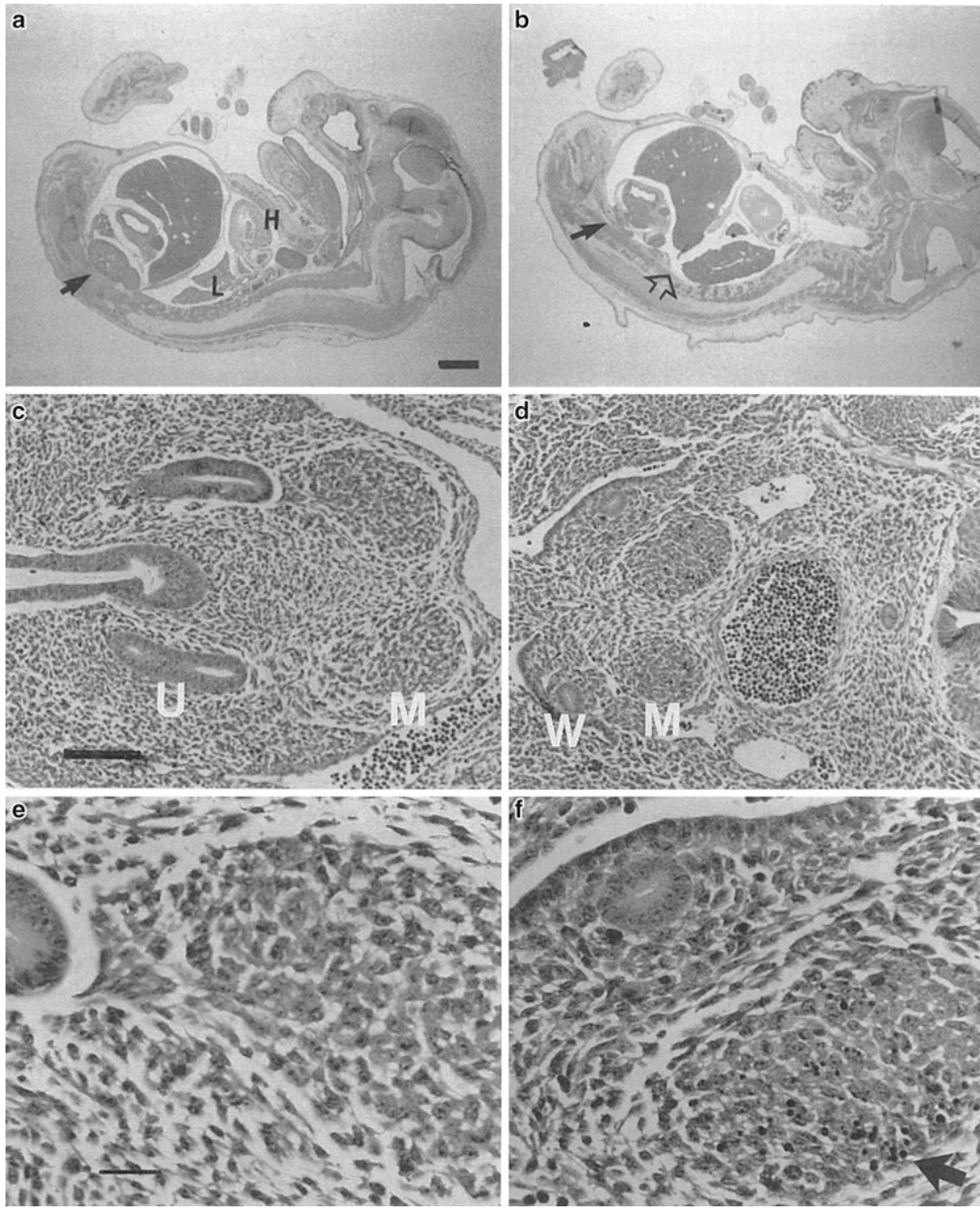


**Fig. 3** Wt1 mutant phenotype (Adapted from Armstrong et al. [42]). (**a**, **b**) E14.5 embryos; *arrows* show embryonic kidney in wild type (**a**) and missing kidney in $Wt1^{-/-}$ (**b**); (**c**, **d**) E11.5 urogenital area showing ureteric bud (*U*) and metanephric mesenchyme (*M*) in wild type (**c**) and metanephric mesenchyme (*M*) without ureteric bud in $Wt1^{-/-}$ embryo. (**e**, **f**) High-power image of metanephric mesenchyme in wild type (**e**) and $Wt1^{-/-}$ (**f**) E11.5 embryos. Apoptotic cells (dark fragmented nuclei) are present in $Wt1^{-/-}$ (*arrow*)

signaling pathways as targets of WT1 may explain the apoptosis of the metanephric mesenchyme in WT1 mutant embryos [39]. Additionally, the identification of *Wnt4* as an additional target gene is consistent with the observations that YAC rescued embryos and the conditional mutant embryos fail to undergo MET [41]. Nevertheless, the situation is probably more complex, and WT1 is probably orchestrating the expression of many other genes that regulate multiple signal transduction pathways involved in nephrogenesis.

## Other Tumor Suppressor Genes for Wilms' Tumor

*WTX and β-catenin*: The finding of many mutations in the β-catenin gene (*CTNNB1*) in Wilms' tumors has emphasized the role of Wnt/β-catenin signaling in the progression of Wilms' tumor [54–58]. These mutations in *CTNNB1* most typically affect the domain associated with degradation, i.e., these mutations constitutively stabilize β-catenin in the tumor [54, 58, 59]. Moreover, mutations in *CTNNB1* and *WT1* are often found in the same tumor and sometimes combined with mutations in the other Wilms' tumor suppressor gene, *WTX* [16, 17, 58, 59]. The WTX protein antagonizes Wnt/β-catenin signaling by forming an association with a β-catenin degradation complex that promotes the ubiquitination and degradation of β-catenin [16, 60]. *WTX* mutations can either be found coexistent with *WT1* mutations or independently of mutations in *WT1* [56, 61]. Regardless, the combination of WT1 and WTX mutations still accounts for less than half of all Wilms' tumors, suggesting that other genes and/or processes remain to be identified in the initiation and progression of these tumors [56]. Furthermore, in some Wilms' tumors where *WTX* mutations have been found, they are not present in adjacent nephrogenic rests (see below) but only in the tumor, suggesting that mutation of *WTX* is a relatively late event in tumor formation [56, 61].

Observing both *WT1* and *CTNNB1* mutations in Wilms' tumors brings forward questions of whether *WT1* and β-catenin act together in normal kidney development and whether the initiation and/or progression of Wilms' tumor involves the same signal transduction that regulates the growth, self-renewal, and differentiation of kidney progenitor cells during normal kidney development. WT1 and β-catenin do not appear to be components of the same transcriptional complex. However, WT1 does appear to regulate expression of *CXXC5* (*RINF*) that in turn regulates Wnt/β-catenin signaling [62]. We may hypothesize that WT1-mediated expression of CXXC5 may modulate Wnt/β-catenin to regulate the numbers of cells undergoing MET to maintain a balance between progenitor self-renewal and nephron differentiation. The role of CXXC5 in Wilms' tumor is not yet known. Perhaps loss of *WT1* leads to decreased expression of CXXC5 that then leads to increased β-catenin transcriptional activity.

*11p15*: Loss of heterozygosity at 11p15 is a second long-standing observation in Wilms' tumors, often occurring independently of any changes at 11p13 [19, 63–65]. It is intriguing that in contrast to the early success at finding a classic tumor suppressor gene at 11p13, similar searches have not been successful at 11p15. However, 11p15 is a highly studied locus as it contains the *H19* and *IGF2* (insulin-like growth factor 2) genes that undergo reciprocal imprinting via DNA methylation, *IGF2* being expressed from the paternal allele and *H19* from the maternal allele [66]. Loss of heterozygosity or loss of imprinting (LOI) at the IGF2 locusresulting in biallelic overexpression of *IGF2* in the tumor is a common phenotype among Wilms' tumors [18, 67–69]. Beckwith-Wiedemann syndrome (BWS), a fetal overgrowth syndrome where overgrowth of many organs is observed, is also associated with overexpression of *IGF2* [70–72]. Indeed, embryonal-type tumors, most commonly Wilms' tumors, are commonly observed in BWS. Moreover, although Wilms'-like tumors do not develop in mice heterozygous for *WT1*, a Wilms' tumor phenotype was obtained in mice by conditional mutation of *WT1* and concomitant transgenic overexpression of IGF2 [53].

## The Cell of Origin for Wilms' Tumor

*WT1* is expressed in both *Six2* progenitors and *Foxd1*-expressing stroma, but lineage-tracing

studies have demonstrated that the *Six2* domain defines the stem-progenitor cell in the embryonic kidney [73] and thus the Six2 pool is usually assumed to be the cell of origin for Wilms' tumors. This assumption is challenged by a recent study in which Lin28 is overexpressed in embryonic kidneys of transgenic mice, resulting in a Wilms' tumor-like phenotype characterized by abundant Six2-expressing cells [74]. Lin28 is expressed in stem cell (and other) populations where it affects the stability of microRNAs, particularly the Let-7 family [75, 76]. Unexpectedly, the Wilms'-like phenotype was obtained only when *Lin28* was overexpressed under control of a *WT1*-Cre knockin. Progenitor overgrowth did not result from either *Six2*, *Foxd1*, or ureteric bud-specific Cre-directed overexpression of Lin28. The *Lin28* Wilms' tumor result suggests either that *WT1* may be expressed in a pre-Six2 progenitor outside the Six2 domain that is the real Wilms' precursor cel, or that *Lin28* overexpression must occur in multiple cell types, i.e., a *Six2* cell and a non-*Six2*-expressing cell, both of which express *WT1*, to obtain the Wilms'-like phenotype. Of great implications for regenerative biology of the kidney, the Wilms' tumor-like phenotype could be reversed in these mice by terminating expression of *Lin28*, with subsequent differentiation of this overgrowth of progenitor-like cells, which was presumably mediated by Wnt signals from ureteric bud-like structures that accompanied this progenitor overgrowth.

## Other Influences on Kidney Progenitor Cell Expansion

Interactions between progenitors and surrounding stroma have come to the forefront in understanding the regulation of progenitor growth and differentiation. This first became evident through the knockout of *Foxd1*, a transcription factor expressed in the stroma surrounding the cap mesenchyme that led to expansion of the *Six2*-expressing progenitor cells [77]. The aforementioned Lin28 result may also be a consequence of Lin28 overexpression in both progenitors and stromal cells [74]. Additionally, a protocadherin *Fat4*, expressed by the stroma, is also required for maintaining proper boundaries of the progenitor domain [78]. Fat4 turns out to regulate the activity of YAP, a component of the Hippo signaling pathway, in the kidney progenitor population. Abnormal expression and activation of YAP has also recently been described in Wilms' tumors [79]. However, in contrast to Wilms' tumors, progenitor overgrowth in Foxd1 or Fat4 mutant mice is relatively circumscribed, indicating that loss of whatever constraint the stroma places on progenitor cells is not sufficient by itself to lead to tumor formation.

## The Relationship of Wilm's Tumors to Nephron Progenitor Cells

In their most basic characterization, Wilms' tumors result from unrestrained growth and aberrant differentiation of kidney progenitor cells. In reality, this is a gross oversimplification as there is significant histological complexity to Wilms' tumors; some tumors show an epithelial predominance and others a blastemal or mesenchymal predominance. Adding to this complexity, different tumor subtypes are known that contain cell types plausibly obtained from kidney progenitor cells but also cell types such as stroma and smooth muscle that would not be expected to derive from kidney progenitors. In addition, two distinct precursor structures are known: perilobar nephrogenic rest (PLNR) and intralobar nephrogenic rest (ILNR) [5]. As suggested by this nomenclature, PLNRs are located in the peripheral tissue of the kidney, and ILNR are located deep within the parenchyma of the kidney. *WT1* mutations tend to be associated with ILNR, and LOH at 11p15 is more commonly found in PLNR [58, 68, 80].

Recently, an updated and expanded categorization of Wilms' tumors was suggested by a study that systematically applied transcriptional profiling and mutational analysis to over 200 Wilms' tumors [6]. Four (and possibly five) types of Wilms' tumors were defined, shown as S1–S5 in Fig. 4. S1 was characterized by a strong epithelial component that might be derived from cells emerging after initial induction of the nephron. This class did not have mutations in *WT1* (or *CTNNB1* or WTX), a finding consistent with the requirement for *WT1* for MET, and tumors

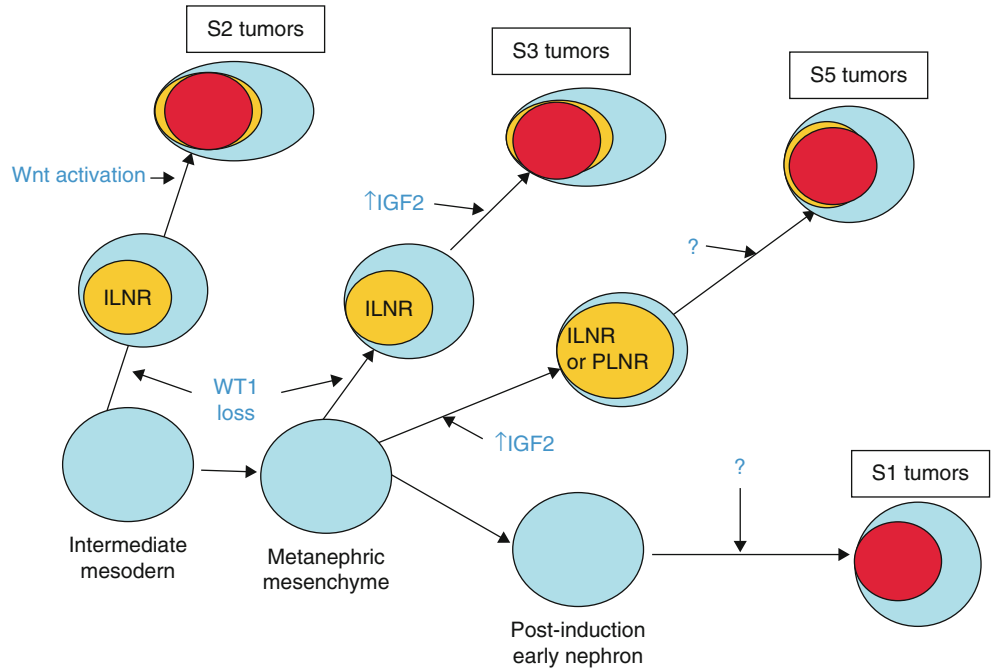


**Fig. 4** A schematic of possible origins of different types of Wilms' tumors (according to Gadd et al. [6]) (Reprinted under permission from Elsevier)

actually showed high expression of *WT1*. In contrast, WT1 was lost in S2 and S3 tumors that were also characterized by activating mutations in β-catenin in the former or increased expression of IGF2 in the latter. S2 and S3 tumors were associated with ILNR, and their gene expression patterns suggested that they arise from either the intermediate mesoderm or metanephric mesenchyme respectively. S5 tumors, in contrast to S2 and S3, were also suggested to be derived from the metanephric mesenchyme. However, S5 tumors show increased expression of Igf2 but did not show loss of *WT1*. This group was the only group with PLNR, although ILNR was also present. A smaller and less well-defined S4 group was similar to S2 though with some significant differences in patterns of gene expression.

Most studies that have characterized WT1 function in kidney development have demonstrated a transcriptional activation function for WT1, with target genes including *Fgf's 8*, *16* and *20, Bmp7*, *VegfA*, and *Pax2* that are required to maintain the progenitor population [39, 40] (though in other tissues such as epicardium, WT1 acts in a repressive complex [41]). Therefore, to achieve an understanding of WT1's role in Wilms' tumor, we must integrate two seemingly contradictory findings: (1) WT1 has a positive effect on maintaining kidney progenitor cells, and (2) loss of *WT1* leads to Wilms' tumor, that is in some sense an uncontrolled proliferation of progenitor cells. Furthermore, some Wilms' tumors retain expression of *WT1*. One possible explanation takes into account that tumors presumably arise from a single cell that has undergone LOH, but remains in the midst of cells that retain gene function. This is obviously quite distinct from the situation in *Wt1* mutant mouse embryos in which all cells are devoid of Wt1 and no kidney progenitors survive. In the case of a single cell undergoing LOH, it is possible that it is "rescued" in a non-cell-autonomous manner until other changes in gene expression or in the tumor microenvironment make the tumor a self-sustaining entity.

An alternative explanation is suggested by previously mentioned studies on *WT1* conditional mutant mice. In this study, an additional signal, overexpression of Igf2, was required to obtain Wilms'-like tumors. Additionally, the role of WT1 in nephron differentiation should be considered. WT1 is not only required to maintain progenitors but also for MET and subsequent steps in nephron differentiation. In the absence of WT1, nephron progenitor cells may persist in a progenitor state, or as poorly differentiated nephrons, while continuing to proliferate and form tumors. This is consistent with the phenotype of the conditional knockout of *WT1*, where *Six2*-expressing progenitors are present though they fail to differentiate [53]. Moreover, aforementioned studies using transgenic *WT1*-expressing YACs demonstrated that lower levels of WT1 could rescue survival of nephron progenitor cells but was not sufficient to allow these cells to progress to pretubular aggregates nor to form nephrons [50, 52].

## Conclusion

A potential model for the formation of Wilms' tumors that synthesizes current knowledge would suggest that low expression of WT1 maintains progenitors but does not allow their differentiation into nephrons. In those tumors that have lost expression of *WT1*, these cells may either represent early blastemal cells similar to those that are briefly present in *Wt1* mutant embryos at E10.5 before they undergo apoptosis or, alternatively, that harbor other mutations such as those that increase expression of Igf2 due to loss of imprinting or perhaps increase expression of Lin28, as well as mutations that prevent degradation of β-catenin, that together allow progenitors to maintain their viability independently of WT1.

## Syndromes Associated with WTs

As previously mentioned in the discussion of the identification and cloning of the WT1 gene, ten to fifteen percent of WTs occur in children with recognized malformations, including hemihypertrophy, cryptorchidism, hypospadias, or in association with a recognizable genetic syndrome [81].

### WAGR Syndrome (WT, Aniridia, Genitourinary Malformation, Mental Retardation Syndrome [21, 82, 83])

WAGR syndrome is caused by a microdeletion at 11p13 that deletes both *WT1* and *Pax6* [82, 83]. WAGR is associated with aniridia in all cases resulting from hemizygosity for *Pax6* [84–86] but is variably associated with WT (50 % risk of WT) [87] and genitourinary malformations due to hemizygosity for *WT1*. WAGR is also variably associated with mental retardation and congenital heart disease; however, the gene(s) on 11p13 responsible for these defects have not been identified [88].

### Denys-Drash, Frasier and Beckwidth-Wiedeman Syndromes

DDS includes the triad of WT (90 % risk of WT development) [36, 89], genitourinary malformations, and nephropathy (mesangial sclerosis), but various combinations of these features have been reported [13, 90, 91]. DDS is caused by intragenic *WT1* point mutations that either eliminate or alter the structure of the zinc finger region. The most common mutation is an arginine-to-tryptophan transition in exon 9 (Arg 394) or other missense alterations in the zinc finger domains encoded by exons 8 and 9 [4, 92]. The increased severity of kidney disease associated with DDS, as compared with WAGR, raises the possibility of a dominant-negative effect that is mediated by dimerization of mutant and wild-type proteins through their N terminal domains [93, 94].

Frasier syndrome bears similarity to DDS and is characterized by gonadal dysgenesis, often resulting in XY sex reversal in males [4], progressive glomerular nephropathy (focal segmental glomerulosclerosis) [95], or gonadoblastoma. Interestingly Frasier syndrome (FS) [37, 96] much less commonly (less than 5 %) includes WTs among its features. FS is caused by mutations in intron 9 of *WT1* that affect splicing and prevent expression of the + KTS isoforms of WT1 (discussed below) [37, 96].

Beckwith-*W*iedemann *s*yndrome (BWS) is the most common WT-associated condition, affecting

1 in 13, 000 children, and is probably related to a large degree to LOI at 11p15 [64, 97, 98], resulting in hyperexpression of IGF2. BWS is characterized by prenatal overgrowth and increased incidence of embryonal tumors of liver (hepatoblastoma), muscle (rhabdomyosarcoma), and kidney. This syndrome carries a 10 % risk of WT [99]. While the genetics of WT formation in BWS is not completely understood, at least 20 % of BWS patients exhibit paternal uniparental disomy for 11p15 that contains the *IGF2* and *H19* imprinting locus strongly associated with sporadic WT [64], and these children have a high risk (64 %) of developing embryonal tumors [98]. In addition, familial BWS is linked to chromosome 11p15 [20]. A third, unidentified tumor suppressor gene on 11p15 has been linked to rhabodomyosarcoma [100], suggesting that at least three genes on 11p15 may predispose to growth abnormalities and WT as well as other embryonal tumors.

Other genetic syndromes associated with increased incidence of WT [101, 102] include Simpson-Golabi-Behmel syndrome (linked to Xp26) [103–106], Perlman syndrome [107–110], Sotos syndrome (linked to 5q35) [111, 112], and Bloom's syndrome (linked to 15q26) [113, 114].

### Familial Wilms' Tumor

True familial WT is extremely rare, accounting for only 1–2 % of all cases [10], suggesting that de novo germline mutations rather than familial transmission of a mutant allele underlie the genetic predisposition [4]. In addition, reduced fertility may be associated with germline mutations in genes that regulate urogenital development [99]. The low number of familial cases may reflect the historic lethality of this cancer before individuals with tumors reached reproductive age. With the advent of effective therapy in the past few decades, such that most individuals with WTs survive to adulthood, it will be important to observe in the future whether familial cases become more common in the population. Two familial WT genes have been mapped – *FWT1* (*Familial WT 1 locus*; also known as *WT4*) at 17q12-21 [115] and *FWT2* at 19q13.4 [116], but neither gene has been identified. In addition, familial cases unlinked to any previously identified loci have been reported, indicating that other familial WT genes may exist [117].

## Treatment

The modern-day treatment of WT is a paradigm of the success of multimodality management, as well as testament to the importance of collaborative national and international studies in pediatric cancer. Clinical trials which led to identification of active chemotherapy agents, as well as appreciation of the radiosensitivity of WT, along with advances in surgical techniques and postoperative care, have led to remarkable improvement in the outcomes of children with WT. A universally lethal disease at the turn of the nineteenth century, survival increased to about 25 % with surgery only in the early 1900s; the use of routine postoperative radiation therapy resulted in an almost 50 % survival rate in the 1950s; the discovery of the effectiveness of chemotherapy drugs (initially vincristine and actinomycin) increased survival to the 70–80 % range in the 1970s [118]. Further improvements in both the overall outcome of patients with renal tumors and a decrease in overall toxicity through limiting exposure to unnecessary therapy for low-risk patients have come about through the work of large collaborative groups. Although many groups have made important contributions, the two largest are the International Society of Pediatric Oncology (SIOP) and the National Wilms Tumor Study Group (NWTS.), which was supplanted by the Children's Oncology Group (COG) in 2002. Although these two groups (SIOP and NWTS/COG) have fundamentally different approaches to the treatment of WT, both have strategies which have resulted in overall survival (OS) rates approaching 90 % [119–121]. SIOP therapies have been based on prenephrectomy chemotherapy, and NWTS/COG approach has advocated upfront nephrectomy in almost all cases. Although outcome from each approach has been excellent, it is difficult to extrapolate improvements in therapy from

one group to the other, given the confounding variable of the surgical timing, as the divergence in the approach results in differences in staging and therapeutic stratification systems.

## Risk Stratification

### Staging

The treatment of WT is stratified according to the risk of relapse of the tumor, with lower-stage and favorable-histology tumors receiving less intensive therapy than higher-stage, unfavorable-histology tumors. Known prognostic factors, such as age of the patient, size of the tumor, stage, histology, and genetic findings, are used to risk-stratify the patients. NWTS/COG staging is based on anatomical staging at presentation; SIOP staging is based on postchemotherapy findings. A comparison of the two systems is presented in Table 2.

### Histology

The most powerful prognostic factor for outcome in WT is the histology of the tumor. NWTS and COG define WT as favorable histology (FH) if anaplasia is not identified (Fig. 5). Anaplasia may be focal or diffuse and is defined by the presence of large mitotic figures, large and bizarre nuclei, and hyperchromasia (Fig. 5). Anaplasia is associated with worse outcome [122, 123] and merits intensification of therapy. Patients with low-stage focal anaplasia do better than those with diffuse anaplasia [124, 125].

Rhabdoid tumor of the kidney (Fig. 6) and clear cell sarcoma were initially believed to be subsets of unfavorable histology of WT but are now understood to be completely distinct tumor types [124, 126].

SIOP bases its histological classification of WT largely on response to therapy. A revised working classification of all renal tumors was developed by SIOP in 2001 [127] (Table 3). WTs are classified into three risk groups: high risk (blastemal or diffuse anaplasia), intermediate risk (regressive, stromal, mixed, epithelial, or focal anaplasia), and low risk (completely necrotic or cystic partially differentiated).

### Age

Increasing age has been shown to be correlated with decreased prognosis by both cooperative groups [128, 129]. Age is used by COG as a prognostic factor, along with tumor size. A subset of patients less than 2 years of age with tumors less than 550 g have been shown to do well with nephrectomy only [130, 131]. Adult event-free survival rates of WT have been shown to be lower than WT in pediatric patients but may be confounded by greater toxicity of treatment seen in adults [132–134].

### Biological Factors

As with other tumors, there is much interest in identifying biological factors that correlate with prognosis. Combined LOH of 1p and 16q was found to be a significant adverse prognostic factor in the fifth NWTS trial [135] and was used prospectively to risk-stratify patients on the first generation of COG renal tumor protocols. Patients with LOH of 1p and 16q were treated with intensification of therapy and were found to have improved event-free survival (EFS) and overall survival (OS) [136]. 1q has also been identified as an adverse prognostic factor in FHWT in a cohort of patients on NWTS 4 [137] and validated to be independent of stage in a cohort from NWTS 5 [138].

## Surgical Considerations in Renal Tumors

Surgery was the first modality used in the treatment of renal tumors, and it continues to be of critical importance today. Regardless of tumor type or multimodality treatment protocol, surgery serves as the mainstay to achieve local control of, histopathologically assess, and anatomically stage children with renal tumors.

**Table 2** Staging systems for pediatric renal tumors

| Stage | COG (before chemotherapy) | SIOP (after chemotherapy) |
|---|---|---|
| I | (a) Tumor is limited to the kidney and completely excited<br>(b) The tumor was not ruptured before or during removal<br>(c) The vessels of the renal sinus are not involved beyond 2 mm<br>(d) There is no residual tumor apparent beyond the margins of excision | (a) The tumor is limited to kidney or surrounded with fibrous pseudocapsule if outside of the normal contours of the kidney. The renal capsule or pseudocapsule may be infiltrated with the tumor but does not reach the outer surface and is completely resected (resection margins "clear")<br>(b) The tumor may be protruding into the pelvic system and "dipping" into the ureter (but it is not infiltrating their walls)<br>(c) The vessels of the renal sinus are not involved<br>(d) Intrarenal vessel involvement may be present |
| II | (a) Tumor extends beyond the kidney but is completely excised<br>(b) No residual tumor is apparent at or beyond the margins of excision<br>(c) Tumor thrombus in vessels outside the kidney is stage II if the thrombus is removed en bloc with the tumor. *Although tumor biopsy or local spillage confined to the flank were considered stage II by NWTSG in the past, such events will be considered stage III in COG studies* | (a) The tumor extends beyond kidney or penetrates through the renal capsule and/or fibrous pseudocapsule into perirenal fat but is completely resected (resection margins "clear")<br>(b) The tumor infiltrates the renal sinus and/or invades blood and lymphatic vessels outside the renal parenchyma but is completely resected<br>(c) The tumor infiltrates adjacent organs or vena cava but is completely resected |
| III | Residual tumor confined to the abdomen<br>(a) Lymph nodes in the renal hilum, the periaortic chains, or beyond are found to contain tumor<br>(b) Diffuse peritoneal contamination by the tumor<br>(c) Implants are found on the peritoneal surfaces<br>(d) Tumor extends beyond the surgical margins either microscopically or grossly<br>(e) Tumor is not completely respectable because of local infiltration into vital structures | (a) Incomplete excision of the tumor which extends beyond resection margins (gross or microscopic tumor remains postoperatively)<br>(b) Any abdominal lymph nodes are involved<br>(c) Tumor rupture before or intraoperatively (irrespective of other criteria for staging)<br>(d) The tumor has penetrated though the peritoneal surface<br>(e) Tumor implants are found on the peritoneal surface<br>(f) Tumor thrombi present at resection margins of vessels or ureter, transected or removed piecemeal by surgeon<br>(g) The tumor has been surgically biopsied (wedge biopsy) prior to preoperative chemotherapy or surgery |
| IV | Presence of hematogenous metastases or metastases to distant lymph nodes | Hematogenous metastases (lung, liver, bone, brain, etc.) or lymph node metastases outside the abdominal-pelvic region |
| V | Bilateral renal involvement at the time of initial diagnosis | Bilateral renal tumors at diagnosis. Each side should be substaged according to the above criteria |

NWTS/COG and SIOP staging systems differ mostly in timing of staging, prior to chemotherapy versus after chemotherapy

## History and Physical Exam

Children with renal masses frequently present asymptomatically and are often diagnosed either by the caregiver during a routine activity (bathing) or by the healthcare professional on a well-child visit. Often the child can appear very well, and the diagnosis can be surprising to the parents and healthcare professionals. Patients can also present with symptoms of hematuria or with

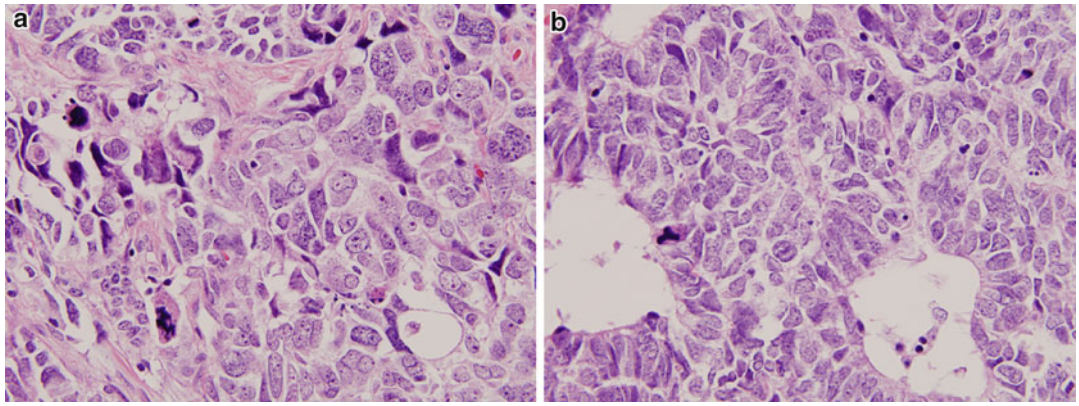


**Fig. 5** Anaplasia in Wilms' tumor. Microscopic-view anaplasia in Wilms' tumor. (**a**) There is diffuse nuclear enlargement, at least three times normal size (compare with tumor cells in *top center*), with marked pleomorphism. (**b**) Abnormal, enlarged mitotic figures reflect an increased DNA content

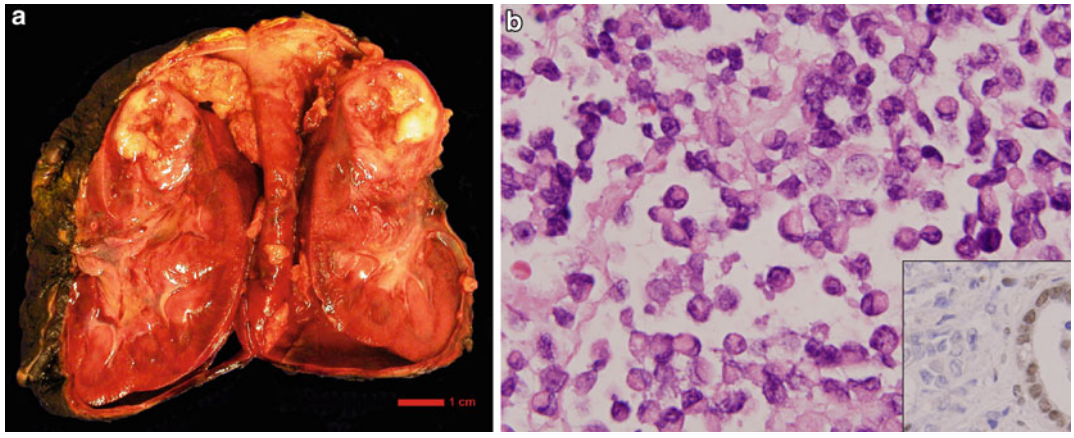


**Fig. 6** Rhabdoid Gross and Microscopic Images. (**a**) Rhabdoid tumor of the superior pole with extrarenal extension extending to Gerota's fascia. The tumor ruptured the renal capsule and formed a desmoplastic neocapsule seen at the superior portion of the specimen. There was extensive microscopic extension into the renal sinus vein. (**b**) Microscopic appearance of a rhabdoid tumor. The tumor cells are frequently discohesive with vesicular nuclei and prominent nucleoli. The nuclei are often indented by an eosinophilic cytoplasmic inclusion composed of whorled aggregates of intermediate filaments. Rhabdoid tumors are characterized by a loss of chromosome 22q11.2 in an area involving the *INI1* gene. The *inset* is an immunohistochemical stain for *INI1* demonstrating retention in normal renal tubular cells (*right*) and loss in the tumor cells (*left*)

gastrointestinal complaints, most often constipation. Findings of an abnormal hemogram or urinalysis testing or unexplained hypertension are not uncommon in both symptomatic and asymptomatic patients. Any of these findings should prompt a thorough abdominal exam and consideration of abdominal imaging.

Surgical consultation is warranted from the time of diagnosis. Once the presence of a mass is confirmed, additional history of associated medical problems that might compromise therapy or predispose the child to risks of peritreatment morbidity should be established. History should include any evidence of developmental delay or

**Table 3** Revised S.I.O.P. working classification of pediatric renal tumors

| |
|---|
| A. For pretreated cases |
| I. Low-risk tumors |
| Mesoblastic nephroma |
| Cystic partially differentiated neproblastoma |
| Completely necrotic nephroblastoma |
| II. Intermediate-risk tumors |
| Nephroblastoma – epithelial type |
| Nephroblastoma – stromal type |
| Nephroblastoma – mixed type |
| Nephroblastoma – regressive type |
| Nephroblastoma – focal anaplasia |
| III. High-risk tumors |
| Nephroblastoma – blastemal type |
| Nephroblastoma – diffuse anaplasia |
| Clear cell sarcoma of the kidney |
| Rhabdoid tumor of the kidney |
| B. For primary nephrectomy cases |
| I. Low-risk tumors |
| Mesoblastic nephroma |
| Cystic partially differentiated nephroblastoma |
| II. Intermediate-risk tumors |
| Nonanaplastic nephroblastoma and its variants |
| Nephroblastoma – focal anaplasia |
| III. High-risk tumors |
| Nephroblastoma – diffuse anaplasia |
| Clear cell sarcoma of the kidney |
| Rhabdoid tumor of the kidney |

unusual growth patterns that may be consistent with predisposing genetic syndromes, as well as any possible history of bleeding disorders in the patient or the family. The accurate assessment of vital signs cannot be overstated. The degree of hypertension in these children can be significant, and this may change the perioperative anesthetic management. The degree of thoracic and abdominal compromise from the mass should also be investigated thoroughly to determine the anesthetic and operative risk for the patient as well. Despite very large masses, most children do not have significant respiratory embarrassment at presentation unless there is considerable metastatic pulmonary disease. Documenting the resting respiratory rate, decreased or absent breath sounds, and presence of effusions or consolidative processes is important. The abdominal exam should focus on the site of the mass and any evidence for involvement of the contralateral side. The presence of ascites should also be considered. A genitourinary exam is also important to investigate the presence of hernias, hydroceles, or varicolceles that may give indications about the size, location, and vascular structures affected by the mass. Tenderness on exam should also alert the physician to the presence of tumor hemorrhage or rupture with subsequent peritoneal irritation.

## Laboratory Evaluation

Baseline laboratory studies include urinalysis, complete blood count with differential, chemistry profile, liver function tests, coagulation profile, and blood typing for possible transfusion during surgical intervention. An association of WT and von Willebrand disease is well established and should be investigated preoperatively [139, 140].

## Radiographic Evaluation

Radiographic studies consist of plain radiography and axial imaging. Abdominal and chest radiograph series are procured to evaluate the presence of disease and associated findings of ascites, effusions, consolidative processes, or the suggestion of metastatic disease. These studies are followed by either computed tomography (CT) (Fig. 7) or magnetic resonance (MR) (Fig. 8) imaging techniques with axial, coronal, and sagittal formatting to enable three-dimensional reconstruction and hence the adequate documentation of tumor size, location, organ invasion, intravascular involvement, lymphadenopathy, the presence of contralateral disease, the presence of a solitary kidney, horseshoe kidney, or other anatomic variant, the presence of metastatic disease, and the suggestion of tumor spillage or rupture at diagnosis. Furthermore, one must make sure that the tumor in question truly arises from the kidney and not from simply the retroperitoneum or an adjacent organ

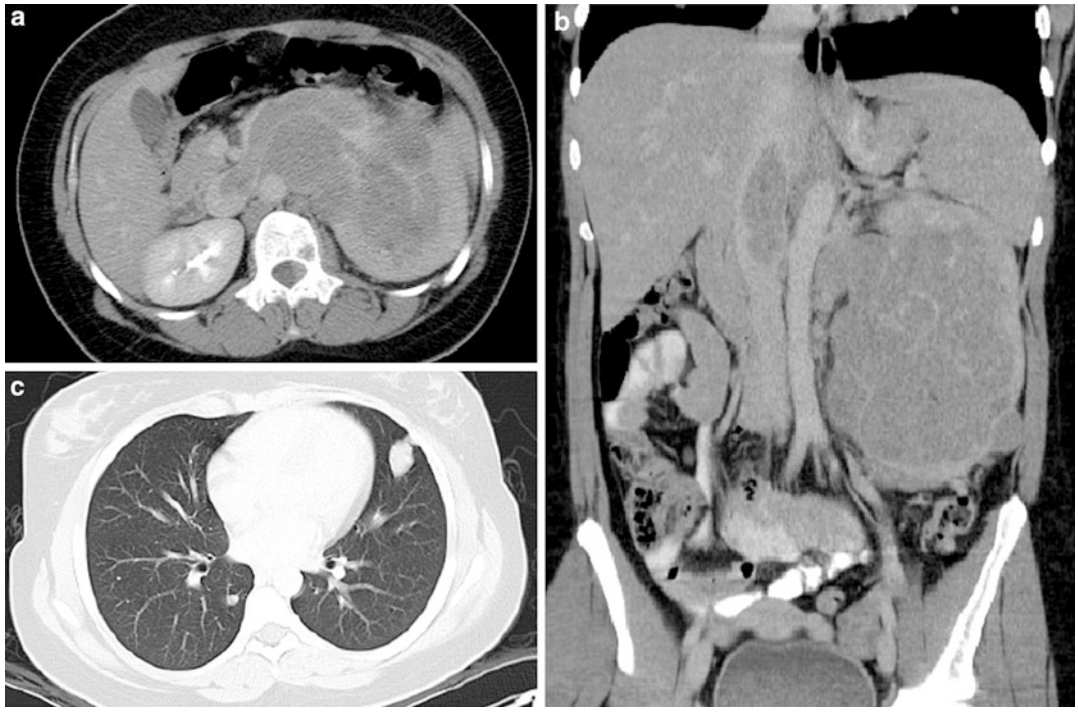


**Fig. 7** CT images (axial (**a**) and coronal (**b**)) showing left renal mass with renal vein and IVC extension with evidence of pulmonary metastasis (**c**)

(germ cell tumor, sarcoma, or neuroblastoma). Differentiating this fact can be difficult, especially with neuroblastoma, but with primary renal tumors the parenchyma is splayed out around the mass ("claw sign" (Fig. 9)) as opposed to simply being compressed or indented. Delayed sequences can also be ordered to evaluate for the presence of tumor within the collecting system (MR or CT ureterogram). Ureteral involvement can also be documented on an intravenous pyelogram. One has to consider the risk of radiation-induced malignancy when contemplating which exam to order (CT vs. MR) [141], but accurate preoperative planning must take precedence over the concern for secondary malignancies if there is any question. A comparison of preoperative CT or MRI for patients with WT supported either as a reasonable for preoperative imaging [142]. Both CT and MRI were found to have high specificity, with relatively low sensitivity for detection of local lymph node metastasis and capsular penetration. The study concluded that the choice of imaging modality for initial staging of WT should be based on institutional expertise, with the primary consideration of specific clinical information being sought from the study, and in addition, consideration of radiation exposure and need for sedation. The identification of preoperative rupture is clinically important information. A COG study retrospectively evaluated the diagnostic performance of CT in identifying the presence or absence of preoperative Wilms' tumor rupture, using rupture found at surgery as the standard. The study concluded that CT has moderate specificity but relatively low sensitivity in the detection of preoperative rupture, with ascites beyond the cul-de-sac the most sensitive finding factor predictive of rupture [143]. Adjuvants to CT and MRI include vascular ultrasonography (US) that is probably more sensitive for diagnosing inferior vena cava and renal vein involvement. If renal vein and/or IVC

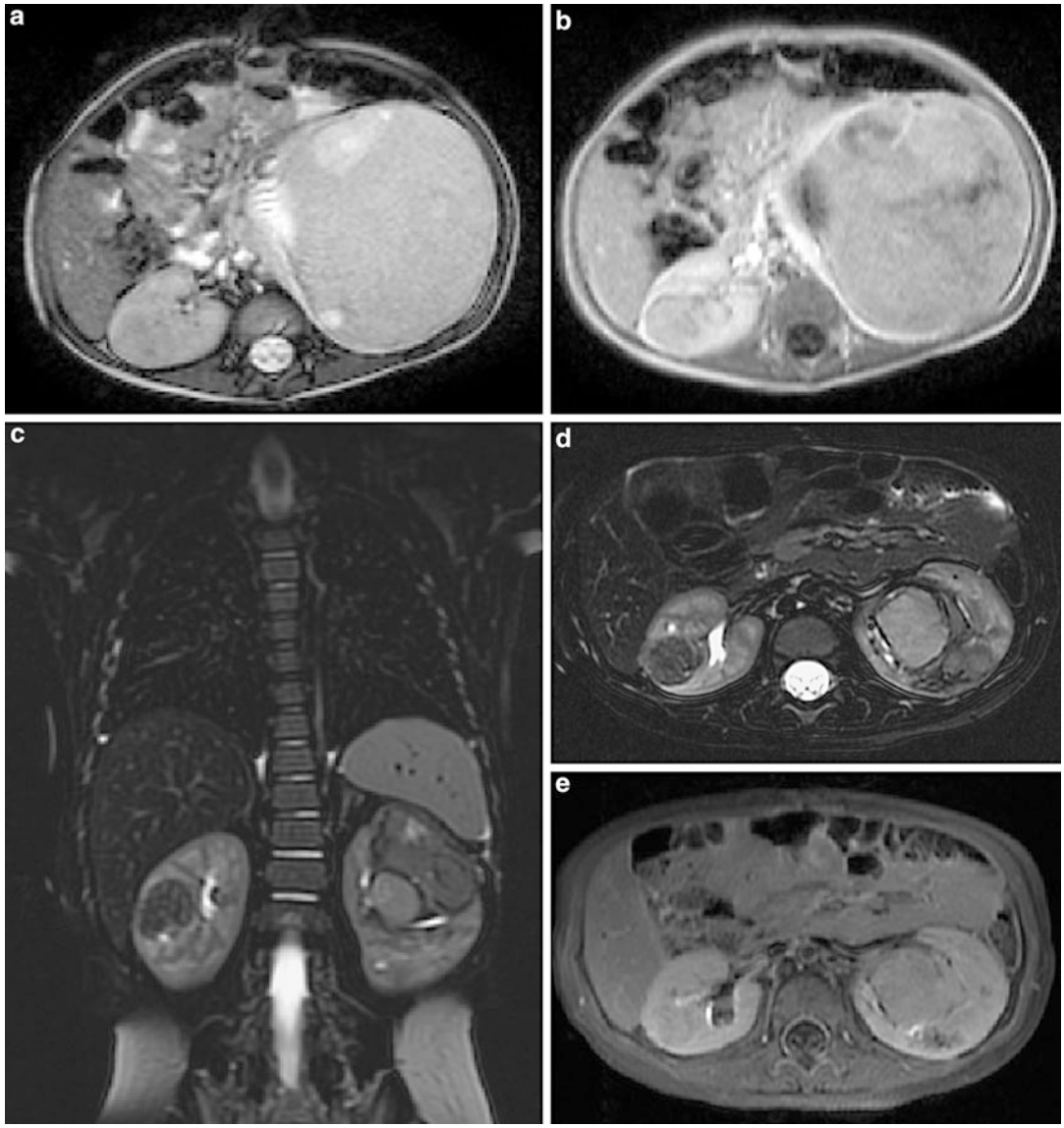


**Fig. 8** MRI bilateral nephroblastoma. (**a**) [T1] and (**b**) [T2] at diagnosis showing bilateral masses. After 2 months of chemo Rx masses have decreased in size (**c**) [Coronal T2], (**d**) [Axial T2], and (**e**) [Axial T1]

involvement is discovered, then further studies may be warranted to document the degree of tumor thrombus progression including the presence of atrial (echocardiogram) or suprahepatic vein IVC involvement (MR or CT venogram). Furthermore, US is also an excellent modality to investigate the kidney parenchyma to better define the architecture and assist in defining the characteristics of the mass and the contralateral kidney. Nuclear imaging studies do not have a role in these patients except to possibly document the baseline glomerular filtration rate and renal function contributed by each kidney in anticipation of a nephrectomy. However, these tests are seldom performed preoperatively and often do not change preoperative management of the patient. A bone scan (Fig. 10) may be ordered to document the presence of bony metastasis if the mass is thought to be a clear cell sarcoma of the kidney. Bone scan is not routinely done in WT. A CT of the brain is

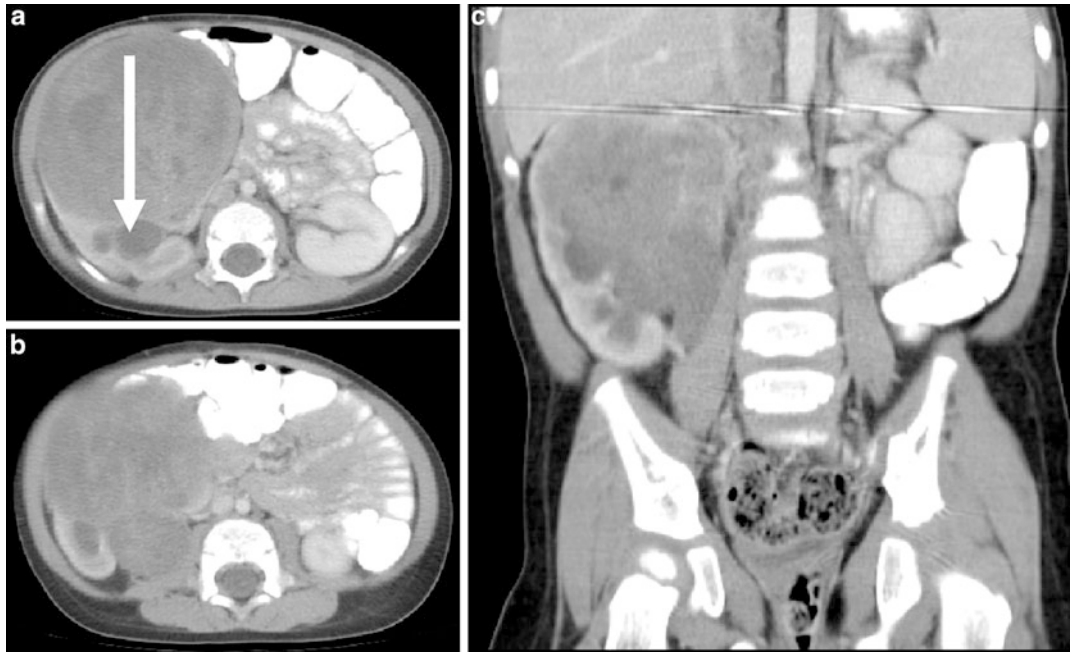


**Fig. 9** CT images (**a**) [axial], (**b**) [axial], and (**c**) [coronal] of right renal mass with evidence of a "claw sign" (*white arrow*) and with extension into the renal pelvis/proximal ureter causing obstruction

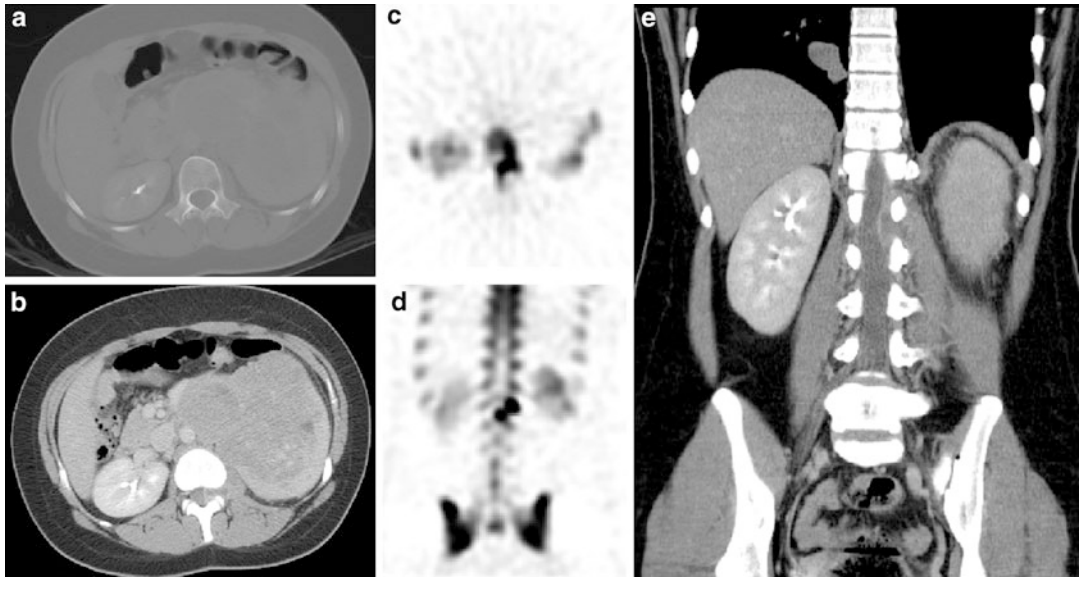


**Fig. 10** CT images (**a**) [bone window] and (**b**) [abdominal window] showing intraspinal extension of tumor and bone metastasis, (**c**) (axial) and (**d**) (coronal) display corresponding o bone scan images, and (**e**) CT coronal image shows extent of intraspinal spread

recommended to evaluate for metastasis in renal rhabdoid tumors and clear cell sarcoma and can be considered in renal cell carcinoma but not in other variants as the other tumors are not prone to neural involvement at time of diagnosis.

Finally, special attention should be considered for renal masses that do not fit the classical radiological description of known lesions as they may be pseudotumors. An excellent review has recently been published by Malkan and colleagues [144]. Careful multidisciplinary review should be undertaken in these cases to ensure the risks of a renal malignancy are balanced by the need for renal parenchyma preservation.

## Anesthetic Evaluation and Perioperative Considerations

Once the child has been properly assessed and evaluated, primary resection as opposed to biopsy and neoadjuvant chemotherapy is espoused by most North American centers. This pathway differs from the regimens proposed by SIOP, and this issue will be discussed in greater detail below. Prior to surgery, anesthetic preparation concerning the child's pulmonary function, renal function, degree of anemia and hypertension, and the extent of the planned resection is performed. Discussions between the surgical team and the anesthesia team are critical to assess the risk of hemorrhage and the probable conduct of the operation. An intra-arterial line is of vast importance for hemodynamic monitoring and arterial blood gas sampling during the operation to ensure optimal respiratory function. A nasogastric tube and transurethral bladder drainage catheter ("foley" catheter) are inserted as well to drain the gut and to monitor urine output. Furthermore, gross hematuria can also be assessed during the operation with the use of a transurethral bladder catheter. Several intravenous lines are also placed in the upper extremities for rapid fluid administration and resuscitation during the operation, and the largest bore intravenous catheters that can be placed are recommended. Furthermore, the lower extremities are avoided as IV sites if possible, so as to ensure resuscitation can proceed in the event that the IVC is clamped during the operation. Previously typed blood products should be available in the operating room prior to beginning the operation. Finally, an epidural catheter or other regional analgesic technique (paravertebral catheter) is recommended for intraoperative hemodynamic stability and postoperative pain management. These catheters blunt the body's physiological response to the operative insult by controlling the sensation of pain from the beginning of the case. The patient's hemodynamics are generally more stable with fewer swings in the patient's blood pressure and heart rate. Furthermore, with the incisional pain blunted postoperatively by these techniques, the patient can usually be extubated at the end of the operation assuming that there were no intraoperative complications and hemorrhage was kept to a minimum. These adjuvant analgesic techniques can then be used in the postoperative period for all analgesia needs, and it can remain in until there is return of bowel function and an oral pain regimen can be started (usually within 5–7 days).

## Operative Considerations

The operation then begins with the child positioned either supine or slightly raised on an ipsilateral flank roll to 15–20° of elevation from the operating room table. These positions afford the greatest exposure to the abdomen – retroperitoneal and intraperitoneal spaces. A report from the NWTSG documented the importance of the type and size of the incision with which to remove the involved kidney without subsequent rupture or intraoperative complications [145]. A generous transverse or bilateral subcostal incision is generally recommended as opposed to flank or paramedian incisions secondary to the higher reported rates of rupture of the tumors [145]. Furthermore, an ipsilateral thoracoabdominal incision centered over the greatest diameter of the mass to ensure adequate exposure to the entire retroperitoneum and adjacent chest cavity can also be employed. This latter approach allows for a wide field of view via the abdominal portion of the incision, and the thoracic extension of the

incision provides the unique exposure to the retroperitoneum superiorly and posteriorly where the tumor is most likely to be adherent to the diaphragm and surrounding soft tissues. Furthermore, the entire IVC can be exposed (right-sided tumors) for adequate proximal and distal control if a caval or renal vein thrombectomy is needed, or for left-sided tumors the incision can be carried over to the right anterior superior iliac spine to allow for adequate exposure of the IVC from the left side. At the conclusion of the operation, a thoracostomy tube may be required but not always as the pneumothorax can usually be evacuated without issue. Regardless of the type of incision, upon entering the abdomen, a peritoneal survey is conducted to look for evidence of occult metastatic disease. The entire peritoneal surface is palpated, as is the liver and contralateral kidney. Any free fluid is removed and sent for cytology, especially if there is evidence of rupture. Once these maneuvers are performed, the ipsilateral colon is mobilized and brought to the center via the medial visceral rotation technique. Care should be taken to define the tissue planes appropriately so as not to injure the colonic mesentery or to dissect too closely to the renal capsule so as to increase the risk of inadvertent perforation. Early recommendations had advocated dissecting the hilum first to gain vascular control, but this led to increased intraoperative hemorrhage and other morbidities. It is now recommended to defer the renal hilar dissection until the kidney has been fully mobilized and the renal pedicle is easier and safer to manipulate, isolate, and divide. The kidney and tumor should be circumferentially dissected off the retroperitoneal structures. The ipsilateral adrenal gland is often removed as well. Utmost care must be taken so as not to injure the tumor capsule and allow for iatrogenic rupture and tumor spillage. A generous margin of soft tissue should be included with the kidney and mass if needed and possible to decrease the risk of perforation. This may even necessitate removing a portion of the diaphragm. Prior to dividing the renal vein, directly palpate the renal vein and IVC to ensure there is no tumor thrombus. If present, then complete resection of all tumor including a caval thrombectomy is in order so as to not cut across the tumor and create iatrogenic intraperitoneal spillage. If the mass on exploration is too extensive as to require adjacent organ resection (colon, spleen, liver, etc.) or intravascular involvement precludes safe tumor thrombectomy, then only a biopsy of the mass should be performed and adjuvant therapy begun prior to formal resection and local control. If the kidney and tumor can be removed, then the ipsilateral lymph nodes should be sampled so as to adequately stage the tumor, regardless of histopathological type. The lymph node areas involved should be hilar, paraaortic, and paracaval. A formal retroperitoneal lymph node dissection is neither warranted nor indicated as earlier studies have confirmed [146]. All renal tumor types necessitate lymph node sampling, though data are only available for nephroblastoma. Studies conducted through NWTSG have shown that gross inspection of the lymph nodes by the operative surgeon is not adequate to define lymph node involvement in nephroblastoma [147]. Inadequate lymph node sampling has led to understaging patients and hence undertreatment with an increased incidence of local recurrence as demonstrated in NWTSG 4 [145]. Finally, the ureter should be transected as close to the bladder as possible without forming a diverticulum or outpouching that can then serve as a source of infection. Generally, the ureter is carefully traced to the pelvic rim and dissected anteriorly to the junction with the bladder and then transected where convenient. Palpation of the ureter should also take place prior to transaction to ensure there is no intraureteral tumor involvement. If the ureter is transected across tumor, then it is considered spillage with subsequent possible upstaging of the tumor and resultant increased therapy. Cystoscopy and ureteroscopy (or retrograde ureterograms) are only advocated for those with preoperative gross hematuria to define the possibility or bladder or ureter involvement [148].

At the conclusion of the operation, and under the same anesthetic, consideration should be given to the placement of an intravenous vascular access device for adjuvant therapy where appropriate. An intraoperative frozen section can be performed on the tumor prior to abdominal

closure to determine the histopathological subtype. Once known, a discussion between pathologist, oncologist, and surgeon should be held to determine the need for adjuvant chemotherapy. If the tumor type is amenable to chemotherapy, then permanent vascular access should be placed at the same operative setting. If there is any doubt about the diagnosis or if the tumor is not amenable to adjuvant therapy (renal cell carcinoma), then the placement of a vascular access device is deferred. Finally, in those children younger than 2 years of age and with small tumors (<550 g) who may have Stage I disease, an option for surgery only is also a possibility and may forgo the need for placement of a vascular access device at the upfront surgical resection.

## Postoperative Course

Postoperatively, the patient is generally extubated in the operating room if there are no intraoperative complications, significant resuscitation with crystalloid or colloid fluids, and a functioning epidural catheter. The patient is transferred to the intensive care unit for monitoring for 24 h, and then he is transferred to the floor the next day. The nasogastric tube is left in place until there is adequate bowel function and enteral intake is begun. The epidural catheter is generally left in until an oral pain management regimen is started or the catheter is not functioning. Once the epidural catheter is removed, the bladder catheter is removed. Attention should be directed to ensure adequate hemodynamic parameters, urine output and euvolemia, and normal renal function by laboratory monitoring during the postoperative period. Once the patient is adequately ambulating, eating, drinking, has normal renal function, and is on an oral pain control regimen, he is discharged or transferred to the oncology service for the administration of chemotherapy. This usually occurs within 7 days after surgery. NWTSG reviews in the past 30 years have shown that small bowel obstruction (SBO) is the most frequent postoperative complication [145, 149]. However, a special note should be made concerning early postoperative SBO in these patients as an intussusception can occur in these patients for an as yet unknown reason. It will present early in the postoperative period with signs and symptoms consistent with an SBO. However, worsening abdominal pain and increasing nasogastric tube output should alert the surgeon to order abdominal radiographs and an US to document the presence of this condition. If needed, reoperation is indicated to relieve the obstruction, or depending on the age of the patient, an air contrast enema can be used to reduce the intussusception.

## Surgical Questions and Controversies

### Neoadjuvant Therapy Versus Upfront Resection

Primary nephrectomy with subsequent adjuvant therapy has been and continues to be the NWTSG/COG recommendation for all renal masses. This view is not shared by SIOP, however, and they have recommended neoadjuvant chemotherapy – with or without a tissue biopsy – for over three decades. Both approaches have merit, and both have resulted in comparably good overall outcomes. From a surgical perspective, the SIOP recommendation is based on many factors, not the least of which is a greater risk of tumor spillage and rupture in patients undergoing upfront nephrectomy [150]. SIOP has reported greater rates of these complications than NWTS studies [151].

Another argument for surgical resection prior to chemotherapy is that this approach allows for procurement of untreated tissue for full histological and biological assessment, as well as complete surgical staging, including biopsy of suspicious sites and lymph node sampling. NWTSG review of surgery-related factors predicting local recurrence revealed that failure to sample lymph nodes was an adverse prognostic factor, even when compared to patients with documented nodes positive for tumor [145]. The hypothesis to explain this is that a subset of patients that did not have lymph node sampling were understaged and therefore undertreated. Results of SIOP 6, where adjuvant radiotherapy was withheld in a cohort with negative lymph

nodes after resection but with preoperative chemotherapy, demonstrated the importance of accurate lymph mode sampling. The study was stopped midway after there was an increase in local recurrence in this cohort when compared to the radiotherapy cohort, and these results seem to support this concern [152, 153]. The SIOP perspective on this "loss of staging information," however, views that patients who respond well to therapy and are found to be lower stage at the time of resection may appropriately be treated with less intensive therapy, particularly with avoidance of anthracycline and radiotherapy [154].

Another controversy in WT management involving the surgeon is the use of neoadjuvant chemotherapy with or without a tissue biopsy. The SIOP approach allows neoadjuvant chemotherapy based on diagnosis made from imaging studies and does not mandate a pretherapy biopsy. A series of reports from the NWTSG and SIOP addressed concerns with this approach [151, 155]. Namely, without a tissue biopsy, the mass could be benign or a different malignancy, and it was in almost 7–10 % of cases reported in these studies [151, 155]. A study from the UK further highlighted this result where almost 12 % of the patients had different pathological findings at time of nephrectomy [156]. The SIOP approach accepts this risk in exchange for reduced operative morbidity and potential downstaging by time of surgery for patients who receive upfront chemotherapy. Both approaches have resulted in excellent overall survival for the majority of patients with FHWT.

Even for those who advocate upfront nephrectomy in the majority of cases, it is clear that not all patients with WT should undergo primary resection. In order to preserve as much renal tissue as possible, patients with WT occurring in a single kidney, horseshoe kidney, bilaterally, or where a unilateral lesion is in a child with a known predisposition for a metachronous renal tumor should not undergo upfront nephrectomy. Patients presenting with significant respiratory compromise from extensive metastatic disease are not appropriate for initial surgery. Two studies by the NWTSG explored which renal masses should receive a primary biopsy and neoadjuvant therapy. These reports documented the intraoperative and perioperative morbidity from surgery for nephroblastoma, especially intraoperative hemorrhage, adjacent vascular or organ injury, and mortality. Tumors that were very large (>10 cm), had extensive IVC involvement (above the hepatic veins and into the right atrium), and required resection of adjacent organs should all undergo biopsy and neoadjuvant chemotherapy prior to resection for local control. These studies also pointed out that resections performed through suboptimal incisions (flank or paramedian laparotomy) and by nonpediatric specialists were also at greater risk of intraoperative perforation and spillage and increased morbidity [145, 157]. A COG study of patients enrolled on the Renal Tumor Biology and Risk Classification Study AREN03B2 determined that intraoperative tumor spill occurs in about one out of every ten cases of primary nephroureterectomies for Wilms' tumor and that right-sided and larger tumors are at higher risk of intraoperative rupture [158]. Tumors that appear to have perforated with free intraperitoneal spillage at diagnosis may also warrant biopsy to confirm the pathological diagnosis and then neoadjuvant chemotherapy.

The technique of biopsy, percutaneous versus open, has also been an area of debate and study [159]. Biopsies performed via a percutaneous core needle technique increase the risk of discordant pathology and seeding of the needle tract. Open biopsy with lymph node sampling at the time of diagnosis is another method that has traditionally been used. Based on results of NWTS studies demonstrating that patients undergoing any type of prechemotherapy biopsy had higher rates of relapse, all patients undergoing initial biopsy will be considered stage III in the COG staging system [160].

## Gross Hematuria at Presentation

Ureteral extension of nephroblastoma is a rare phenomenon present in only 2 % of cases in a recent NWTSG review [148]. This correlates with the few reports in the literature to date.

In reviewing the NWTSG reports, the authors found that of the cohort of children with ureteral involvement, 49 % had evidence of gross hematuria. This symptom serves as a significant clue to the presence of tumor extension into and through the collecting system, and hence, due diligence should be undertaken by the treating medical personnel. Preoperative imaging studies may find evidence of ureteral tumor thrombus in almost 63 % of patients, and CT was the most helpful modality. Prior to resection, however, cystoscopy, retrograde ureterograms, and direct palpation of the ureter to determine the presence of tumor thrombus are all warranted so as to define the extent of disease and have a complete resection. If the tumor thrombus is inadvertently missed and transected at surgery, then this would be considered intraoperative tumor spillage with subsequent tumor upstaging.

## Pulmonary Metastases

Patients with WT and pulmonary metastasis have been shown to do better with intensified chemotherapy with or without radiation therapy [161–163]. Although centers have recommended primary pulmonary metastasectomy to spare the morbidity of expanded therapy [162, 164], the NWTSG has demonstrated the superior efficacy of chemotherapy and radiotherapy over chemotherapy and surgery, regardless of pathological subtype [165, 166]. Green and colleagues demonstrated that pulmonary metastasectomy did not have an effect on outcome in patients treated on NWTS 1–3 studies. The SIOP approach to patients with pulmonary disease, however, does include possible pulmonary nodule resection. Patients are treated with 6 weeks of upfront therapy, and if the lung nodules respond completely to chemotherapy, or are surgically resected, the patients are treated without lung radiation, with good overall survival [167]. Ehrlich and colleagues demonstrated the importance of pretreatment biopsy of pulmonary lesions not radiographically consistent with metastatic disease as critical to avoiding overtreatment of children who may have other reasons for small pulmonary lesions [168].

## Intravascular Extension

A minority of children present with evidence of intravascular involvement with nephroblastoma (4 %) [169]. Diagnosis includes a combination of axial imaging (CT and/or MR) in addition to ultrasonography, including echocardiography to establish atrial involvement if warranted. Surgical extirpation of all disease – including the entire thrombus – is recommended. Furthermore, if all intravascular disease can be resected, there is no change in prognosis [170]. However, recommended timing of the resection has changed. An upfront resection followed by adjuvant therapy was initially recommended, but it has too great a morbidity in comparison to neoadjuvant chemotherapy and subsequent nephrectomy [145, 171]. A recent report from NWTSG documented the success of this approach and the clear ability of neoadjuvant chemotherapy to safely facilitate the subsequent nephrectomy and thrombectomy [169]. Specifically, the surgical morbidity was reduced by 50 % (26–13 %) with neoadjuvant chemotherapy, and the most severe complications occurred in the upfront surgery cohort.

## Bilateral Disease

Bilateral renal mass in children has been defined as stage V disease. Diagnosis and staging of these patients is similar to those children who present with unilateral disease save for the overriding mandate to save renal parenchyma. Whereas North American and European centers have differed on the management of unilateral disease (neoadjuvant chemotherapy vs. upfront resection), a common pathway has emerged in the treatment of children with bilateral disease. The goal of treatment in this cohort of children has been renal preservation to avoid the need for permanent renal replacement therapy. The current Children's Oncology Group protocol mirrored SIOP's approach and discouraged pretreatment biopsies (open or percutaneous). However, if tumors do not respond to neoadjuvant chemotherapy, then biopsy is recommended to ensure

concordant histopathological results and adequate chemotherapeutic regimens. Discordant tumors (unfavorable on one side and favorable on the other side) exist, and if missed, this scenario can allow for the undertreatment of the patient. Ideally, after neoadjuvant chemotherapy (three-drug regimen assuming favorable histology), successful partial nephrectomies can be performed. The NWTSG evaluated this cohort of patients in NWTSG-4 [172], and total gross resection of disease was accomplished in 88 % of cases. However, there was a higher percentage of both local recurrence (8 %) and positive margins (16 %) in this cohort. These results were deemed acceptable secondary to a substantial, successful partial nephrectomy rate (72 %) and overall survival (81 % at 4 years). The success of this pathway was also echoed by other authors [173].

## The Role of Partial Nephrectomy

Nephron-sparing surgery for unilateral nephroblastoma has not been adequately studied using prospective, randomized trials. Data amassed from the cohort of patients with bilateral tumors has shown this surgical extirpative modality to be an effective procedure when married to pretreatment biopsy and neoadjuvant chemotherapy (see prior section on Bilateral Tumors). The dominant philosophy when dealing with the children with bilateral tumors is to preserve renal parenchyma and avoid permanent renal replacement therapy. Pursuant to this goal, several groups [174–176] have attempted to apply parenchymal sparing surgery to unilateral disease recognizing the long-term morbidity of radical nephrectomy for unilateral tumors, including other renal injury (trauma, infection, obstruction), decreased glomerular filtration rate and the onset of renal failure, and metachronous nephroblastoma in the contralateral kidney. Haecker and colleagues evaluated their cohort of patients undergoing partial nephrectomy in nephroblastoma and recommended that it only be used for patients with small, favorable-histology tumors after neoadjuvant chemotherapy [175]. There was a higher local recurrence rate in the partial nephrectomy cohort, as well as a lower survival in unfavorable-histology tumors. Hence, the authors concluded that partial nephrectomy is feasible in small lesions, histologically favorable tumors that responded to neoadjuvant chemotherapy. Linni and colleagues published their result in analyzing the role of partial nephrectomy in unilateral nephroblastoma and recommended that this approach is not ready for universal application [176]. However, they did stress that in specific cases it is reasonable to consider partial nephrectomy if the tumor decreases by 50 % or greater in volume after neoadjuvant chemotherapy, if the tumor is easy to resect (unipolar lesion), if preservation of greater than 50 % of the kidney remains after resection, and if there are pathologically negative para-aortic lymph nodes. Results of the UKW-3 trial have been reported by Arul and colleagues, addressing the feasibility of unilateral, partial nephrectomy in a cohort of patients with favorable-histology nephroblastoma [174]. The study attempted to determine the ability of the surgeon to adequately define the resection plane ("marking") on the nephrectomy specimen ex vivo in light of the following criteria: (1) clear resection margins, (2) no vascular invasion, (3) no pelvic invasion, and (4) $>50$ % of the kidney preserved. The study was unsuccessful as there were no specimens officially "marked," but of the specimens identified by the surgeon as being a candidate for partial nephrectomy, 70 % were deemed pathologically not to meet the above criteria to be eligible for a partial nephrectomy. However, whereas intraoperative ultrasound was not available during this study 18 years ago, it may facilitate partial nephrectomy by defining the proper plane of dissection today and is recommended by the author a routine manner of practice (CBW). A COG study of patients enrolled on the Renal Tumor Biology and Risk Stratification Study AREN03B2 identified as Very Low Risk (patients with FHWT, age $< 2$ years, tumor weigh $<550$ g) examined the feasibility of performing partial nephrectomies on this cohort of patients with small low-stage tumors, using preoperative imaging. Partial nephrectomy was deemed possible in only 8 % (5 of 60) patients [177].

## The Role of Laparoscopy

The role of laparoscopic partial and radical nephrectomy is well established in adult renal cancers [178]. However, there is minimal data to support these approaches in pediatric patients and especially in the case of nephroblastoma. The role of minimally invasive surgery to resect other pediatric malignancies has been reported [179], but North American centers that stressed the importance of primary resections with adjuvant chemotherapy following surgery for nephroblastoma have not encouraged primary laparoscopic radical nephrectomies. Generally the tumors are large, bulky, and the concern for extirpation without rupture is of paramount importance so as not to intensify the postoperative therapy a child should receive. A minimally invasive approach for tumor biopsy (unilateral or bilateral) in patients deemed poor candidates for primary resection is both feasible and realistic. European centers that espoused neoadjuvant chemotherapy with tumor reduction have a cohort of patients whose tumors are more amenable to this minimally invasive approach. Duarte and colleagues documented the success of laparoscopic nephrectomy after neoadjuvant chemotherapy following SIOP protocols in two separate reports [180, 181]. They report on a total of 10 patients with no evidence of recurrence (mean follow-up 5–23 months), no complications, and no port-site implants. The authors document that the renal tumors are smaller and encased in a fibrous capsule after neoadjuvant chemotherapy which facilitates the ability to safely and completely resect these tumors and involved lymph nodes. However, the operative times for this approach are longer in comparison to open procedures.

## Chemotherapy

Multiple chemotherapy agents are active in the treatment of WT. These drugs act through a wide spectrum of mechanisms and have both overlapping and unique toxicity profiles (Table 4). NWTS and SIOP studies have helped refine the schedules and dosages appropriate to the patient's stage and histology, balancing the risk of relapse with avoidance of the risk of toxicity from the chemotherapy. It is well established that low-stage FH WT can be effectively treated with vincristine and actinomycin, with minimal acute and long-term toxicity [152, 182]. Doxorubicin is added for higher-stage patients. Although doxorubicin is a very active agent in all WT, it confers both a greater risk of toxicity on therapy, largely due to myelosuppression, and a small but real risk of long-term cardiac toxicity [183]. Cyclophosphamide, ifosphamide, etoposide, and carboplatin are active chemotherapy agents with significant risk of toxicity that are reserved for high-risk patients, including some patients with diffuse anaplasia, Stage IV disease, poor initial response to therapy, and some patients with RTK and CCS. Toxicities of these drugs include significant myelosuppression and subsequent increased risk of serious infections, decreased renal function, hearing loss, hemorrhagic cystitis, and secondary leukemias (Table 4). Irinotecan, topotecan, and ifosfamide are also agents used in very high-risk patients, largely in the relapse setting [184, 185]. Very high-dose chemotherapy with stem cell transplant has been successful in some relapsed patients but has proven to be very difficult to study given the very small number of patients [186].

## Special Circumstance

Children with WT, particularly bilateral WT, are at risk for development of renal failure during treatment. Patients may become anephric if surgery is necessitated in critical areas of both kidneys. Patients with remaining renal tissue after surgery may develop renal failure due to chemotherapy agents or radiotherapy. The three main drugs use in newly diagnosed WT, vincristine, actinomycin, and doxorubicin, can be given safely and effectively to patients with renal failure [187]. In a review of 28 of 5,910 children registered on NWTS studies 1-IV, treated with chemotherapy with concomitant renal failure, it was concluded that reduction of dosing of these agents is not necessary and that reasonable cure rates were

**Table 4** Chemotherapy agents commonly used in renal tumors

| Drug | Category | Mechanism of action | Common toxicity[a] |
|---|---|---|---|
| Vincristine | Vinca alkaloid | Mitotic inhibitor; inhibition of microtubule assembly and cellular metaphase arrest | Vesicant, NT, A, SIADH, hypotension, A |
| Dactinomycin | Antitumor antibiotics | Intercalation; DNA strand breaks (Topo II) | M, N and V, A, mucostitis, vesicant, hepatic (VOD) |
| Doxorubicin | Antitumor antibiotics | Intercalation; DNA strand breaks (Topo II); free radical formation | M, mucostitis, N and V, A, diarrhea, vesicant, cardiac (acute, chronic) |
| Cyclophosphamide | Alkylating agents | (Prodrug) alkylation; crosslinking | M, N and V, A, cystitis, water retention; cardiac (HD) |
| Etoposide | Plant products | DNA strand breaks (Topo II) | M, A, N and V, mucostitis, mild NT, hypotension, HSR, secondary leukemia, diarrhea (p.o.) |
| Carboplatin | Alkylating agents | Platination; crosslinking | M (Plt), N and V, A, hepatic (mild), HSR |
| Ifosfadime | Alkylating agents | (Prodrug) alkylation; crosslinking | M, N and V, A, cystitis, NT, renal; cardiac (HD) |
| Topotecan | Plant products | DNA strand breaks (Topo II) | M, diarrhea, mucostitis, N and V, A, rash, hepatic |
| Irinotecan | Plant products | (Prodrug) DNA strand breaks (Topo II) | M, diarrhea, N and V, A, hepatic, dehydration, ileus |

[a]*M* myelosuppresion, *SIADH* secretion of inappropriate diuretic hormone, *a* alopecia, *N* and *V* nausea and vomiting, *nt* neurotoxicity

observed. These patients do require close individual monitoring and accurate pharmacologic and pharmacokinetic studies are vital.

## Radiation Therapy

WT is very radiosensitive, and it was this modality that offered the first true cures in WT. However, radiation therapy carries the risk of significant long-term toxicities, including secondary malignancies, scoliosis, radiation pneumonitis, cardiac toxicity, pregnancy-related complications, and renal compromise or failure. Early NWTS and SIOP studies have both demonstrated that low-stage patients could be cured without radiotherapy, therefore radiation therapy is reserved for patients with higher-risk disease [120, 152, 188]. The appropriate use of radiation therapy in patients with FH WT is still being investigated. Patients with stage IV pulmonary disease have been shown to have better outcome with radiation therapy on NWTS compared to similar patients treated on a UK Children's Cancer Study Group trial [120, 163]. However, SIOP studies show good outcomes while withholding radiation therapy in a subset of patients with initial pulmonary disease that resolves quickly with chemotherapy [163]. Building on this, the first COG study for patients with higher-risk (Stage IV) FHWT was designed to protocol to assess whether patients treated with a backbone of NWTS therapy that show resolution of pulmonary metastasis within 6 weeks can safely avoid radiation therapy. Preliminary results show that an EFS of 75 % was maintained in the group of patients with complete pulmonary response after 6 weeks of initial chemotherapy (vincristine, actinomycin, and doxorubicin) who were spared lung radiation [189].

## Screening

For patients with genetic syndromes associated with increased risk of developing WT, routine radiological surveillance is recommended. Although not unanimously agreed upon, a schedule of US every 3–4 months through age 7 has

been shown to aid in detection of WT and proposed to be cost effective in identifying tumors at an earlier stage [190–192].

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