Wilms tumour

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ABSTRACT

Wilms tumour (WT) is a childhood embryonal tumour that is paradigmatic of the intersection between disrupted organogenesis and tumourigenesis. Many WT genes play a critical (non-redundant) role in early nephrogenesis. Improving patient outcomes requires advances in understanding and targeting of the multiple genes and cellular control pathways now identified as active in WT development.

Decades of clinical and basic research have helped to gradually optimize clinical care. Curative therapy is achievable in 90% of affected children, even those with disseminated disease, yet survival disparities within and between countries exist and deserve commitment to change. Updated epidemiological studies have also provided novel insights on global incidence variations.

Introduction of biology-driven approaches to risk stratification and new drug development has been slower in WT than in other childhood tumours. Current prognostic classification for children with WT is grounded on clinical and pathologic findings and in dedicated protocols on molecular alterations. Treatment includes conventional cytotoxic chemotherapy and surgery, and radiation therapy in some cases. Advanced imaging to capture tumour composition, optimising irradiation techniques to reduce target volumes, and evaluation of newer surgical procedures represent key areas for future research.

INTRODUCTION

Wilms tumour (WT) is the most common renal tumour in infants and young children[1,2]. WT is intimately linked to early nephrogenesis, which it resembles morphologically[3] and transcriptionally[4,5]. WT may occur sporadically or in the context of bilateral tumours, multifocal disease and specified genetic predisposition syndromes that frequently include either genitourinary malformation or overgrowth[3]. Beyond genetic predisposition, external causative factors for WT are not yet defined. The molecular drivers frequently involve blockade of genetic pathways that guide normal embryogenesis of the genitourinary tract but are not restricted to these. Indeed, the genetic changes that underpin WT are diverse and surprisingly involve ~40 genes.

The implementation of international co-operative group trials and studies across North America, Australia, New Zealand, Europe and Brazil has contributed significantly to improved outcomes[6–8]. Two international multidisciplinary cooperative consortia — Children's Oncology Group (COG) Renal Tumour Committee, previously known as the National Wilms Tumour Study Group (NWTSG) and International Society of Paediatric Oncology (SIOP) Renal Tumour Study Group (RTSG) — have conducted large multicentre studies since 1969 and 1971 respectively, which have defined the current diagnostic and therapeutic approach to patients with WT (**FIG. 1**). These groups continue research to optimize disease and patient risk classification, and treatment strategies[9–11].

In the COG, WTs are treated with primary resection (if possible), followed by risk-adapted adjuvant therapy, whereas in the context of SIOP cooperation, neoadjuvant chemotherapy followed by resection and adjuvant therapy is the preferred treatment approach. Regardless of the initial approach, the overall survival for children with WT is remarkable with rates of >90%. Such satisfying survival rates have been achieved at the same time as fine-tuning treatment by adopting well-studied prognostic factors, leading to a two drug regimen (vincristine and actinomycin D) prescribed in nearly two thirds of affected children[7,10]. Notably, striking survival disparities still exist within countries[12] and between different parts of the world, which remain to be addressed[13,14]. However, 20% of patients relapse after first-line therapy and up to 25% of survivors report severe late morbidity of treatment[15,16]. Addressing the long term effect of radical nephrectomy on renal function and cardiovascular function will likely drive more attention on expanding the role of nephron-sparing surgery (NSS)[17].

Molecular studies are expanding the landscape of cancer genes implicated in WT beyond exclusive roles in nephrogenesis[3]. The use of next-generation integrative genomic and epigenomic tumour analysis have provided important insights on WT biology. Comparisons of progenitor cell regulation in fetal kidney with their disrupted counterparts in WT should provide further insights into tumour formation[18]. Targeting WT tumour genes with a non-redundant role in nephrogenesis and targeting the fetal renal transcriptome warrant further therapeutic exploration. Interventions that could prevent the evolution of nephrogenic rests to malignant WT could transform therapy in this setting and even lead to preventative strategies in children known to be at high risk of developing WT.

This Primer describes our current understanding of WT epidemiology, disease susceptibility and mechanisms, as well as elements of clinical care, including diagnostics and risk-stratified treatment of newly-diagnosed disease. In addition, we also outline potential opportunities to further translate new biological insights into improved clinical outcomes. We discuss how the widespread implementation of standardized diagnostics and treatments for as many children as possible, regardless of socioeconomic status or geographic region of origin, may propel further clinical advances.

EPIDEMIOLOGY

Global disease burden

Malignant renal tumours comprise 5% of all cancers occurring before the age of 15 years[19]. Every year ~14,000 children (0–14 years of age) are diagnosed worldwide and 5,000 children die from these diseases, with regional variation in mortality **(FIG. 2)**[20]. The incidence of childhood renal tumours is not associated with economic status, but mortality is higher in low-income areas than higher income areas (0.5 per million in high-income areas versus 7.5 per million in low-income areas).

WT is the most common renal tumour in children[1] and studies have reported variation in incidence between regions or ethnicities **(FIG. 3)**[2,21]. The annual incidence rate of WT in East Asia is lower than in North America or Europe (4.3 per million versus 8–9 per million)[2]. In the USA, children with Afro-American ancestry have the highest incidence (9.7 per million) whilst those with Asian-Pacific Islander ancestry have the lowest (3.7 per million)[2]. However, owing to the lack of population-based childhood cancer registries in resource-constrained regions, or because of the low quality of the data (that is, not all cancers are reported or not all children are reported), the estimation of global incidence has been difficult[14,22,23]. In addition, 50% of patients from areas with less resources have metastases at diagnosis[24].

Up to 17% of WT occur as part of a recognizable malformation syndrome[25], 10% of which are associated with known WT predisposition **(TABLE 1)**[26]. Overgrowth syndromes, in particular Beckwith–Wiedemann syndrome carry ~5% risk of developing WT, ranging from 0.2% to 24% according to the underlying genetic cause[27–29]. Syndromes involving genitourinary anomalies combined with aniridia and variable intellectual disability, or with nephrotic syndrome are associated with mutations of the gene *WT1* on chromosome 11p13 and carry a greatly increased risk of developing WT[3,30,31].

No temporal trends in the incidence of WT was observed within the period 1996–2010 (Ref[2]), suggesting that environmental factors play a marginal role in WT aetiology. Nevertheless, modifiable risk factors for WT are not well understood.

Influence of sex and age

WT is one of the few childhood cancers that is ~10% more common in girls than in boys[19]. The age-specific incidence of WT peaked at 1 year of age in boys at 17.9 per million person-years. However, in girls, a similar peak remained almost constant at 1, 2 and 3 years of age, with the respective incidence of 17.8, 18.0 and 18.1 per million person-years **(FIG. 4)**.

WT often presents as a solitary lesion, but ~7% are reported to be multicentric and 5–9% bilateral[1,2,32]. Unilateral tumours occur at a slightly older age than bilateral ones **(FIG. 4)**. The age distribution at diagnosis varies by region and ethnicity, with patients with WT in East Asia being younger at diagnosis than those in the rest of the world, and this observation may be mainly due to earlier onset of the disease[2,21,33] **(FIG. 4)**. As one possible reason of the variation in age at onset, somatic tumour genetic analysis shows a lower frequency of tumours with *H19–IGF2* loss of imprinting among Japanese patients with WT than in Caucasian populations[34]. *H19–IGF2* loss of imprinting driven WTs are associated with overgrowth syndromes and with perilobar nephrogenic rests; both these features are more common in Caucasian children at diagnosis than in Japanese children (median age at diagnosis was 39 months in UK patients with WT versus 28 months in a similar Japanese patient cohort)[33–35]. The observation of the incidence peak in infancy and the lower total incidence in East Asian population is consistent with the genetic origin of WT aetiology.

Studies with large samples from many countries and different ethnic groups will be needed to validate the likelihood that the genetic heterogeneity of WT explains this variation in clinical features by ethnicity.

MECHANISMS/ PATHOPHYSIOLOGY

WT is an embryonal malignancy thought to arise through abortive or disrupted development[36]. During kidney embryogenesis, intermediate mesoderm differentiates into metanephric mesenchyme, which condenses around the branching ureteric bud structures. This metanephric mesenchyme undergoes a mesenchymal to epithelial transformation to form renal vesicles, which expand and give rise to the majority of cell types of the functional kidney[37]. In WT, this process can be disrupted at different levels leading to variable mixtures of blastemal, epithelial and stromal cells that may even exhibit myogenic differentiation. Histology is partly shaped by the underlying genetic defects but may also reflect the timing of divergence from normal nephrogenesis **(FIG. 5**.

Our understanding of the genetic cause of WT has long been limited to mutations of *WT1*, *CTNNB1* and *WTX* as well as loss of *H19–IGF2* imprinting, but these alterations only explain a subset of cases[38]. Additional features like allele loss on chromosomes 1p and 16q or gain of 1q may underpin aggressive clinical behaviour in some cases but do not provide mechanistic insight into tumour development or therapeutic targets[39–41]. Next generation sequencing analyses have unveiled many additional drivers, mostly chromatin-modifying and transcription factors as well as miRNA processing genes, many of which are involved in normal renal development **(TABLE 2; Box 1)**[42–44]. A surprisingly large fraction of WT (up to 17%) occur in the context of genetic malformation syndromes associated with tumour predisposition **(TABLE 1)**[25]. The paradigms are WAGR syndrome and Beckwith–Wiedemann syndromes, which led to the identification that defects in the tumour suppressor gene *WT1* and loss of *H19–IGF2* imprinting predisposes to WT.

WT1, CTNNB1 and stromal WT

WT1 was originally identified through homozygous deletions in WT[45,46]. Nevertheless, the functions of this zinc finger protein are more complex — germline inactivation leads to male genitourinary anomalies, such as hypospadias, cryptorchidism, through haploinsufficiency and an increased risk for developing WT (>50%)[47]. Additionally, dominant negative mutations, especially of the zinc finger proteins that abrogate DNA binding lead to Denys-Drash syndrome with intersex and renal failure due to diffuse mesangial sclerosis and a >90% increased WT risk[48]. Of note, Frasier syndrome, where intronic mutations prevent formation of certain *WT1* splice isoforms rather than altering the WT1 protein amino acid sequence, includes different forms of intersex and renal failure, and carries a risk for gonadoblastoma in streak gonads rather than WT[49,50].

Mutations in *WT1* are often paired with frequent alterations of *CTNNB1,* which lead to constitutive Wnt signalling[51]. In most cases, point mutations or deletions are observed in the phosphodegron motif in exon 3, leading to ß-Catenin stabilization and nuclear accumulation, where it acts as co-activators with the TCF–LEF transcriptional factors. These tumours usually exhibit stromal predominant histology, decreased response to preoperative chemotherapy and represent up to 15% of cases in Caucasian populations[52]. Notably, although the incidence of WT in Japanese children is only 50% of that found in Caucasians, an increased rate of *WT1* mutations (81%) are observed in bilateral cases, which points to differences in genetic constitutions[53]. *WT1*-driven stromal tumours occur at a median age of 22 months and are characterized by the presence of intralobar nephrogenic rests as presumed precursor lesions. *WTX* may likewise facilitate Wnt signalling as it is part of the

ß-Catenin degradation complex. Mutations or loss of expression of *WTX* are observed in up to 30% across histological subtypes, but with intratumoural heterogeneity, suggestive of a late event[54].

H19–IGF2 imprinting

Chromosome 11p15.5 is frequently altered in WT through copy-neutral loss of heterozygosity with invariant loss of the maternal allele or loss of imprinting with epigenetic changes on the maternal allele. The net outcome being hypermethylation of the imprinting center IC1 with elevated expression of the neighbouring growth factor gene *IGF2* and the long non-coding RNA *H19*, among others. With ~70% incidence of such alterations, overexpression of *IGF2* is the most frequent change in WT[43,44,52]. However, tumour initiation must need additional events as loss of imprinting occurs somatically in Beckwith-Wiedemann syndrome, conferring an elevated, yet still limited WT risk, which varies depending on the pathomechanism involved[27].

microRNA biogenesis mutations

An unexpected addition to WT driver genes is microRNA (miRNA) processing genes. miRNA biogenesis covers a stepwise maturation process from pri-miRNA via pre-miRNA to mature miRNA. Mutations in WT primarily affect the so-called microprocessor genes *DROSHA* and *DGCR8*, which are involved in pri-miRNA processing[43,44,55,56]. Heterozygous *DROSHA* mutations tend to inactivate the catalytic core of one of the two RNAse III domains that processes pri-miRNA molecules. *DGCR8* mutations affect a single amino acid (E518K) in one of the double-stranded RNA binding domains and the mutations occur homozygously or with monoallelic expression of the mutant. The net result is a reduced and unbalanced miRNA processing. *DGCR8* mutations has been observed predominantly in girls, which remains to be explained.

DICER1, which encodes the second RNAse III type enzyme, is rarely mutated in WT, but predisposes to pleuropulmonary blastoma and is implicated in the very rare entity, anaplastic sarcoma of kidney[57,58]. The catalytic centre is often mutated on the single functional allele, leading to a partial processing defect with a deficiency in miRNA-5p and largely unaffected miRNA-3p levels.

Studies have reported further mutations in *XPO5* (encoding exportin 5), the *DICER1* cofactor *TARBP2* and downstream *let-7* miRNA modulators such as *DIS3L2* or *LIN28B* at a lower frequency in the 1% range and the mechanistic details are yet unclear. Nevertheless, almost all steps of miRNA biogenesis can be critically altered to drive WT formation and several of these mutations are rather specific to WT. The fact that most mutations do not fully abrogate miRNA production implies that specific miRNA subsets are important to control deviation from regular developmental progression or cell proliferation and survival.

MYCN and transcriptional control

Alterations in *MYCN* may contribute to WT biology in several ways. Elevated expression levels have been described especially in relapsing and fatal cases. Furthermore, studies have identified specific P44L point mutations or copy number gains with one or a few additional copies[44,55,59]. Proline 44 is located immediately upstream of the conserved MYC box I that interacts with AURKB, FBXW7 (Ref[60]) and GSK3 to control N-Myc stability. Stabilization occurs through dephosphorylation at Threonine-58 by the phosphatase EYA1, which is recruited to the nucleus by the transcription factor SIX2 (Ref[61]). This process provides a direct link to the paralogous genes *SIX1* and *SIX2* that control early kidney development. *SIX1* and *SIX2* can be found as drivers of blastemal predominant WT if their DNA binding domain becomes subtly altered by stereotypic Q177R mutations[44].

Intriguingly, several MYC-interacting protein complexes can be targets of mutations in WT. The obligate heterodimerization partner MAX can exhibit R60Q mutations in the helix-loop-helix domain to alter its transcriptional potency. N-Myc exerts its effects on transcriptional control through a multitude of interactions with the core transcriptional machinery to regulate polymerase pausing. The PAF1 transcription complex is one of the critical interactors in this respect and several of its components like *CDC73*, *MLLT1–ENL* and *CTR9* were shown to be mutated in familial and sporadic cases of WT[62]. Collectively, these data indicate that *MYCN* hyperactivity through various means can contribute to WT through a multitude of mechanisms.

Epigenetic modifiers

A striking genotype phenotype correlation is observed in epithelial predominant WT, which is often driven by inactivating *TRIM28* mutations (Ref[63–66]). Gene expression analyses have identified these tumours as more mature, post-induction tumours with excellent prognosis. *TRIM28* is part of a chromatin silencing complex that has an important function in the repression of endogenous retroviral transcript in embryonic cells. Indeed, these tumours show strong induction of transcripts from repetitive elements, but the mechanistic links to oncogenic transformation in these tumours with otherwise few mutations remains to be established.

Besides *TRIM28*, studies have described a whole array of epigenetic regulators as potential drivers in WT. These regulators include *REST*, *RERE*, *CHD4*, *KDM3B*, *BCOR* and *BCORL1*, which are all components of large protein complexes with diverse enzymatic activities[42,44]. There is a spectrum of dominant and recessive as well as truncating or missense mutations, some being heritable. Intriguingly, *BCOR* is also the main culprit to drive clear cell sarcoma of the kidney, another childhood renal tumour. In this case the gene is not inactivated as in WT, but harbours small C-terminal tandem duplications corresponding to ~30 amino acids that encompass the binding domains for *PCGF-1* and *KDM2B* as part of the polycomb repressive complex (PRC1) that controls, for example, mesodermal differentiation[67,68].

***TP53* and anaplasia**

WTs generally have a low mutation load that increases with patient age, and karyotypes tend to be stable[43,44]. However, the mutation load is different in diffuse anaplastic WT, which frequently harbour oncogenic *TP53* mutations and consequent genomic instability. In most cases, the wild-type allele is lost and the cells are characterized by chromosomal instability including chromothripsis and deregulation of cell cycle and DNA repair genes[59,69–71]. *TP53*-mutated tumours exhibit strong positive p53 staining owing to the accumulation of the mutant protein, although a smaller fraction demonstrate negative staining due to null mutations. *TP53* alterations are secondary events in WT progression, in line with WT being reported as a rare feature in Li-Fraumeni syndrome[72].

Whether *TP53* mutation confers an additional risk independent of the high-risk status of morphological anaplasia is still unknown. Several other genes that fall into the category of genome maintenance and repair, such as *BRCA2*, *PALB2* or *TRIP13*, have been found to be mutated in WT[73]. Whether such mutations likewise increase mutation load or chromosomal aberrations remains to be determined, and no reports are available on aneuploidy yet.

Nephrogenic rests

The underlying genetic defects also have an impact on the presence of nephrogenic rests in the kidney that occur in 30–40% of cases[74,75]. These precursor lesions are foci of embryonic renal cells that abnormally persist beyond 36 weeks of gestation. Nephrogenic rests are histologically and anatomically classified as either perilobar or intralobar[74]. *WT1*-related WTs frequently carry few

intralobar nephrogenic rests, centrally-located within or adjacent to the renal medulla, suggestive of an early developmental lesion. *TRIM28*-associated or Beckwith–Wiedemann syndrome-associated WTs tend to harbour perilobar nephrogenic rests in the adjacent kidney tissue rather than intralobar nephrogenic rests. These perilobar nephrogenic rests may even encompass the entire renal cortex in extreme cases. Although few samples have been assayed thus far, nephrogenic rests seem to carry even fewer mutations than their adjacent WT[5,76,77].

Bilateral Wilms tumour

Almost one in ten children present with bilateral WT or bilateral disease (WT with nephrogenic rests or nephroblastomatosis visible on imaging in the contralateral kidney), especially in syndromic cases[32]. *WT1* is the most prominent driver in these cases[32,52], together with specific imprinting abnormalities at 11p15 affecting *IGF2*, though neither explain the majority of cases. *TRIM28* inactivation is also frequent in bilateral and familial tumours[64–66,73]. Importantly, findings show that bilateral tumours can be due to early postzygotic founder mutations in somatic cells that emerge before the divergence of left and right kidney primordia[5]. Individual clones may expand to yield mosaic kidneys with molecular evidence of clonal (mosaic) nephrogenesis. Thus, it may be justified to compare bilateral or multifocal tumours with blood and surrounding normal kidney tissue as controls to differentiate putative germline mutations, postzygotic mosaic events or single tumours with metastatic disease.

Heterogeneity and subclassification

Molecular analysis has unveiled intratumoural heterogeneity of WTs, with either chromosomal copy number alterations or mutations, for example, in *WTX* or *TP53* being present in only a fraction of cells as evidence of tumour evolution[78]. These differences may become clearer with single cell or single nucleus analyses, which already highlighted a great cellular diversity[4]. Even the main driver genes stratify WTs according to age (for example, *TRIM28*, *WT1* at younger age (generally occurring <2 years of age), *TP53* (occurring generally >4 years of age, and Beckwith–Wiedemann syndrome at later age (occurring at 3–4 years of age)), location of nephrogenic rests (intralobar versus perilobar), or histology (*WT1* – stromal, *TRIM28* – epithelial and *TP53* – anaplastic) **(FIG. 5)**. Nevertheless, the majority of triphasic or blastemal predominant WT do not carry defining genetic alterations.

Liquid biopsies

Although WT represents >80% of paediatric renal tumours, other intrarenal tumours exist that are important to differentiate as therapeutic approaches are markedly diverse[31]. These non-Wilms renal tumours are often characterized by rather specific molecular alterations **(FIG. 5)**. These tumours may become amenable to liquid biopsy diagnostics looking for diagnostic changes or entity-specific patterns of methylation[79]. In particular, if neo-adjuvant chemotherapy approach is planned and the clinical pattern is unusual, such tests will become helpful to rule out non-WT from the start, or to follow response to treatment during follow-up. The fact that patients with paediatric kidney tumours often have large amounts of circulating tumour DNA makes this approach rather promising[80].

Tumour models

Modelling WT in the mouse has been difficult with only few successful scenarios, the first using *Wt1* ablation together with *Igf2* upregulation[81]. Other researchers have successfully employed *Lin28* overexpression or *Dis3l2* mutation[82,83]. On the other hand, prototypic *Drosha* mutations or *Wtx* deletions did not yield evidence of WT formation but led to either kidney agenesis or aberrant kidney development and functional impairment[84,85].

Modelling efforts, including patient-derived xenografts (PDX)[86], can now be complemented with spheroid and organoid techniques to grow tumour cells *in vitro* for genetic and histologic characterization and for therapeutic compound testing[87–89]. These models will become an invaluable resource to test novel agents in relapsing cases that poorly respond to conventional regimens, provided a time frame suitable for clinical feedback can be accomplished[90].

DIAGNOSIS, SCREENING AND PREVENTION

Clinical presentation

Most children with WT are asymptomatic at presentation and predominantly have a distended abdomen with a palpable mass[91]. Frequently, the parents notice such a mass during dressing or cuddling. Alternatively, WT is identified by the general practitioner or the paediatrician during a regular clinical assessment of a well-child or a child with non-specific symptoms. WT usually reveals a non-tender, large flank mass, which does not move with respiration in contrast to splenomegaly. Approximately only one in five children have distinct symptoms; pain, haematuria, fever, hypertension, urinary tract infections, constipation and weight loss are among the most common complaints at presentation[31,91]. Although rare, symptoms related to metastases, such as dyspnoea (lung), abdominal pain (liver) or tumour thrombus in the renal vein or vena cava, or varicocele may occur[92]. Ultimately, a few children with severe subcapsular haemorrhage may present with rapid abdominal enlargement, anaemia and severe pain. Age at presentation is typically from 2–5 years and incidence of WT in children >10 years is rare. In children with known predisposing syndromes, WT may be captured during routine screening and often at an earlier age or stage and these children are even more likely to be asymptomatic than children without predisposing syndromes[93].

In low-income countries (LICs), usually interactions between multiple factors contribute to a delayed diagnosis compared with high-income regions (HICs)[94,95]. These factors include family or relatives' awareness of a possible cancer, contacting and arrival to primary care, health care staff recognition of cancer and transfer to tertiary care. Furthermore, a much higher number of children in LICs have a distended abdomen due to other conditions, for example, malnutrition, parasitic infections and benign blood diseases than high-income regions. Hence, identifying, differentiating and prioritizing investigations of the relatively few cases of WT is challenging. Moreover, the latency to diagnosis (patient interval and diagnostic interval) prolongs further, as diagnosis is not only dependent on the recognition by the family, but also by the lack of awareness by the primary care medical personnel and poor referral networks[96]. These factors result in a larger proportion of children presenting with symptoms, a larger tumour volume, more advanced local stage and a higher percentage with metastases in low-income regions than high-income regions[14,24].

Diagnosis, classification and staging Diagnosis of WT can be made reliably on histology, especially in cases where all three characteristic components — blastemal, epithelial and stromal — are evident. These components may be mixed in any proportion, but WTs showing one or two components are not rare. Epithelial and stromal components may show different lines of differentiation and degrees of differentiation, resulting in a countless number of histological appearances **(FIG. 6)**. WTs composed of only one component may represent a diagnostic challenge and ancillary techniques may be needed to establish the diagnosis[97]. However, no immunohistochemical markers or molecular biology findings are 100% specific for WT. In addition, preoperative chemotherapy, when used, alters the histological appearance of WT, and may result in marked tumour necrosis, or maturation of tumour components. Approximately 7–8% of

WTs demonstrate anaplasia, defined as the presence of cells with hyperchromatic, pleomorphic nuclei that are three times larger than adjacent cells and have atypical mitotic figures[98], and it may occur in any tumour component (blastemal, epithelial, or stromal). The definition of anaplasia was further refined to specify whether the anaplasia is diffuse or focal based on the anatomical distribution of anaplastic cells within the tumour[99]. Focal anaplasia is diagnosed as clearly defined one or two foci showing the above-mentioned nuclear criteria with sharp demarcation within the primary intrarenal tumour and without evidence of anaplasia or prominent nuclear atypia (defined as nuclear unrest) in other areas. According to SIOP, up to two foci up to 15 mm in size is allowed for the diagnosis of focal anaplasia[9] whereas according to COG, up to four foci up to 20 mm in size is allowed[99]. Diffuse anaplasia is defined as nonlocalized anaplasia, which may present in any of these situations: focal anaplasia with marked nuclear unrest in the non-anaplastic tumour; anaplasia beyond the tumour capsule; anaplastic cells in intrarenal or extrarenal vessels, renal sinus, extracapsular sites, in metastases, or in biopsy. Despite well-established criteria, anaplasia represents a diagnostic problem, with ~30–50% discrepancy between institutional pathologists and central pathology review[100,101]. Anaplasia is very rare in the first two years of life, and increases after four years of age. Anaplasia is usually neither obliterated nor induced by preoperative chemotherapy.

As SIOP and COG have different treatment initial strategies, relevant differences exist in histological classifications of WTs between the two groups. COG classification includes anaplastic (focal and diffuse) and non-anaplastic (favourable histology) WTs based on assessment of a chemo-naïve tumour after up-front surgery. SIOP classification is based on the assessment of percentage of preoperative chemotherapy-induced changes and viable tumour components, and includes three major WT risk groups, low-risk (completely necrotic WT), high-risk (blastemal type and diffuse anaplasia) and intermediate-risk tumours (all other types) **(Table 3)**. To correctly subclassify the WT, the percentages of chemotherapy-induced changes and viable tumour components are assessed and taken into account[9]. COG has reported histology and outcomes for patients not eligible for up-front surgery using the SIOP post-chemotherapy histological classification system but to date has not used this system to guide subsequent treatment in unilateral cases[102]. The staging criteria between COG and SIOP also differ, making a direct comparison of outcomes stage-by-stage difficult **(Supplementary TABLE 1)**.

Diagnostic imaging

Abdominal ultrasonography is efficient and globally the most available means of investigating suspected WT[103]. Ultrasonography provides information about the organ of origin, extension into the renal and inferior cava veins or urinary collecting system, the contralateral kidney, associated urogenital abnormalities and may identify liver or lymph node metastases. In resource-limited regions, ultrasonography is sufficient for abdominal staging and can be complemented by chest X-ray, recognizing that X-ray may miss smaller pulmonary lesions (typically <1 cm)[95,104]. In better-resourced settings, cross-sectional imaging is usually undertaken preoperatively with abdominal CT or MRI[105]. The main drawback of CT is radiation exposure but the procedure is rapid, allows continuous imaging of the chest and abdomen, has moderate specificity for detection of preoperative spill, may help distinguish nephrogenic rests from WT and gives excellent pulmonary detail[106–108]. Noteworthy, COG and SIOP incorporate centrally-reviewed CT identification and response to therapy of lung nodules into current risk stratification treatment algorithms[10,109]. The main hurdle of abdominal MRI is that moderate to deep sedation is often required in young children but it provides excellent organ details for bilateral disease or liver metastases. Abdominal MRI is preferentially recommended for better assessment of potential nephrogenic rests and their distinction from true WT, and in SIOP to attempt correlating apparent diffusion coefficient mapping with histopathology prediction after preoperative chemotherapy[105,110].

Fluorodeoxyglucose (FDG)-PET imaging is not routinely used for WT[105]. Bone scan or cross-sectional imaging of other sites is reserved for patients with signs or symptoms suspicious for distant extra-pulmonary metastases. Non-pulmonary and non-hepatic metastatic disease are very rare at primary diagnosis of non-anaplastic WT and is more likely observed in anaplastic WT, clear cell sarcoma of the kidney, malignant rhabdoid tumour, renal cell carcinoma or at WT relapse[111–113].

Laboratory testing

Baseline blood work should be drawn to confirm adequate renal function, support subsequent chemotherapy and to rule out acquired von Willebrand's disorder, which although uncommon may be associated with substantial bleeding risks and can be pre-emptively managed[114].

SIOP diagnostic algorithms recommend percutaneous image-guided coaxial core needle biopsy through a retroperitoneal approach for patients 7 years of age or older or for patients with imaging findings unusual for WT (psoas muscle infiltration, numerous calcifications, vessel encasement or massive lymphadenopathy)[10,115,116]. The currently-used cut-off of 7 years to consider a biopsy is under revision, and based on epidemiological data describing peak of incidence of WT versus other non-WTs[2], a new consensus towards raising the age threshold for biopsy providing there are no other atypical presenting features, is forming[105,115]. COG recommends all patients be strongly considered for primary nephrectomy, but if not feasible, open or tru-cut needle biopsy should be undertaken with a minimum of 10–12 cores. Notably, needle biopsy cannot reliably distinguish WT from nephrogenic rests, and often misses anaplasia[115].

Patients with syndromic features should be referred to medical genetics for counselling and possible testing. Circulating blood or urine tumour DNA is being explored for diagnostic and response or relapse assessment but is not yet standard of care[80,117,118].

Prognosis and prognostic features

It is important to recognise that prognostic markers must be interpreted in the context of the accompanying treatment regimen. This principle is relevant to WT as COG studies advocate for immediate nephrectomy for most patients whereas SIOP studies advocate for preoperative chemotherapy[119]. Thereafter, prognostic factors used for clinical treatment stratification differ between COG and SIOP[120,121]. In both groups, tumour histology and stage are key prognostic indicators, although applied differently and together with other factors in clinical practice. Diffuse anaplasia is regarded as high-risk tumour in COG and SIOP, whereas focal anaplasia is regarded as intermediate-risk tumour in SIOP but as high-risk in COG. In SIOP, blastemal type after preoperative chemotherapy is also regarded as high-risk tumour and completely necrotic type as low-risk tumour[122] **(TABLE 3)**. Similarly, staging criteria are also different; for example, any tumour biopsy results in upstaging in COG to local stage III whereas in SIOP, fine needle aspiration and percutaneous core needle biopsy are ignored for staging purposes[31], and the presence of necrotic tumour or chemotherapy-induced changes in the renal sinus, renal veins and/or within the perirenal fat is not a reason for upstaging to stage II in SIOP[9] **(Supplementary table 1)**. Some of SIOP criteria have undergone important changes in comparison with the previous SIOP–2001 trial and study criteria. For example, in the current SIOP protocol, the presence of nonviable tumour or chemotherapy-induced changes only at a resection margin is not regarded as stage III[9].

Other prognostic factors in SIOP include tumour histological response to preoperative chemotherapy and tumour volume (>500 ml) after chemotherapy for certain WT types. Additional prognostic factors in COG include age, tumour weight and biomarkers or tumour biology, that is, loss of heterozygosity for chromosomes 1p/16q, loss of heterozygosity at chromosome 11p15, and

gain at chromosome 1q[121]. For both groups, response of lung metastases to neo-adjuvant chemotherapy indicates chemosensitivity and dictates the intensity of subsequent treatment; for example, if lung lesions are not present at 6 weeks after induction chemotherapy, radiotherapy can be omitted in some patients[109,123].

Although the SIOP and COG strategies differ in their upfront treatment approach, overall survival rates are similar at ~90%[7,39,124]. Patients with stage IV anaplastic WT and/or blastemal type WT have substantially poorer outcomes, with an overall survival rate of <50% despite very intensive therapy[125,126].

Despite the good prognosis for most children with WT, ~20% of patients will relapse, predominantly within two years of diagnosis[113,127,128]. Overall survival rate after relapse is ~50% but varies considerably according to the initial treatment received (which in turns reflects initial tumour stage and histology), time to relapse, site of relapse, and patient age[113,129,130]. Surveillance with abdominal ultrasonography and X-ray are offered, and patients with asymptomatic relapse detected by surveillance seem to have better outcomes[113]. Evidence from COG shows a lack of benefit for improved survival after relapse if CT imaging had been used instead of X-ray and ultrasonography in follow-up surveillance[128]. SIOP data also suggest surveillance beyond two years post completion of therapy has low yield because of the extremely low relapse rate thereafter[113].

Screening

Genetic testing in children with cancer but also in other (potentially) unhealthy children presenting with certain abnormalities or syndromes is emerging. This testing includes formalized national and regional whole exome or genome sequencing programs to detect cancer predisposition in many HICs. Accordingly, both novel genes and syndromes associated with WT are revealed as well as identification of additional children with an increased risk of developing WT, expanding the criteria for screening programs[131]. Regular screening for early diagnosis in children with a known WT predisposition syndrome is reported to detect smaller and lower-stage tumours but robust evidence is lacking regarding the balanced clinical benefits[93]. In addition, the benefits should outweigh the costs and burden. The latter is reflected in the different thresholds for performing screening, which typically varies between 1–5% childhood risk of developing WT[29].

Screening is typically offered to children with various cancer predisposition syndromes, such as *WT1*-related syndromes and Beckwith–Wiedemann syndrome or isolated hemihypertrophy (with at least one Beckwith-Wiedemann syndrome feature). Renal ultrasonography is the recommended screening modality, which avoids radiation and does not require anaesthesia in young children. The screening interval is every three months based on the rather rapid growth rate of the tumour and imaging should be performed by an experienced paediatric ultrasonographer[93]. Screening should start when the WT predisposition is established and continue, irrespective of the underlying condition, until the child is approximately seven years old. At this age, the risk of WT development is greatly reduced[29].

The purpose of WT screening is to enable early nephron-sparing surgery, to give less intensive (that is, less toxic) chemotherapy, and to avoid radiotherapy. Patients with predisposition syndromes may develop metachronous WT in the contralateral kidney. Hence, the aim is, on balance, to preserve maximal kidney function and ultimately avoid end-stage renal disease whilst still maintaining oncological control. Genetic testing, screening and nephron-sparing surgery in LICs are rarely available and consequently, more children progress and succumb to end-stage renal diseases in

settings with limited options for dialyses and/or renal transplantation than in high-income regions[132]. High-income regions are researching the potential for (epi)mutation detection in circulating tumour DNA for early diagnosis; however, this detection technique is not yet ready to be used as an alternative to surveillance with ultrasonography in clinical practice[117,118,133].

MANAGEMENT

Nephrectomy with adequate lymph node sampling is universally the mainstay of treatment for WT. However, the timing of surgery differs between SIOP and COG, and underpins the differences in risk-stratification[134,135]. The SIOP WT studies have centred around pre-nephrectomy therapy since their beginning in 1971. Neo-adjuvant chemotherapy allows for assessment of *in vivo* histological response to treatment (that is, completely necrotic tumour indicates high responsiveness whilst a predominance of remaining blastemal cells is a marker of chemotherapy resistance), which may be used to guide therapeutic stratification after nephrectomy. According to SIOP protocols patients are divided into low-risk, intermediate-risk and high-risk groups mainly on the degree of tumour necrosis and the relative proportion of each of the three cell types (epithelial, stromal, or blastemal) remaining in the viable component of the resected tumour. On the other hand, the COG approach of upfront nephrectomy allows for immediate histologic diagnosis, molecular analysis of tumour samples unaltered by chemotherapy, and drug naïve local staging assessment (such as the presence of tumour spill or lymph node involvement). This knowledge can identify a subset of children with very low-risk tumours who may be treated with nephrectomy alone[136]. Each approach has its pros and cons, yet survival rates are similar with an overall survival rate of > 90%. In both groups, the management of WT incorporates risk-based adjuvant chemotherapy and radiotherapy informed by multiple prognostic factors[6] **(Supplementary table 2)**.

COG perspective

COG has a recommended strategy of primary nephrectomy for unilateral renal masses in patients without WT predisposition (achievable in >90% of cases) or failing feasibility of nephrectomy, core needle or open biopsy to guide subsequent therapy[135]. An exception to upfront biopsy is for bilateral or bilaterally-predisposed syndromic patients who should receive neo-adjuvant chemotherapy (without biopsy) with the aim of preserving renal-units, with surgery at 6 or 12 weeks after initiation of chemotherapy[137,138]. The primary surgery using a transabdominal or thoraco-abdominal approach allows accurate pre-chemotherapy staging including assessment of chemotherapy naïve histology and prognostic molecular testing. Essential surgical tasks in completing a tumour-nephrectomy include avoidance of tumour spill, ipsilateral hilar and regional lymph node sampling, and assessment and control of extra-renal tumour extension including renal vein and ureter[139–142]. Less conventional approaches such as laparoscopic nephrectomy, partial nephrectomy and split renal techniques may be carefully considered for patients with selected small tumours and in expert hands but at this point is confined to a small number of patients[143–146].

Chemotherapy is a mainstay of adjuvant therapy except in very low-risk tumours (defined as stage I, favourable histology WT, <550 g with negative lymph nodes and no syndromic features) where observation alone following nephrectomy may be sufficient, especially in the absence of loss of heterozygosity at chromosome 11p15(Ref[147]). Based on COG staging, the bulk of patients with favourable histology WT without certain adverse biomarkers receive regimen EE4A (vincristine and actinomycin D for 18 weeks) for stage I and II, or regimen DD4A (vincristine, doxorubicin and actinomycin D for 24 weeks) for stage III and stage IV favourable histology WTs[102,109,148–150]. COG

uses CT imaging to identify lung metastases although it is recognized that up to one third of lesions <1 cm in diameter may be benign nodules. Biopsy of lung nodules is encouraged if there is any doubt about the nature of the lesion. In addition, round, noncalcified lung nodules not in a fissure visible on chest CT scan are considered stage IV, regardless of size, unless histologically proven not to be WT[102]. The COG study AREN0533 demonstrated that ~40% of patients have complete resolution of pulmonary metastases after 6 weeks of three-drug induction therapy (regimen DD4A) and of these, patients with tumours without 1q gain can safely have radiation omitted[109]. Patients with incomplete response of lung nodules after 6 weeks of DD4A chemotherapy received whole-lung irradiation and escalated to chemotherapy regimen M.

In the setting of loss of heterozygosity at 1p/16q, evidence shows that intensifying therapy to regimen DD4A for stage I and II or to regimen M (DD4A + cyclophosphamide or etoposide) for stage III and IV improves event-free survival outcome[39,151]. Patients with diffuse anaplastic tumours seem to benefit from a multi-agent regimen UH-2 (Ref[125]). This regimen is associated with considerable toxicity and further modifications are currently being tested in COG protocol AREN1921 (NCT 04322318) **(Supplementary table 3)**. A variety of strategies for salvage of relapsed patients are used based on risk. Low-risk relapsed patients are usually managed with stratum B with an expected outcome of ~71% event-free survival rate[152] and higher risk relapsed patients are typically managed with regimen C[153] or ICE (ifosfamide, carboplatin and etoposide) with an expected outcome of ~42% event-free survival rate. Some centres use autologous bone marrow transplantation as consolidation therapy for high-risk patients but this strategy has never been the subject of a randomized trial to confirm efficacy[154]. A detailed summary of the impacts of the first generation of COG studies on WT was published in 2021 and forms the basis of standard management approaches in the COG for those patients not participating in a research study[155].

Newer COG research protocols are testing further refined chemo-algorithms incorporating stage, lymph node status, additional somatic molecular biomarkers, cardioprotection with dexrazoxane and new agents[40,102,125,151]. WT is highly radiosensitive[156]; radiation therapy is utilized for the regional management of stage III or IV favourable histology WT, relapsed and anaplastic WT. COG protocols are incorporating intensity modulated radiation therapy[157], and doses range from 10.6 to 30.6 Gy depending upon residual tumour and site[156,158]. National Cancer Cooperative Network[159] guidelines provide further detailed management guidelines and recommend that all children with renal tumours participate in a clinical trial.

SIOP perspective

According to the SIOP strategy, all patients with suspected WT >6 months of age receive either four weeks of preoperative chemotherapy with actinomycin D and vincristine (if localized) or six weeks of actinomycin D, vincristine and doxorubicin (if metastatic). SIOP-9 trial showed no advantage on down-staging to more stage I tumours nor on reducing intraoperative tumour rupture by further prolonging the pre-nephrectomy regimen to 8 weeks[160]. The SIOP approach accounts for the risk of misdiagnosis of WT by recommending upfront nephrectomy for infants <6 months old, and percutaneous core needle biopsy for older children (7 years and older) or children with uncertain clinical pictures[115].

Radical nephrectomy is regarded as standard in most of patients with unilateral WT; however, the systematic use of preoperative chemotherapy may extend nephron-sparing surgery opportunities in selected patients with unilateral non syndromic tumours[134] to maximize preservation of renal function in patients. Following surgery, the histopathological features of the tumour stratify patients into three risk groups **(TABLE 3)**[122]; the histological risk group together with tumour stage is used

to direct the intensity of adjuvant chemotherapy and the need for radiotherapy **(Supplementary tables 2 and 4)**.

The experimental arm of the SIOP-2001 trial has been adopted as the new standard regimen for most patients with stage II−III intermediate-risk histology WT[7,10]. This regimen consists of 27 weeks of postoperative treatment with vincristine and actinomycin D without doxorubicin. This schedule resulted in a non-significant decrease in event-free survival and had no effect on overall survival when randomly compared with the historical standard arm of 27 weeks of these two drugs (vincristine and actinomycin D) plus five doses of doxorubicin at 50 mg/m^7. The use of doxorubicin in patients with intermediate-risk stage II–III tumours is currently recommended only for non-stromal or non-epithelial type large-volume (that is, ≥500 ml after pre-nephrectomy chemotherapy) tumours, based on a post-hoc analysis conducted on SIOP 2001 cases[10].

Radiotherapy to the flank is administered to patients with stage II WT with diffuse anaplasia, stage III WT (intermediate-risk and all high-risk), and doses range from 14.4 to 25.2 Gy (±10.8 Gy boost only for macroscopic residual disease)[10,161]. To decrease organ toxicity whilst preserving oncological outcome, the conventional approach of flank irradiation is currently being adapted into a guideline for highly conformal image-guided flank target-volume delineation[162].

For metastatic disease, CT-only nodules are treated as metastases in the current SIOP protocol if they have a transverse diameter ≥3 mm and imaging appearance suspicious for metastatic nodules after centralized radiological review[10]. Following standard 6-week 3-drug preoperative regimen, 61–67% of patients have complete metastatic response before nephrectomy[123]. Afterward, current SIOP guideline advice stratifying patients to adjuvant regimens consisting of either vincristine plus increasing cumulative doses of doxorubicin (ranging between 150–250 mg/m^2) or a four-drug regimen including etoposide, carboplatin, cyclophosphamide, and doxorubicin (cumulative dose 300 mg/m^2). In patients with remaining lung nodules, metastatectomy and histological confirmation of metastasis is advised. Stratification is based on local stage of the primary tumour, histology of the primary tumour and the metastatic tumour (if resected), the size of metastases, and their response to preoperative chemotherapy and surgery **(Supplementary tables 2 and 4)**.

Pulmonary radiotherapy is administered for lung metastases lacking complete response by postoperative week 10. Evidence suggests that the majority of patients achieving a complete response after induction chemotherapy with or without surgery have satisfactory survival probability even without radiotherapy to the lungs (5-year event-free survival 84%, 5-year overall survival 92%)[123]. Patients with viable metastases at surgery or high-risk histology of the primary tumour receive radiotherapy to the lungs.

Patients with metastatic and high-risk disease are a rare subgroup with dismal prognosis, justifying testing of novel and more intensive regimens in first-line therapy[126]. Including combinations of vincristine, irinotecan, cyclophosphamide, carboplatin, etoposide, and doxorubicin, followed by high-dose melphalan and autologous stem cell rescue are currently being explored by the SIOP-RTSG[10,126,130].

For bilateral tumours, SIOP guideline aims to limit preoperative chemotherapy to a maximum of 12 weeks, with time intervals for evaluation to 6 weeks, also comparable with the COG approach. In order to maximize the possibility of bilateral nephron-sparing surgery, an approach of using carboplatin-etoposide in case of unsatisfactory response to vincristine-actinomycin D is under evaluation[10]. Adjuvant postoperative treatment guideline generally follows the same principles as for unilateral WT.

Low- and middle-income regions

Survival in low-income and middle-income countries (LMICs) is much lower than in HICs, with overall survival rates ranging from 11% in Sudan to 46% in Malawi[163–166]. In LMICs factors affecting a good outcome include delay in diagnosis with advanced disease[94,167], lack of diagnostic services, insufficient trained personnel, chemotherapy and radiation[14,95,168,169], misdiagnosis[167], and abandonment of therapy[14,169]. Mortality is increased owing to toxicity from surgery and/or chemotherapy, coupled with malnutrition[167,170–172]. Addressing these psychosocial issues and malnutrition (chronic and acute) may significantly add to improved outcomes with time[95,170,173]. As the countries gain experience, there is a need for support for the development of local priorities, advance curative therapies and palliative care.

Trained physicians, nurses and ancillary personnel are central in providing quality care. The WHO Global Initiative for Childhood Cancer developed the framework of care CureAll to provide early diagnosis networks to referral to centres of excellence; to introduce childhood cancer to the Universal Health Coverage schemas and Cancer Control Plans; to introduce cancer and supportive care regimens of care; and evaluate and monitoring schemas to measure progress. These strategic plans are coupled to enabling actions — advocacy, leveraged financing and linked Governance[174].

The SIOP approach with pre-nephrectomy chemotherapy provides the optimum and safest strategy in resource-limited settings. For large abdominal tumours (>500 ml), upfront surgery result in a high risk of surgical complications, tumour rupture and infection[175]. Patients with severe malnutrition may have decreased clearance of chemotherapy and dose adjustment may be necessary with parallel monitoring of liver function and recovery of myelosuppression[172,176]. In a preoperative chemotherapy scenario, close attention to the interpretation of pathology according to the SIOP risk classification is key to correct selection of postoperative treatment intensity, but requires specifically trained pathologists[9,10].

In LMICs, almost no clinical trials are available, with limited data and outcomes[177]. Encouraging prospective registration studies and participation in clinical trials has the benefit of building expert clinical capacity, improving facilities and funding treatment and associated costs with the effect of improved survival[177], all according to the local sustainability and capacity building[178].

As an example, the Collaborative WT Africa Project is a multinational prospective clinical study open in seven sub-Saharan countries, which have registered prospective outcomes by implementing the SIOP adapted treatment regimen for WT[164,179,180]. A minimum requirement of an ultrasonography of the abdomen was used for diagnosis. The guidelines recommended preoperative chemotherapy followed by surgery and further chemotherapy. The preoperative treatment included either a four-week two-drug (vincristine and actinomycin D) or a six-week three-drug (vincristine, actinomycin D and doxorubicin) regimen depending on the presence of local or metastatic disease, respectively[104]. Prolongation of preoperative chemotherapy was an option in cases with large tumour volume. Patients weighing <12 kg or with severe acute malnutrition were given two-thirds of the calculated dose of the chemotherapy[164]. The goal was then to achieve safe nephrectomy with lymph node sampling in patients with improved clinical and nutritional conditions, and tumour shrinking, which are all related to a reduced incidence of intraoperative morbidity. Postoperative chemotherapy aimed to follow the standard SIOP guideline, but with spacing the administration of vincristine every three weeks at a dose of 2 mg/m^2 as also used for children >1 year of age in specific phases of some COG regimens (capped at 2 mg absolute dose), reducing the burden of frequent travel to hospital[181]. Acknowledging deficits in radiotherapy provision (lacking across most of the African network), radiation therapy was used only in Kumasi and Accra in Ghana for metastatic disease and for stage III abdominal tumour[179].

The lessons learnt from this structured guideline was the need for team members to work according to shared vision, mission and principles[178]. The importance of using local site leaders to set the priorities for a successful clinical trial and keeping processes as simple as possible for data completeness was also appreciated. Good communication, transparency and trust was found to be the cornerstone for successful local implementation of a multi-national clinical trial in LMICs.

Just as clinical investigation is the cornerstone for best therapies and practices in HICs, research is needed to address the best therapy in different settings (better if tuned on prognostic indicators that have been studied and validated in the local context), best practices, and quality data to further improve outcomes[164,165]. Multidisciplinary care meeting with mentors improves management and experience of the local and regional groups.

Long-term complications

Despite the greatly improved therapy for WT over time, survivors still report a high frequency (25%) of severe chronic health conditions in adult life[15,16,182,183]. Patients with WT have a higher risk of death than the general population. In an analysis of children enrolled in the NWTS group between 1969 and1995, the standardized mortality ratio was 24.3 during the first five years after diagnosis, but remained increased for >20 years after diagnosis (standardized mortality ratio 4.3)[184]. Although the primary tumour remained the most frequent cause of death >5 years after diagnosis, secondary malignant tumours, cardiac disease and end-stage renal disease were also major causes of mortality.

The hazard ratios (HR) for hypertension (8.2), congestive heart failure (23.6) and renal failure (50.7) are all increased among five-year survivors of WT compared with the sibling group[15,185,186]. The risk of congestive heart failure increases with the cumulative dose of doxorubicin administered, with a critical threshold of 240 mg/m^2. Cardiotoxicity is potentiated by the concurrent use of radiotherapy, with girls and infants more susceptible than boys[15,186]. Similarly, doxorubicin seems to potentiate the adverse effects related to radiotherapy, likely owing to its radio sensitization of cells. These adverse effects include abnormal tissue growth within the targeted area and secondary malignancies.

The 20-year cumulative incidence of end-stage renal disease is reported to be <1% for unilateral WT and ~10% for patients with bilateral disease[187–190]. The risk factors associated with end-stage renal disease owing to chronic renal failure are stromal predominant histology (HR = 6.4), intralobar nephrogenic rests (HR = 5.9), and an age at diagnosis of less than 24 months or 48 months (HR = 1.7 and 2.8, respectively)[191]. Given the increased risk of cardiovascular morbidity with chronic kidney disease, identifying patients with a high risk of progressive renal impairment early is imperative to preserve the quality of life of long-term survivors. The wider availability and accuracy of patient genotyping may identify more molecular fingerprints with implications for renal function into adulthood, in order to select a subset of patients without clinical renal impairment at WT presentation, yet who might benefit from nephron-sparing surgical procedures.

Gonadal dysfunction

Gonadal dysfunction is observed in female WT survivors[192,193], and is strongly associated with exposure of the ovaries to radiotherapy (at any dose) and treatment with alkylating drugs[192,194]. The first-line chemotherapy with two drugs used (that is, vincristine and actinomycin D), in general, does not affect either ovarian reserve or male fertility. Whole-abdomen radiation usually results in primary ovarian failure or premature menopause. Additionally, WT treatment exposures including anthracyclines and lung radiation pose cardiovascular risks that can affect pregnancy outcomes[192]. WT survivors should receive personalized counseling about the type and magnitude of reproductive

health risks on the basis of their specific treatment exposure, with older girls with unfavourable histology or high-risk WT being at increased risk. Patients at the highest risk should be offered fertility preservation whenever possible, and after accurate counseling[195]. In this view, prior abdominopelvic surgery (see nephrectomy) should not be regarded as a barrier to laparoscopic oophorectomy with tissue cryopreservation for fertility preservation.

QUALITY OF LIFE

Parents, charities and survivors of WT have worked closely with researchers and scientists to ensure that research is focused on what's important to families, and to highlight areas of need. The Wilms Tumour Link Group, is an example of a parent-led research group in the UK focused on identifying priorities for future research and uses a social media group of >600 members from around the world to communicate research updates. Parents of children with WT have participated and presented at international scientific meetings and are considered to be partners in the research process, amplifying the patient voice within childhood cancer research[90].

This level of parent and patient involvement in research provides an important opportunity for physicians to work collaboratively. This collaboration facilitates the chance to have a greater impact on what is researched and highlights that not only cure is important, but also the child quality of life and a happy, healthy life post cancer. The active involvement of parents and survivors in research helps to translate findings in an equitable and accessible way. Findings are all too often kept within scientific journals that do not allow access to non-academics, so those that are affected by the disease are less informed. Working collaboratively and honestly with families is the key to patient-driven research with real-life translatable outcomes.

As a result of their better quality of life and physical functioning, children surviving renal tumours can hopefully also enjoy an increased involvement in sports. Patient counselling should include explaining any potential contraindication for practising sports carrying a risk for abdominal injuries[196].

Practice guidelines, where available, addressing the participation of children and adolescents with a solitary kidney (like most survivors of WT) in high-impact sports do not share a common vision worldwide[197]. In Italy, unlike rest of Europe and USA[198], having only one kidney automatically disqualifies an individual wishing to participate in any organized competitive contact sports, including basketball and soccer, and sometimes, volleyball.

To instigate positive changes in cancer care through exercise, and to endorse change in patients sensitively, patients, families, health-care teams must be made more aware of current evidence-based information to provide a framework for the harmonization of guidelines for sport participation of renal tumour survivors, to ensure that they can exercise freely yet safely.

OUTLOOK

Basic research

Increased understanding of the aberrant molecular pathways active in Wilms tumourigenesis has identified many potential targeted therapeutic approaches that could be applied in a clinical setting[36]. These include miRNA therapeutic modulation[43,44], Wnt signalling[90] and p53-specific

biological targeting agents in anaplastic WTs[69,70]. In addition, retinoic acid, although ineffective as a WT therapy in the all-trans form[199], may impart a differentiation effect on pre-cancerous nephrotic rests in the 13-cis form, potentially mitigating WT development in a selected group of patients at risk, particularly those with hyperplastic nephroblastomatosis[200,201]. Although the options seem intriguing, the main challenges are the relatively few patients in each molecular subgroup, WT intratumoural heterogeneity[78], few actionable known targets, selection and conduct of targeted trials and coordination of timely enrolment in the background of competitive trials[90,202].

Translational and clinical research

Some novel targets for WT have emerged, mostly based on PDX-dependent drug screens, leading to a few phase I and II WT trials. Examples include phase II study of IGF1-based inhibition (cixutumumab), anti-VEGF based therapy (sorafenib; cabozantinib), aurora-A-kinase inhibition (alisertib), and anti-mitotic based therapies either through direct microtubule inhibitory activity (ixabepilone) or via antibody drug conjugate linking an antimitotic agent (DM1) to an anti-CD56 antibody (lorvotuzumab) (lorvotuzumab mertansine, IMGN901)[202]. With the advance of β-Catenin targeting, the COG will soon launch the study of tegavivint, a specific β-Catenin inhibitor, to include a WT cohort[203].

Advances in refined personalized multilayered biologically-derived WT treatment will emerge, in the shorter term, via expanded creation and use of tumour models, ideally sufficient in number to represent the majority of WT biological subtypes[86,87]. Development of organoids, spheroids, and PDX, from basic investigation to real-time patient-specific drug screening, is now feasible, with plans evolving to launch an international patient-individualized relapse WT protocol harnessing this opportunity[90,204].

Novel imaging investigations also hold promise to advance WT treatment. For example, diffusion-weighted imaging (DWI)-MRI has been implemented as standard for diagnostic and post-chemotherapy assessment[105]. Such techniques may non-invasively quantify and risk stratify patients with WT prior to surgery, with radiological surrogates (apparent diffusion coefficient mapping) for both necrosis (particularly relevant when tumour size remains stable) and blastemal type histology[205]. Radiogenomics holds promise to further expand the utility of imaging in patient care of individuals with WT, as does artificial learning algorithms, for example, for the detection and quantification of lung nodules (and elsewhere), which dictates intensity of treatment. The import of such technology is magnified by the shift from chest X-rays to adequate CTs, which provide detailed information on lung lesions, but also reveal that even experienced radiologists have considerable inter-rater and intra-rater variation when interpreting such lesions[206].

WT may be amenable to advancement of liquid biopsy techniques for diagnostics, monitoring on therapy, and detection of minimal residual disease[80,118,207]. With the inclusion of serial blood or urine sampling on front-line and relapse WT studies (for example, the COG study AREN1921 focusing on patients with newly-diagnosed anaplastic WT and patients with relapsed favourable histology WTT), such advances seem promising in the near-future (NCT04322318)[208].

Cooperative group efforts

Both the COG and the SIOP groups have advanced well-organized prospective clinical trials and studies that tightly integrate biological aims and clinical insight, both linked to specific clinical protocols (AREN1921; NCT 04322318) or via overarching biobanking and risk-stratification studies (AREN03B2;NCT00898365, SIOP UMBRELLA)[10]. Cross-validation (meta-analysis) of data between these groups, especially on small cohorts of rare patients (such as those with anaplastic tumours, bilateral tumours or relapsing disease) and strategic efforts to synergize

intervention trials or observational studies holds promise to continue to advance diagnostics, risk stratification, and therapeutic options. Such 'harmonization' between cooperative groups has been formally advanced in the form of the 'Harmonica initiative', integrating multidisciplinary dialogue, meetings, consensus building, specific research focus and overall strategies on a trans-continental, inter-cooperative group level[6,90,127,202]. Likewise, dialogue continues regarding potential trans-Atlantic collaborative trials among the Innovative Therapies for Children with Cancer (ITCC), Paediatric Early Phase Clinical Trials Network (PEP-CTN), Paediatric Preclinical Testing Consortium, and parent representatives[90].

Global efforts

Childhood cancer therapy in LMIC lags behind in diagnosis, therapy and survival, with minimal clinical or biological research. In 2018, the WHO launched the Global Initiative for Childhood Cancer[174]. In 2021, the WHO Cancer Section published the technical package 'CureAll Framework: WHO Global Initiative for Childhood Cancer technical package', designed to provide guidance to member states for the implementation of childhood cancer services in resource-constrained settings. Six tracer cancers, including WT, are targeted to provide guidance for diagnosis, therapy and supportive and survivorship care. With the help of International Paediatric Cancer partners (academic, regional and global societies and non-Governmental Organizations), the aim is to establish the necessary training and design of basic, translational and clinical research[174]. Hence, progress in WT survival rates is expected to become more visible in the current decade.

Syndromes	Locus	Genetic lesion	Phenotype	Estimated risk of WT (%)	Refs
WAGR	11p13	11p13 deletion encompassing *WT1*	Aniridia, genitourinary anomalies, delayed-onset renal failure	~50	[209]
Denys-Drash	11p13	Point mutation zinc-finger region of *WT1*	Early-onset nephrotic syndrome (diffuse mesangial sclerosis), ambiguous genitalia	~75	[210]
Frasier	11p13	Point mutation in *WT1* intron 9 donor splice site	Ambiguous genitalia, streak gonads, focal segmental glomerulosclerosis, diffuse mesangial sclerosis	8	
Beckwith-Wiedemann	11p15	Dysregulation of imprinted genes including *IGF2* and *H19*	Overgrowth syndrome. Organomegaly, large birth weight, macroglossia, omphalocele, hemihypertrophy, ear pits and creases, neonatal hypoglycemia	0.2–24	[211]
Simpson-Golabi-Behmel	Xq26.2	*GPC3* mutations/deletions	Overgrowth syndrome. Pre- and postnatal overgrowth, visceral and skeletal abnormalities (course facies), congenital heart defects, a variable degree of psychomotor impairment	~3	[211]
Li-Fraumeni	17p13	Heterozygous *TP53* mutations. Genome instability disease	Familial predisposition to cancer	Low, but several cases reported	[212]
Mosaic variegated aneuploidy	15q15	Biallelic *BUB1B* or *TRIP13* mutations. Genome instability disease	Microcephaly, intellectual disabilities, cataracts, heart defects	<70	[213,214]
Fanconi anemia D1	13q12	Biallelic *BRCA2/FANCD1* mutations. Genome instability disease	Short stature, radial ray defects, bone marrow failure, but heterogeneous clinical presentation (one-third of individuals with FA have a normal appearance)	20–40	[215,216]
Hyperparathyroid-jaw tumour	1q25-q31	Heterozygous *HRPT2* mutations	Fibro-osseous lesions of jaw, parathyroid tumours	Low, but several cases reported	[217,218]
Bloom	15q26	Biallelic *BLM* mutations. Genome instability disease	Short stature, photosensitivity, microcephaly, insulin resistance, and immunodeficiency	3	[219]
Perlman	2q37	Biallelic inactivating variants in *DIS3L2*	Prenatal overgrowth, facial dysmorphism, developmental delay, cryptorchidism, renal dysplasia	~64	[220]
Trisomy 18 (Edward)	18q11.2-q23	Complete trisomy 18 (95%); Mosaic trisomy 18 (5%)	Congenital cardiac anomalies; dysmorphic facial features, clenched hands, and rocker-bottom feet	Case reports	[221]
Mulibrey nanism	17q22-q23	Biallelic *TRIM37* mutations	Growth deficiencies, cardiomyopathies, characteristic facies, a predisposition towards developing metabolic disorders (type II diabetes mellitus) (Finnish population)	~6–8%	[222,223]

Table 1. Heritable syndromes associated with an increased risk of Wilms tumour

Table 2. The landscape of cancer genes that are potentially operative in Wilms tumour genesis.

Gene	Role in tumourigenesis	Notes	Reported frequency[42]	Potential targeted therapeutic approaches	Refs
TP53	Tumour suppressor gene	Strongly associated with anaplasia; potential driver of disease progression	~5% (50–90% in DA)	p53-specific biological targeting agents	69–71,90
CTNNB1	Oncogene	Stabilizing mutations of the exon 3 phosphodegron or mutations of ARM repeats leading to reduced APC binding; upregulation of Wnt pathway	~15%	β-catenin/transducin β-like protein 1 inhibitor (tegavivint, COG trial)	38,42,203,224,51
WT1	Tumour suppressor gene	Germline mutations are associated with genitourinary anomalies or intersex; stromal predominant tumours; association with ILNR	~10–20%	Immunotherapy	38,45,46,90
WTX	Tumour suppressor gene	Negatively regulates the Wnt pathway	~10–20%	NA	38,54
SIX1, *SIX2*	Implicated in renal development	Specificity for blastemal regions; association with PLNR	5–10%	NA	43,44
DROSHA, *DGCR8*, *DICER1* & others	miRNA processing genes	*DROSHA*: heterozygous mutations of catalytic core; *DGCR8*: homozygous mutation (E518K) of dsRBD; more frequent in blastemal predominant tumours; association with PLNR	~15%	Targeting of miRNA processing	43,44,55,90
MYCN	Oncogene	Copy number gain or specific P44L mutation	~15%	Drugging MYC; MYCN Oncogenic transcription factor	59,90,225
H19–IGF2 locus	Epigenetic abnormalities at the imprinted loci on 11p15	LOI or loss of maternal allele (pUPD) at the BWS imprinting center 1 (IC1) leading to increased *IGF2* expression; association with PLNR	~50–80%	Targeting of IGF2; methylation and epigenetic targeting agents	38,43,44,52,226

DA, diffuse anaplasia; LOI, loss of imprinting; ILNR, intralobar nephrogenic rest; PLNR, perilobar nephrogenic rest; COG, Children's Oncology Group; pUPD, paternal uniparental disomy; NA, not available

Table 3. Risk classification according to SIOP Renal Tumour Study Group

	For pretreated cases	For primary nephrectomy cases
Low-risk tumours	Congenital mesoblastic nephroma Cystic partially differentiated WT Completely necrotic WT	Congenital mesoblastic nephroma Cystic partially differentiated WT
Intermediate-risk tumours	WT epithelial type WT stromal type WT mixed type WT regressive type WT focal anaplasia	Non-anaplastic WT and its variants WT focal anaplasia
High-risk tumours	WT blastemal type WT diffuse anaplasia Clear cell sarcoma of the kidney Rhabdoid tumour of the kidney Renal cell carcinoma	WT diffuse anaplasia Clear cell sarcoma of the kidney Rhabdoid tumour of the kidney Renal cell carcinoma

WT, Wilms tumour.

Data from reference [9,122].

Figure legends

Fig 1. Timeline of key clinical advances that established the modern clinical management of children with Wilms tumour 1. The National Wilms Tumor study group (NWTS), which was supplanted by the Children's Oncology Group (COG) in 2002, and the International Society of Paediatric Oncology (SIOP) initiated organized protocols[155,227–229]. 2. Researchers started to collect data on the associations between WT-specific therapies and late toxicity in survivors[227]. 3. In 1978, anaplastic morphology was shown to correlate with an increased mortality from WT[98]. 4. SIOP progressively recognised that histologic subtypes after neo-adjuvant chemotherapy were a prognostic factor[122,160,228,230]. 5. In 1990, SIOP established the Pediatric Oncology in Developing Countries (PODC) committee, to promote pediatric oncology in poorly-resourced countries. 6. Researchers successfully pioneered to avoid lung radiotherapy in subgroups of patients with metastases (good responders), setting the new standard[231]. 7. SIOP-9 trial (1987–1991) showed no benefit from prolonging pre-nephrectomy chemotherapy to 8 weeks with respect to stage distribution, the 4-week schedule becoming the standard for non-metastatic WT[160]. 8. Actinomycin D could be administered in a single dose rather than divided over 5 days, thereby reducing hospital accesses for children and health care delivery costs[232,233]. 9. Nephrectomy alone in children with very low risk WT (defined as <24 months of age, with stage I favourable histology tumour weighing <550 g) showed to be a valid option, avoiding the risks of central line placement and chemotherapy[136]. 9. Risk stratification of WTs implemented with loss of heterozygosity (LOH) at chromosomes 1p and 16q as adverse prognostic markers[39]. 10. Current standard treatment for children with stage II and III intermediate-risk histology after preoperative chemotherapy is without doxorubicin (vincristine and actinomycin D)[7]. 12. In 2018, the WHO launched the Global Initiative for Childhood Cancer, with the goal of improving outcome for children with cancer around the world, initially focusing on six common cancers including WT[174].

Fig. 2. The estimated mortality for kidney cancers according to geographical area. Estimated age-standardised mortality rates in 2020, kidney cancers, in children aged 0-14 years in the world[234]

Fig. 3. The incidence of WT according to geographical area and ethnicity. Age-standardised incidence rates of renal tumours in children 0-14 years of age by world region and ethnicity, 2001–2010 (N=15,320). ASR, age-standardised incidence rate; Unspecified, unspecified malignant renal tumours (Adapted from[2]).

Fig. 4. The age-specific incidence of WT according to gender, laterality and geographical area. a) Age-specific incidence of Wilms tumour (WT) in children 0–14 years of age, all world regions combined, by sex (N=13,838) and laterality* (N=6,396), 2001–2010. *Only the registries providing information on the laterality for at least 95% WT cases are included. b) Age-specific incidence of WT in children 0–14 years of age, by world region, 2001–2010 (N=13,838). (Adapted from Ref[2]).

Fig. 5. Biology of paediatric renal tumours. Cells deriving from intermediate mesoderm form the nephrogenic niche and develop into the various cell types of normal kidney. Molecular alterations in these cells may result in diverse renal tumours: ~80% being WTs and ~20% other primary renal tumours. In a paradigm of disrupted organ development eventually leading to tumorigenesis, remains of the multipotent nephrogenic zone of the fetal kidney may persist after birth and appear in up to 1% of routine infant post mortem autopsies as nephrogenic rests. The natural history and fate of nephrogenic rests is, however, uncertain: these cells may terminate their differentiation, or eventually regress and become sclerotic and obsolescent, while others progress to form hyperplastic nephrogenic rests, with typical genetic changes. Nephrogenic rests are found in over 90% of bilateral cases and ~30-40% of unilateral sporadic WT cases. WTs are then characterized by the acquisition of additional genetic and epigenetic changes, some of them being quite specific for

histological subtypes. The percentages indicate the frequency of mutation in sporadic cases. It is unclear if WTs may originate directly from nephrogenic blastema without progression through nephrogenic rest stages. Abbreviations: WT, Wilms tumour; CMN, congenital mesoblastic nephroma; CCSK, clear cell sarcoma of the kidney; RCC, renal cell carcinoma; RTK, rhabdoid tumour of the kidney; LOI, loss of imprinting, LOH, loss of heterozigosity.

Fig. 6. Different histological patterns of WT. The figure shows the different histological patterns of Wilms tumour (WT). Shown are mixed type, with the blastemal and epithelial component (panel a); blastemal type WT (panel b); mixed type consisting of the mature epithelial and stromal components (panel c); epithelial type composed of moderately differentiated tubules (panel d); stromal type with heterologous elements including cartilage and skeletal muscle (panel e); anaplasia in Wilms tumour, with atypical mitoses, nuclear enlargement and hyperchromasia (panel f).

Box 1: Wilms tumour predisposition and driver genes.

Most genes implicated in Wilms tumorigenesis act in gene expression control and growth factor signalling. Approximately 50% of the genes can be present in mutant form in germline or constitutional DNA conferring increased WT risk[51].

Kidney development

CTNNB1, SIX1, SIX2, WT[a]

Transcriptional machinery

CDC73[a], *CREBBP, CTR9*[a], *FBXW7*[a], *MAX, MLLT1, MYCN*

Chromatin biology or epigenetic modifiers

ARID1A, ASXL1[a], *BCOR(L1)*[a], *BRD7, CHD4, HDAC4, KDM3B*[a], *RERE, REST*[a], *TRIM28*[a], *TRIM37*[a]

MicroRNA processing and RNA metabolism

DGCR8, DICER1[a], *DIS3L2*[a], *DROSHA, LIN28B, NONO, NYNRIN*[a], *TARBP, XPO5*

Growth factor signalling

ACTB, AMER1, FGFR1, GPC3[a], *IGF2 (BWS-IC1)*[a], *MAP3H4, NF1*[a], *PIK3CA*[a]

Genome maintenance

BLM[a], *BRCA2*[a], *BUB1B*[a], *CHEK2, PALB2*[a], *TP53*[a], *TRIP13*[a]

[a]Syndromal or familial WT genes

Box 2: Challenges and priorities for managing patients with Wilms tumour in low and middle-income countries

Challenges

- Highly constrained healthcare budgets resulting in insufficient paediatric oncologists, surgeons, anaesthetists and pathologists; shortage of chemotherapeutic agents (which leads to incomplete Wilms tumour (WT) treatment); limited or lacking infrastructure and facilities for imaging and radiation therapy.
- Lack of high-quality specialized paediatric surgical training to perform complex operations (WT with intracaval extension, nephron-sparing surgery).
- Inadequate reporting or data collection within national or hospital registries precludes accurate outcomes assessment.
- Inadequate specialist cancer services.
- Late clinical presentation (delay in diagnosis) owing to family or relatives' reduced awareness about cancer; contacting and arrival to primary care; healthcare staff recognition of cancer (a much higher number of children in low-income countries have a distended abdomen than in high-income countries due to many other non-malignant conditions, thus it is challenging to differentiate and prioritize investigations for the relative few cases of WT).
- Many patients are diagnosed with already advanced or metastatic tumours.
- Toxicity from surgery and/or chemotherapy can increase mortality and contribute to treatment abandonment.
- Malnutrition is a major concern for higher drug toxicity and treatment-related death.
- Burden of associated co-morbidities (infections).
- Patient quality of life largely unrecognized and unprioritized.

Priorities and areas for improvement

- Comprehensive registries are the first steps to appropriate resource allocation according to local needs and to monitor improvement.
- Earlier diagnosis through increased education among primary health providers concerning WT diagnosis, and parent education on healthy living and concerning symptoms.
- Adapted treatment regimens to accommodate frail children, to reduce toxicity, and to face specific (temporary or permanent) drug regimen shortage.
- Nutritional programs, best with locally available calories-dense foods and fortifiers.
- Implementation of family education programs may increase compliance with cancer care reducing abandonment.
- Twinning programs (pairing of hospitals in resource-limited countries with hospitals in developed countries) to improve local medical expertise and education.
- Clinical trials answering locally relevant questions (such as prognostic factors).
- Prioritizing resources to focus on curable clinical situations.
- Palliative care as the main priority for advanced malignancies.

Box 3. Patient experience

The statements provided have not been edited and the patients' emphases remain in place.

"Teenage years, the best ones in everyone's life. I was living unforgettable moments, going out and having parties with my friends. And then, after some medical checks, hell overnight. I had cancer. At first, I started imagining what I would have had to go through, how much I would have suffered. I was lost in doubts, fear and contrasting feelings.
To start chemotherapy shocked me. Eight hours, each impressed in my mind, in which milliards of medicine's drops came into my body. I felt exhausted.
As I was left alone for a moment in that hospital room, I abandoned myself to tears at the idea of repeating all of that the next day, and for eight more courses: that thought killed me. I came in that realization in that right moment.
I remember how important it was, for me, to have my friends around and to spend as much time as possible together. I remember they were the only ones who made me laugh, who made me feel normal, like nothing had ever changed. They made me breath, giving me the oxygen I needed. They reminded me how strong I was, when I was totally worn out. They recalled me what it meant to live, as sometimes I forgot how to do it.
Then the Covid19 pandemic situation came, and loneliness. My mum and I, stop. Far away from everyone, from everything. Three months of physical pain for chemo that I kept doing, of discouragement and fear. And, if it wasn't enough, there was also the worry of catching the virus.
Finally, after never-ending months, I came back to my lovely Naples. To my friends, to my family. To the sea, as I saw it, I felt free. Everything finally came to an end, and I couldn't believe it."

-G.B., 16 years old.

Box 4. International controversies in advice on sporting activities in people with single kidneys.

- Most children diagnosed with Wilms tumour (WT) become long-term survivors and living with surgically solitary kidney.
- Among injuries occurring during sport exposure, the incidence of injuries to kidney is very low (sporting kidney injuries are 0.07–0.5% of all sports-related injuries), less frequent than head injuries, and usually without serious sequelae[235,236].
- The recommendations for children and adolescents with solitary kidneys to participate in contact or collision sports have changed over time. The last update from the American Academy of Paediatrics (2001) leans toward player participation without restriction in noncontact sports, and with individual assessment for limited-contact, contact, and collision sports to release an unbiased judgment, which is not based only on the fact of having a solitary kidney[198].
- However, national advice toward permission to participation into high-impact sports varies between countries and over time[191].
- Flank protectors have not been rigorously evaluated and an international standard for the protection they may offer is not available[196].
- Individual counselling and decision-making between child, families and oncologist are recommended.

Glossary terms

Nephron-sparing surgery

an operation to remove a kidney tumour by removing only part of the surrounding normal renal parenchyma

Overgrowth syndromes

a heterogeneous group of disorders in which the main characteristic is that either weight, height, or head circumference is 2–3 standard deviations above the mean for sex and age. The different presentations are dependent on the developmental pathways and organ systems affected.

Aniridia

a rare condition characterized by a partial or complete absence of the iris of the eye

Nephrotic syndrome

a rare clinical disorder defined by massive proteinuria (>40 mg/m^2 per hour) responsible for hypoalbuminemia (< 25 g/L), with resulting hyperlipidaemia, oedema, and various complications

Nephrogenic rest

abnormally persistent foci of embryonal cells and regarded as precursor lesions of Wilms tumour. Rests are subdivided into two main types: perilobar, confined to the periphery of the renal lobe, and intralobar, found anywhere within the renal lobe

WAGR syndrome

a rare contiguous gene deletion syndrome (Wilms tumour, aniridia, genitourinary anomalies, and range of developmental delays) with a 45–60% risk of developing WT

Hypospadias

an anatomical congenital malformation of the male external genitalia, characterized by abnormal development of the urethral fold and the ventral foreskin of the penis that causes abnormal positioning of the urethral opening

Cryptorchidism

the absence of at least one testicle from the scrotum

Denys-Drash syndrome

a rare condition caused by mutations in the tumour-suppressor gene *WT1*, characterized by a triad of disorders: ambiguous genitalia, nephrotic syndrome leading to end-stage renal disease, and Wilms tumour

Frasier syndrome

a rare autosomal recessive disorder that presents with male pseudohermaphroditism with gonadal dysgenesis, renal failure in early adulthood and increased risk of developing gonadoblastoma

Chromothripsis

a catastrophic chromosomal shattering event associated with random rejoining

Li-Fraumeni syndrome

an inherited autosomal dominant cancer predisposition disorder that is usually associated with abnormalities in *TP53* located on chromosome 17p13.

Anaplasia

cells with hyperchromatic, pleomorphic nuclei that are three times larger than adjacent cells and have abnormal mitotic figures. Anaplasia is associated with a poor response to chemotherapy

Oophorectomy

a surgical procedure to remove one or both ovaries

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